In February 2013, GlaxoSmithKline (GSK) announced a commitment to further clinical transparency through the public disclosure of GSK Clinical Study Reports (CSRs) on the GSK Clinical Study Register.

The following guiding principles have been applied to the disclosure:

- *Information will be excluded in order to protect the privacy of patients and all named persons associated with the study*
- *Patient data listings will be completely removed* to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the* ***GSK Clinical Study Register****.*
- *Aggregate data will be included; with any direct reference to individual patients excluded*

**Complete removal of patient data listings may mean that page numbers are no longer consecutively numbered*

The GlaxoSmithKline group of companies

A Randomised, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy, Safety and Tolerability of Oral Cilomilast (15 mg bd) When Given as Maintenance Treatment for 12 Months to Subjects with Chronic Obstructive Pulmonary Disease (COPD)

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

Document Number: GM2004/00073/00 **Compound Number: SB-207499**

Investigational Product: Ariflo **Generic Drug Name: Cilomilast**

Indication Studied: Chronic Obstructive Pulmonary Disease

Initiation Date:	01Nov2001
Completion Date:	09 Jan2004
Date of Report:	11 February 2009

Sponsor Signatory: [redacted] MD
(and Medical Officer) Vice President, Respiratory & Immunoinflammation
Medicine Development Centre, Clinical

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

Copyright 2009 the GlaxoSmithKline group of companies. All rights reserved.
Unauthorised copying or use of this information is prohibited.

TABLE OF CONTENTS

Page

Abbreviations 10

1. ETHICS 12
    1.1. Independent Ethics Committee (IEC) 12
    1.2. Ethical Conduct of the Study 12
    1.3. Subject Information and Consent 12

2. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE 12

3. INTRODUCTION 14

4. STUDY OBJECTIVES 15
    4.1. Primary objective 15
    4.2. Secondary objectives 15

5. INVESTIGATIONAL PLAN 15
    5.1. Overall Study Design – Description 18
    5.2. Discussion of Study Design, Including the Choice of Control Group(s) 20
    5.3. Protocol Amendments 20
    5.4. Selection of Study Population 21
        5.4.1. Inclusion Criteria 21
        5.4.2. Exclusion Criteria 22
        5.4.3. Predetermined Criteria for Subject Withdrawal 24
    5.5. Investigational Product(s) 25
        5.5.1. Description of Investigational Product(s) 25
        5.5.2. Dosages and Administration 25
        5.5.3. Dose Rationale 26
        5.5.4. Blinding 26
        5.5.5. Treatment Assignment 26
        5.5.6. Treatment of Investigational Product Overdose 27
    5.6. Prior and Concomitant Medications and Non-Drug Therapies 27
        5.6.1. Permitted Medications 27
        5.6.2. Prohibited Medications 28
    5.7. Study Assessments and Procedures 29
        5.7.1. Demographic and Baseline Assessments 29
        5.7.2. Efficacy Assessments 30
        5.7.3. Health Outcome Assessments 34
        5.7.4. Safety Assessments 35
    5.8. Data Quality Assurance 41
    5.9. Data Analysis Methods 42
        5.9.1. Timings of Planned Analyses 42

5.9.2. Sample Size Considerations 43
5.9.3. Sample size sensitivity 43
5.9.4. Analysis Populations 44
5.9.5. Treatment Comparisons 45
5.9.6. General Considerations for Data Analyses 45
5.9.7. Data Handling Conventions 46
5.9.8. Study Population 56
5.9.9. Efficacy Analyses 59
5.9.10. Safety Analyses 61
5.9.11. Health Outcomes Analyses 61

6. STUDY POPULATION RESULTS 62
6.1. Disposition of Subjects 62
6.2. Protocol Deviations 62
6.3. Populations Analysed 63
6.4. Demographics and Other Baseline Characteristics 64
6.4.1. Demographic Characteristics 64
6.4.2. Baseline Characteristics 65
6.4.3. Other Current Medical Conditions 66
6.4.4. Previous Medications 66
6.4.5. Other Factors Affecting Response to Therapy 67
6.5. Concomitant Medications 67
6.6. Treatment Compliance 69

7. EFFICACY RESULTS 70
7.1. Primary Efficacy Results 70
7.1.1. Pre-bronchodilator trough FEV1 70
7.1.2. Incidence rate of level II/III COPD exacerbations 74
7.2. Secondary Efficacy Results 75
7.2.1. Mean change from baseline in trough post-bronchodilator FEV1 . . . 75
7.2.2. Time to first level 2 (moderate) or level 3 (severe) COPD exacerbation 77
7.2.3. Time to first COPD exacerbation (all levels) 79
7.2.4. Incidence for all COPD exacerbations 81
7.2.5. Quality of life (SGRQ) 82
7.3. Other Efficacy Results 83
7.3.1. Pulmonary function parameters 83
7.3.2. Residual volume 86
7.3.3. Morning PEF from DRC 87
7.3.4. Use of relief medication and % of days with no rescue medication . . 87
7.3.5. Duration of exacerbations 88
7.3.6. Symptom scores and symptom free days 88

7.3.7. Diary card parameters . . . 89
7.3.8. Night-time awakenings . . . 89
7.3.9. SGRQ subscales (symptoms, activity and impact) . . . 90
7.3.10. Global subject assessment . . . 91
7.3.11. Global Investigator assessment . . . 91
7.3.12. Blood CD4+/CD8+ ratio . . . 92
7.3.13. Serum C reactive protein . . . 92
7.4. Subgroup Analyses . . . 93
7.4.1. Gender . . . 93
7.4.2. Percent Predicted FEV1 . . . 93
7.4.3. Smoking Status . . . 94
7.5. Efficacy Conclusions . . . 101
8. SAFETY RESULTS . . . 103
8.1. Extent of Exposure . . . 103
8.2. Adverse Events . . . 103
8.2.1. On-therapy Adverse Events . . . 103
8.3. Serious Adverse Events . . . 108
8.3.1. Fatal Events . . . 108
8.3.2. Non-Fatal Events . . . 108
8.4. Adverse Events Leading to Premature Discontinuation of Investigational Product and/or Study . . . 110
8.5. Other Relevant Adverse Events . . . 111
8.5.1. Gastrointestinal Adverse Events of concern . . . 111
8.5.2. Adverse Events Requiring Concomitant Therapy . . . 118
8.6. Pregnancies . . . 118
8.7. Clinical Laboratory Evaluations . . . 119
8.7.1. Laboratory Values Over Time . . . 119
8.7.2. Individual Subject Changes . . . 119
8.7.3. Abnormalities of Potential Clinical Concern . . . 120
8.8. Other Safety Evaluations . . . 121
8.8.1. Vital signs . . . 121
8.8.2. ECG . . . 123
8.9. Safety Conclusions . . . 126
9. HEALTH OUTCOMES RESULTS . . . 127
9.1. EQ-5D . . . 127
9.2. Resource utilisation and indirect costs . . . 127
9.3. Time off work/normal activities due to COPD . . . 127
9.4. Health Outcomes Conclusion(s) . . . 127
10. DISCUSSION . . . 128
11. CONCLUSIONS . . . 135

12. REFERENCES 137
13. SAFETY DATA SOURCE TABLES 139
14. EFFICACY DATA SOURCE TABLES 323
15. SAFETY DATA SOURCE TABLES 494
16. CASE NARRATIVES 806
16.1. Withdrawals due to Adverse Events 806
16.2. Non-Fatal SAE case narratives 997
16.3. FATAL SAEs 1087
16.4. GIAE 1096
16.5. ECG of Clinical Concern 1135
16.6. Lab Narratives 1282
16.7. Ovital 1346
16.8 Location Table 1382
17. INTENTIONALLY LEFT BLANK 1399
18. HEALTH OUTCOMES DATA SOURCE TABLES 1399
19. EFFICACY DATA SOURCE FIGURES 1406

LIST OF FIGURES

Page

Figure 1 Mean Change from baseline in Pre-bronchodilator FEV1 ITT population . . 71
Figure 2 Mean change from Baseline in Post Bronchodilator FEV 1 ITT population 77
Figure 3 Kaplan-Meier Estimates of Percentage of subjects who are level II/Level III Exacerbation-free ITT population 78
Figure 4 Kaplan-Meier Estimates of Percentage of subjects who are Exacerbation-free – ITT population 80
Figure 5 Mean (SEM)Change from Baseline in SGRQ Total Score ITT population . 83
Figure 6 Mean (SEM) Change from baseline in FVC (L) ITT population 84
Figure 7 Mean (SEM) Change in Baseline in PEF (L/min) ITT population 85
Figure 8 Mean (SEM) Change from Baseline in FEF25-75 (Lsec) ITT population . . 86

LIST OF TABLES

Page

Table 1 Study Design. 16
Table 2 Study medication details 25
Table 3 Examples of permitted medications 28
Table 4 Prohibited medications 29
Table 5 COPD symptom scale. 33
Table 6 Sample size sensitivity (sample size=275/arm) 44
Table 7 Calculating EuroQoL state valuations 50
Table 8 Laboratory Values of Interest and Potential Clinical Concern 54
Table 9 Vital sign Values of Interest and Potential Clinical Concern 55
Table 10 ECG Values of Interest and Potential Clinical Concern 56
Table 11 Number of subjects who completed each phase of the study 62
Table 12 Summary of conduct of study deviations 63
Table 13 Summary of protocol violations resulting in exclusion from the Per Protocol population 64
Table 14 Study populations 64
Table 15 Summary of demographic characteristics at screening - all randomised subjects. 65
Table 16 Baseline characteristics - randomised population. 66
Table 17 Most common (>10% of subjects in any treatment group) medication discontinued at screening - all randomised subjects 67
Table 18 Five most common medications taken during the study - all randomised subjects. 68
Table 19 Most common (>5% subjects in any treatment group) medication given for a COPD exacerbation - all randomised subjects 68
Table 20 Mean difference between treatment groups in change from baseline in pre-bronchodilator trough FEV1 over 52 weeks - ITT population 70
Table 21 Mean difference between treatment groups in change from baseline in pre-bronchodilator trough FEV1 by week in the ITT population 72
Table 22 Summary of tests of significance for prognostic factors affecting the change from baseline in trough FEV1. 73
Table 23 Mean difference between treatment groups in change from baseline in pre-bronchodilator trough FEV1 by week in the PP population 74
Table 24 Summary of level II/III COPD exacerbation rates per patient year - all randomised subjects 74
Table 25 Summary of level II/III COPD exacerbation rates per patient year - PP population 75
Table 26 Mean difference between treatment groups in change from baseline in post-bronchodilator trough FEV1 over 52 weeks - ITT population 75

Table 27 Mean difference between treatment groups in change from baseline in post-bronchodilator trough FEV1 by week in the ITT population 76
Table 28 Summary of level II/III exacerbation-free survival - all randomised subjects 77
Table 29 Summary of level II/III exacerbation-free survival - PP population 78
Table 30 Summary of exacerbation-free survival - all randomised subjects 79
Table 31 Summary of exacerbation-free survival - PP population 80
Table 32 COPD exacerbation rates per patient year - all randomised subjects 81
Table 33 Frequency of COPD by exacerbation level - all randomised subjects 81
Table 34 COPD exacerbation rates per patient year - PP population 82
Table 35 Change from baseline in trough PEF by week - ITT population 85
Table 36 Change from baseline over 52 weeks in trough FEF25-75 - ITT population 86
Table 37 Change from baseline in residual volume by week - ITT population 87
Table 38 Average daily inhaler use ITT population 88
Table 39 Duration (days) of an exacerbation - all randomised subjects 88
Table 40 Average change from baseline over 52 weeks in diary card measured parameters - ITT population 89
Table 41 Average number of night-time awakenings - ITT population 90
Table 42 Average change from baseline over 52 weeks in individual domains of the SGRQ - ITT population 90
Table 43 Patient global assessment of treatment efficacy - ITT population 91
Table 44 Investigator global assessment of treatment efficacy - ITT population 92
Table 45 Change from baseline in serum C reactive protein - ITT population 92
Table 46 Descriptive statistics for pre-bronchodilator FEV1 at study endpoint by gender - ITT population 93
Table 47 Descriptive statistics for pre-bronchodilator FEV1 at study endpoint by ATS severity - ITT population 94
Table 48 Mean difference between treatment groups in pre-bronchodilator trough FEV1 over 52 weeks in the ITT population by smoking status 95
Table 49 Mean difference between treatment groups in pre-bronchodilator trough FEV1 over 52 weeks in the PP population by smoking status 96
Table 50 Summary of smoking status on the exacerbation rate of level II/III exacerbations - all randomised subjects 97
Table 51 Summary by smoking status of number (%) of subjects which remained exacerbation-free of level II/III exacerbations at 52 weeks 98
Table 52 Summary by smoking status of number (%) of subjects which remained exacerbation-free of all exacerbations at 52 weeks 99
Table 53 Summary of smoking status on the exacerbation rate of all exacerbations per patient year - all randomised subjects 100
Table 54 Frequency and rate of COPD by exacerbation level and smoking status - all randomised subjects 100

Table 55 Change from baseline in total SGRQ score by smoking status - comparison with placebo 101
Table 56 Summary of Exposure to study medication 103
Table 57 Number of subjects with Adverse Events on-therapy - safety population . . 104
Table 58 Most commonly (reported by >4% of subjects) in either treatment group reported Adverse Events on-therapy - safety population 105
Table 59 Most common (reported by >1% of subjects in either treatment group) Adverse Events assessed as related to study medication - safety population . . 106
Table 60 Incidence of on-therapy experiences experienced by >= 4 subjects in any treatment group by time of onset within the first 28 days of treatment- Safety population 107
Table 61 Most common(reported by >= 3 subjects in either treatment group) Adverse Events Post-treatment - safety population 108
Table 62 Most common (reported by >=2 subjects in either treatment group) Serious Adverse Events reported on-therapy - safety population 109
Table 63 Serious adverse events assessed as related to study medication - safety population 110
Table 64 Most common (reported by >= 3 subjects in either treatment group) Adverse Events leading to patient withdrawal - safety population 111
Table 65 GI Adverse Events (reported by >= 2 subjects in either treatment group) which lead to patient withdrawal - safety population 112
Table 66 Summary of results for subjects investigated for GIAEs of concern plus frank or occult blood 117
Table 67 Most common (reported by >2% of subjects in either treatment group) Adverse events requiring a change in medication - safety population 118
Table 68 Transition from baseline to a value of concern for haematology analytes on-therapy 119
Table 69 Transition from baseline to a value of concern for biochemistry analytes on-therapy 120
Table 70 Transition from baseline to values of concern on-therapy and at study endpoint in orthostatic vital signs: Safety population 122
Table 71 Transition from baseline to values of concern on-therapy and at study endpoint in sitting vital signs: safety population 123
Table 72 Transition from baseline to a value of concern for ECG parameters on-therapy and at study endpoint 124
Table 73 Most common (reported by >=2% of subjects in either treatment group) new-onset ECG abnormalities on-therapy 125

Abbreviations

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT (SGPT)	Alanine Aminotransferase
ANOVA	Analysis of Variance
AST (SGOT)	Aspartate Aminotransferase
Bd	Twice Daily
Beta-HCG	Beta Chorionic Gonadotrophin
BP	Blood Pressure
BTPS	Body Temperature And Pressure Standard
Cyclic AMP	Cyclic Adenosine Monophosphate
CI	Confidence Interval
Cm	Centimetre
COPD	Chronic Obstructive Pulmonary Disease
CRAMS	Case Report Form Activity System
CRF	Case Report Form
CRO	Contract Research Organisation
DRC	Daily Record Card
DRQ	Data Resolution Query
ECG	Electrocardiogram
FEF_{25-75}	Forced Expiratory Flow At 25-75% Vital Capacity
FEV_1	Forced Expiratory Volume In 1 Second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
GIAE	Gastrointestinal Adverse Event
GI	Gastrointestinal
GSK	GlaxoSmithKline
HR	Heart Rate
ICS	Inhaled corticosteroids
IEC	Independent ethics committee
IRB	Institutional Review Board
ITT	Intent-to-treat
LLN	Lower limit of normal
LTOT	Long-term oxygen therapy
Mcg	Microgram
MDI	Metered dose inhaler
Mg	Milligram
Ml	Millilitre
MmHg	Millimetres of mercury
PA	Postero-anterior
PDE4	Phosphodiesterase 4
PEF	Peak expiratory flow rate
PFT	Pulmonary function test
PP	Per protocol
Prn	Pro re nata (as needed)
PRP	Pulmonary rehabilitation program

QC	Quality control
RAMOS	Registration and Medication Ordering System
RV	Residual volume
R&D	Research and development
SAE	Serious adverse event
SaO2	Transcutaneous oxygen saturation
SGRQ	St. George's respiratory questionnaire
SQL	Standard Query Logic
ULN	Upper limit of normal
URTI	Upper respiratory tract infection

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
AUGMENTIN
BECONASE AQ
BECOTIDE
FLIXOTIDE
FLIXONASE
NICODERM
SEREVENT
VENTOLIN
VOLMAX

Trademarks not owned by the GlaxoSmithKline group of companies
Accolate
Alupent
Atrovent
Azmacort
Biaxin
Bricanyl
Ceclor
Combivent
Decadron
Depo-Provera
Duovent
Foradil
Habitrol
Intal
Isuprel
Medrol
Nasacort
Naslide
Nicorette
Nicotrol
Norplant
Pulmicort
Rhinocort
Rynacrom/Nasalcrom
SAS Proc Lifetest
Singulair
Slo-Bid
Sterapred
Syntaris
Theo-Dur
Tilade
Vancenase AQ

1. ETHICS

1.1. Independent Ethics Committee (IEC)

The study protocol, any amendments, the informed consent, and other information that required pre-approval were reviewed and approved by a national, regional, or investigational centre ethics committee.

1.2. Ethical Conduct of the Study

This study was conducted in accordance with "good clinical practice" (GCP) and all applicable regulatory requirements, including, where applicable, the 1996 version of the Declaration of Helsinki.

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 were provided for each subject's data to be recorded.

2. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

A total of 161 centres from 18 countries were initiated. Of these 137 centres enrolled at least one patient into the run-in phase of the study and a total of 126 centres randomised at least one patient within the double-blind period of the study. No coordinating Investigator was nominated for the study.

Aspects of the study management including preparation of the protocol and approval of the protocol and CRF, the conduct of the Investigator meeting, data management, statistical analyses and clinical study report writing was performed by GSK.

Study initiation and clinical monitoring was performed by a contract research organisation (CRO) in certain countries. In Belgium the CRO used was MSOURCE, in Spain, Parexel were used and in the UK, Quintiles were used. In Germany, the study was handed over to a CRO to monitor once recruitment was completed (EPA EURO PHARMA, Kronberg). The addresses for each CRO involved are as follows:

UK

Quintiles Clinical Development Services (CDS), Quintiles Limited, Station House, Market Street, Bracknell, Berkshire, RG12 1HX

Spain

Parexel ETT, C/Génova 17, 5ª pta, 28004 Madrid

Belgium

MSOURCE, Mechelsesteenweg 455 B5, B-1950 Kraainem (Brussels-Belgium)

Germany

EPA EURO PHARMA Auftragsforschung GmbH, Am Aufstieg 6, D-61476 Kronberg

There was no steering committee for this study.

The central laboratories used in this study were Quest Diagnostics, Heston, Middlesex, UK for all countries except Australia, New Zealand and Taiwan and Dorevitch laboratories, Mayne Health Dorevitch Pathology, Heidelberg, Victoria, Australia for centres in Australia, New Zealand and Taiwan.

All study drugs were packaged and labelled by GlaxoSmithKline (GSK) and distributed to the Investigators by GSK. A code break facility was available at all times either by sealed copies of randomisation codes shipped with medications or via a phone-based electronic system.

3. INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a disease state characterised by progressive development of airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases [GOLD, 2001]. COPD comprises both chronic bronchitis and emphysema and is characterised by inflammatory abnormalities in small airways.

COPD is one of the leading causes of death worldwide, being fourth or fifth highest in developed countries, with an increasing prevalence and mortality [Thom, 1989] which is projected to be the third leading cause of death worldwide by 2020 [Murray, 1997].

Subjects typically have chronic symptoms, particularly breathlessness on exertion, and a productive cough, accompanied by progressive deterioration in lung function, interspersed by exacerbations of their disease. This combination leads to substantial impairment in the patient's health related quality of life [Jones, 1991a]. Long term evaluation of the disease is based on rate of decline in lung function over time, exacerbations, and health status.

Many definitions of COPD exist but in general most definitions include some combination of the following clinical findings: decrease in lung function, worsening of dyspnoea, increase in sputum purulence, and increase in sputum volume. Following an exacerbation, most subjects are expected to experience at least a temporary decrease in functional status and quality of life [Seemungal, 1998] and 50% of those hospitalised for the condition are expected to be re-admitted at least once in the ensuing 6 months [Connors, 1996; Weinberger, 1996].

Cessation of smoking is the single most effective means of improving prognosis in subjects with COPD [Fletcher, 1977] and is associated with a reduction in the accelerated rate of decline in FEV_1 [Doll, 1994]. None of the existing medications for COPD has been conclusively shown to modify the long-term decline in lung function. Therefore, pharmacotherapy for COPD is used predominantly to decrease symptoms and minimise number and severity of exacerbations. The vast majority of subjects are treated with inhaled or oral bronchodilators alone, including anticholinergics, short- and long- acting β_2-agonists and theophylline. Regular treatment with inhaled corticosteroids (ICS) is recommended for symptomatic subjects with a spirometric response to ICS or those with $FEV_1 < 50\%$ predicted normal value and repeated exacerbations requiring treatment with antibiotics or oral corticosteroids [GOLD, 2001].

Cilomilast is a potent and selective phosphodiesterase type 4 (PDE4) inhibitor currently under development for the treatment of COPD. 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 activities, along with the knowledge that PDE4 is the major cyclic AMP-hydrolysing isozyme in these cells [Torphy, 1991].

In two of the recently completed Phase III studies (Studies 039 and 091), administration of cilomilast was shown to result in a significant reduction of exacerbation rates over the 24 weeks of treatment. Although neither studies were powered for exacerbations, study 039, treatment with cilomilast reduced the risk of having an exacerbation by 39% relative to placebo ($p = 0.002$) and the risk of an exacerbation requiring treatment by a physician or hospitalisation by 45% ($p = 0.001$). Similarly, in Study 091, the risk of having an exacerbation was reduced by 30% ($p = 0.005$) and the risk of an exacerbation requiring treatment by a physician or hospitalisation by 32% ($p = 0.010$).

This study was therefore conducted as a pivotal Phase III study to assess the efficacy and safety of cilomilast versus placebo over a longer timeframe of 52 weeks as maintenance treatment in subjects with COPD. The study was powered for exacerbations and intended to confirm and extend the results observed in other Phase III studies. The study design of this study was similar to that of previous studies except that there were two co-primary efficacy parameters in this study based on COPD exacerbations and Clinic FEV_1. The requirement for subjects to be symptomatic during the run-in period was also dropped in this study relative to the original pivotal Phase III studies 039, 042 and 091.

4. STUDY OBJECTIVES

4.1. Primary objective

The primary objective of the study was to assess the clinical efficacy of oral cilomilast 15mg bd as maintenance treatment for subjects with COPD. This was demonstrated over a 52-week treatment period in subjects with COPD who were poorly reversible to bronchodilators by assessment of:

- Reduction in the risk of the occurrence of exacerbations of COPD for subjects treated with cilomilast 15mg bd compared with placebo and
- Superior pulmonary function data (FEV_1) for subjects treated with cilomilast 15mg bd compared with placebo

4.2. Secondary objectives

To further define the clinical safety and tolerability of cilomilast 15mg bd versus placebo as maintenance treatment by assessment of adverse events and laboratory measures over a 52-week period in subjects with COPD.

5. INVESTIGATIONAL PLAN

A detailed time and events schedule is shown in Table 1.

Table 1 Study Design

Visit	1	2	3	4	5	6	7	8	9	10	11	12		13
	Screen		Base-line									End of DB	Early Withdrawal	Follow-up
Time relative to baseline (weeks)[1]	-4	-2	0	+2	+4	+8	+12	+20	+28	+36	+44	+52		+53
Signed written informed consent	X													
Medical & surgical history	X													
Pulmonary symptoms	X													
Postero-anterior chest X-ray[2]	X													
Medication history including flu vaccination[3]	X													
Health Status Assessments: SGRQ and EQ-5D			X						X			x	x	
Patient global assessment			X						X			x	x	
Investigator global assessment			X						X			x	x	
Physical examination [4]	x		X									x	x	x[5]
Smoking status	x	x	X	x	x	x	x	X	X	x	X	x	x	x
Exacerbation assessment	x	x	X	x	x	x	x	X	X	x	X	x	x	x
Resource utilisation				x	x	x	x	X	X	x	X	x	x	x
Diary Card Review		x	X	x	x	x	x	X	X	x	X	x	x	
Baseline signs and symptoms [6]	x	x	X											
Adverse experiences [6]			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
Study medication compliance		x	X	x	x	x	x	X	X	x	X	x	x	
Resting 12-lead ECG	x		X				x		X			x	x	x[5]
Vital signs (BP, HR)[7]	x[7]	x	x[7]	x	x	x	x[7]	X	x[7]	x	X	x[7]	x[7]	x
PFTs pre and post salbutamol: Pre-dose [8]	X		X		x	x	x	X	X	x	X	x	x	x
PFTs: salbutamol reversibility [9]	X		X											
PFTs: ipratropium reversibility		x												
Residual Volume (body box) pre-/post-salbutamol Selected sites only			X						X			x	x	
Laboratory tests	X		X[10]		x	x	x	X	X	x	X	x[10]	x[10]	x[5]
Faecal occult blood test[11]	X	x									X[17]	x	x	

Visit	1	2	3	4	5	6	7	8	9	10	11	12		13
	Screen		Base-line									End of DB	Early Withdrawal	Follow-up
Dispense single-blind med	x[12]	x[13]												
Dispense double-blind med			x[14]	x[13]	x[15]	x[15]	x[15]	x[15]	x[15]	x[15]	X[15]			
Study conclusion record														x[16]

1. All visit dates must be scheduled at the visit interval listed here using the Baseline visit as Day 0.
2. Chest X-ray to be taken at entry to the run-in period or in the 3 months prior to entry to the run-in period
3. Details of 'flu vaccinations will be recorded at every visit
4. Includes respiratory examination.
5. Only if abnormalities are present at Visit 12.
6. Does not include COPD exacerbations
7. Orthostatic vital signs to be measured at Visits 1, 3, 7, 9, and 12
8. Includes FEV_1, FVC, FEF_{25-75} and PEF measured by spirometry by the same study personnel at each visit before dose of study medication is taken.
9. Includes FEV_1, FVC, FEF_{25-75} and PEF measured by spirometry by the same study personnel at each visit 30 minutes after administration of 400 mcg of salbutamol via MDI with or without a spacer, and before dose of study medication is taken.
10. Includes Blood CD4+/CD8+ ratio and serum C Reactive Protein
11. In addition to the usual laboratory tests, three faecal occult blood tests will be performed between Visits 1 and 3, at visit 11(with additional consent) and at the end of the treatment period and at Early Withdrawal
12. Register the patient with RAMOS.
13. The container of study medication issued at the previous visit will be re-issued at this visit
14. Call RAMOS to randomise the patient and to obtain study medication assignment and container number.
15. Call RAMOS to obtain study medication container number(s)
16. Or earlier if the subject withdraws from the study prior to Visit 12.
17. FOB test at visit 11 is optional and should only be collected if patient has signed a specific consent

5.1. Overall Study Design – Description

This Phase III study was a double-blind, placebo controlled, randomised, parallel group study requiring a maximum of 13 visits over a 57-week period. A 4-week single-blind placebo run-in period was followed by 52 weeks of treatment with double-blind study medication. Subjects who completed the double-blind period were asked to return for a safety follow-up visit 7 ± 3 days after the last dose of study medication. Subjects who withdrew from the study before Visit 12 (Week 52) were asked to return for a safety follow up visit 7 ± 3 days after the last dose of study medication and given the option to return for essential assessments only at the previously scheduled visit dates. Subjects eligible to enter the double-blind period were required to meet the randomisation criteria and were randomised in a 1:1 ratio to receive either cilomilast 15mg or matching placebo Tablets twice daily. Study medication was administered immediately after breakfast and evening meal. Assignment to study drug was stratified according to smoking status at baseline prior to randomisation for 'current smokers' and 'ex-smokers'.

Throughout the study (Visit 1 through to Visit 12) subjects completed a daily record card (DRC) with details of morning PEF, COPD symptoms, the use of rescue medication and health outcomes data. An area on the diary was also available to record adverse events and changes of medication. In the event of early discontinuation of study treatment, subjects were urged to continue to complete their DRCs and to attend the remaining scheduled clinic visits for essential assessments (for the 52-week treatment period). The number and severity of COPD exacerbations was assessed by the Investigator at each clinic visit by reviewing the diary card entries as well as specific questioning. Each COPD exacerbation was categorised according to one of the following three levels of severity.

Level I (Mild-self treated): Acute worsening of COPD that was self-managed by the patient at home by increasing the dose of relief salbutamol medication by > 2 occasions/24 hour period on two or more consecutive days compared with their baseline (baseline = mean of last 10 days of run-in period) or use of other additional bronchodilator medication

Level II (Moderate- physician, Investigator treated): Acute worsening of symptoms (cough, sputum production, breathlessness) that required treatment with oral corticosteroids prescribed by a physician or primary care doctor, or as a result of hospital out-patient visit (including Emergency Room).

Exacerbations requiring oral corticosteroids were treated with a standardised course of prednisolone or prednisone Tablets 30mg/day for 10 days, or methylprednisolone Tablets 24mg/day for 10 days.

Level III (Severe - attendance at hospital): Acute worsening of COPD that required the patient to be admitted to hospital for treatment.

If appropriate, courses of antibiotics were prescribed to treat an infection or short courses of recognized COPD therapy (<14days) were permitted for the treatment of Level 1, 2 or 3 exacerbations. However, Investigators were encouraged to use a standard dose of oral

steroids if rescue bronchodilation was not sufficient. Subjects who took any corticosteroids or were hospitalised for the treatment of a COPD exacerbation during the run-in phase were withdrawn from the study prior to randomisation.

Details of all exacerbations were recorded in the COPD Exacerbation Section in the CRF (see Section 5.7.4.2).

The time of resolution of an exacerbation was determined by the Investigator and/or subject. However, some guidance for distinguishing recurrence of a single exacerbation from distinct exacerbation episodes was provided as detailed in Section 5.7.3.2.

Pulmonary function tests were performed at all visits (with the exception of one safety-only visit at Visit 4 (Week 2)). At these visits pulmonary function (FEV_1, FVC, FEF_{25-75} and PEF) was measured at trough levels of study drug, before and after a standard dose of salbutamol (400 mcg) except at Visit 2 (Week –2) when pulmonary function tests were performed before and after a standard dose of ipratropium (80mcg). To ensure consistency and standardisation of pulmonary function data, spirometry equipment was standardised and pulmonary function data reviewed centrally during the single blind run in period to ensure accurate baseline data.

The impact of COPD on patient health status was assessed by the St. Georges Respiratory Questionnaire (SGRQ) and EQ-5D at Baseline, Visit 9 (Week 28) and Visit 12 (Week 52). Investigator and Patient Global Assessments were also completed at these timepoints.

Safety assessments included adverse events (AEs), vital signs, ECGs, and clinical laboratory tests. Additional monitoring was provided for gastrointestinal adverse events (GIAE's). GIAE's of concern were defined as symptoms (i.e., bloody or black stool, abdominal discomfort such as pain or cramps, diarrhoea, vomiting) which caused the patient concern or interfered with daily activities (including eating or sleeping), and were assessed by the Investigator within 24 hours of occurrence. A standardised clinical and laboratory assessment was completed. Further investigation and review was arranged as clinically appropriate at the Investigator's discretion. All events were followed to resolution. Any patient who had a GIAE of concern and a positive faecal occult blood test or melaena during the randomised treatment phase of the study was referred to a gastroenterologist. A colonoscopy showing the transverse section of the colon was recommended with biopsies taken, if appropriate.

A stable dose of anticholinergic medication via a metered dose inhaler (MDI) or salbutamol (on an "as needed" basis) via MDI with or without a spacer (according to the patient's usual practice) were the only COPD medications permitted during the study period from Visit 1 through Visit 12 with the exception of additional medication allowed for the treatment of exacerbations. Combination products (e.g., a combined salbutamol and ipratropium bromide formulation) were not permitted. Subjects using a combined anticholinergic-β_2-agonist were changed to separate single therapies prior to or at Visit 1; subjects maintained equivalent doses of the component bronchodilators.

At all visits, the following restrictions applied:

- Subjects should not have smoked for 2 hours prior to presentation to the clinic.
- At Visits 1 and 2, subjects should not have taken inhaler therapy (i.e., salbutamol and/or anticholinergic agent) for a minimum of 8 hours prior to the clinic visit. If this time period had not been observed, the visit was deferred to the next day and the patient refrained from using these medications for at least 8 hours before pulmonary function tests were performed.
- For all other visits (3 – 12) the patient refrained from taking salbutamol and/or anticholinergic medication for a minimum of 4 hours prior to presentation to the clinic. If this time period had not been observed, 4 hours must have elapsed before pulmonary function tests were performed.

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

The dose of cilomilast selected for this study was based on results from previous phase III randomised, double-blind, placebo-controlled studies which investigated a dose of cilomilast 15mg bd and found it to be efficacious in reducing exacerbations in subjects with COPD. A treatment period of 52 weeks was chosen to assess the efficacy and safety of cilomilast as maintenance therapy.

Subjects in the control group received placebo Tablets twice daily, blinded to match the cilomilast Tablets.

There were no study design issues at the time this study was initiated.

5.3. Protocol Amendments

There were three amendments made to the protocol.

Protocol amendment number 1 dated 26 September 2001 was applicable to all centres in the study and was made prior to the start of enrolment. Changes included the amendment of indirect costs to be recorded on the DRC rather than in the CRF; adding the criterion for salbutamol reversibility to the randomisation inclusion criteria, which was omitted in error; modification of the reference to orthostatic changes in blood pressure at screening and randomisation; correcting the terminology of serum protein C to C reactive protein and amending the measurement of PEF in the clinic by mini Wright PEF meter to measurement by spirometer.

Protocol amendment number 2 dated 1 August 2002 was applicable to all centres in the study. This amendment was issued during the recruitment phase of the study. Changes included the modification of the inclusion and randomisation criteria for FEV_1 salbutamol reversibility; a change to the randomisation criteria for the range of FEV_1 over the baseline period; to highlight the need for patient to provide a faecal sample prior to visit 3; to clarify the timing of faecal occult blood samples; to clarify the early withdrawal procedure for subjects stopping study medication but willing to continue in

the study for essential assessments and to ease visit requirements by allowing afternoon visits as well as morning visits.

Protocol amendment number 3 dated 26 March 2003. This was applicable to all centres and the rationale for this change was to allow an optional, additional Faecal occult blood test at visit 11 (week 44) and to correct an error in the protocol for the printed formula for calculating predicted FEV_1. This amendment was issued following the end of the recruitment period.

5.4. Selection of Study Population

5.4.1. Inclusion Criteria

Subjects were eligible for inclusion in this study only if all of the following criteria applied.

Screening Inclusion Criteria (Visit 1)

- Male or female adults between 40 and 80 years of age, inclusive.

Note: Women of childbearing potential must have been using effective contraceptive measures (i.e., oral contraceptives, Norplant, an Intauterine Device, a diaphragm with spermicide or Depo-Provera) for at least 1 month prior to Visit 1 and should have continued using the same contraceptive method during the study.

- Subjects with a clinical diagnosis of COPD, as defined by GOLD guidelines [GOLD, 2001]. (A diagnosis of COPD was considered in any patient who had symptoms of cough, sputum production, or dyspnoea, and/or a history of exposure to risk factors for the disease. The diagnosis was confirmed by spirometry. The presence of a post-bronchodilator $FEV_1 < 80\%$ of the predicted value in combination with an $FEV_1/FVC < 70\%$ confirmed the presence of airflow limitation that was not fully reversible).
- Subjects with a smoking history of ≥ 10 pack years (1 pack year = 20 cigarettes smoked per day for 1 year or equivalent). Ex-smokers were defined as those who had stopped smoking for at least 6 months prior to Visit 1. Ex-smokers were eligible to enter the study provided they had at least 10 pack years smoking history.
- Subjects with a pre-bronchodilator FEV_1 to FVC ratio (FEV_1: FVC) ≤ 0.7 at Visit 1.
- Subjects with poor reversibility of airway obstruction, defined by ≤10% of the predicted normal or ≤200 ml (or both) increase in FEV_1 after the administration of salbutamol 400 mcg via MDI at Visit 1 (Screening).
- Subjects with a post-salbutamol FEV_1 of ≥ 30 and ≤ 70% of predicted normal for height, age and gender at Visit 1. Subjects were assessed 30 (± 5) minutes after the administration of 400 mcg salbutamol (via MDI with or without a spacer). Predicted normal values were taken from the report of the working party of the European Community for Coal and Steel [ECCS, 1983]

- Subjects in the opinion of the Investigator who were not at risk of severe or life threatening exacerbations of COPD and were able to stop all COPD medications apart from short acting anti-cholinergics and salbutamol from Visit 1.
- Subjects who were willing and able to complete a Daily Record Card (DRC) and use a peak expiratory flow meter satisfactorily.
- Subjects who gave their signed and dated written informed consent to participate.

Randomisation Inclusion Criteria (at Baseline Visit 3)

Subjects who fulfilled the Inclusion Criteria below at the end of 4 week run-in period (Visit 3) entered the double-blind treatment phase of the study:

- Less than 20% change (increase or decrease) in pre-bronchodilator FEV_1 assessed at Screening Visit 2 and at Baseline Visit 3.
- Subjects with poor reversibility of airway obstruction, defined by ≤10% of predicted normal or ≤ 200 ml (or both) increase in FEV_1 after the administration of salbutamol 400mcg via MDI at Visit 1 and Visit 3
- Medication Compliance: ≥ 80% and ≤ 120% compliance in taking single-blind study medication during the placebo run-in period.

5.4.2. Exclusion Criteria

Screening Exclusion Criteria (Visit 1)

The following subjects were not eligible for inclusion into the study:

- Women who were pregnant or lactating.
- Subjects with asthma as the main component of their obstructive airways disease.
- Subjects with poorly controlled COPD, defined as the occurrence of a Level II or Level III exacerbation of COPD, or a hospitalisation or emergency room visit for the treatment of COPD, in the 2 weeks prior to Visit 1.
- Subjects with clinically significant orthostatic changes in blood pressure or heart rate at Visit 1.
- Subjects with a diagnosis or suspicion of sleep apnoea.
- Subjects with known active tuberculosis, lung cancer, clinically overt bronchiectasis, or other known specific pulmonary disease.
- Subjects with sinusitis which in the Investigator's opinion would interfere with the study objectives.
- Subjects with a chest X-ray indicating diagnosis other than COPD that would interfere with the study (chest X-ray was taken at entry to the run-in period or in the 3 months prior to entry to the run-in period).

- Subjects with clinically significant cardiovascular, neurological, renal, endocrine, gastrointestinal, hepatic or haematological abnormalities that were uncontrolled on permitted therapy.
- Subjects with clinically significant gastrointestinal or hepatic abnormalities.
- Subjects who had participated in the acute phase of a Pulmonary Rehabilitation Program within 4 weeks prior to Visit 1 (Screening) or who were going to enter a Pulmonary Rehabilitation Program during the study.
- Subjects with a history of hypersensitivity to PDE4 inhibitors.
- Subjects with a history (or suspected history) of alcohol abuse or any other recreational substance abuse.
- Subjects receiving treatment with inhaled cromolyn sodium or nedocromil, inhaled long-acting β_2-agonists, and/or oral β_2-agonists, combination short acting β_2-agonists and anticholinergics, xanthines, leukotriene modifiers, mucolytics or oral/inhaled corticosteroids. All COPD medications except short-acting anticholinergic medication or salbutamol via MDI were withdrawn prior to or at Visit 1 (Screening).
- Subjects receiving treatment with long term oxygen therapy (LTOT) or those subjects who required supplemental oxygen more often than on an occasional (prn) basis, or subjects who required nocturnal positive pressure for sleep apnoea.
- Subjects who had received an investigational drug within 30 days of entry into this study (Visit 1), or within 5 drug half-lives of the investigational drug (whichever was longer).
- Subjects who had previously participated in a cilomilast study and who received double-blind or open-label study medication.
- Subjects who were unable or unwilling to comply with all protocol specified procedures, including the completion of the quality of life questionnaires.

Note: Subjects who fulfilled all of the Inclusion and Exclusion Criteria at Screening Visit 1 could enter the single-blind placebo run-in phase of the study.

Randomisation Exclusion Criteria (at Baseline Visit 3)

Subjects who fulfilled any of the following Exclusion Criteria at the end of the 4-week run-in period (Visit 3) were not eligible to enter the double-blind treatment phase of the study:

- Subjects who had any changes to their COPD medication (other than ‘as required’ use of salbutamol), received corticosteroids (oral or inhaled) for respiratory disease, or hospitalised for COPD/lower respiratory tract infections during the run-in period.
- Subjects who had received any other medication during the run-in period which in the opinion of the Investigator, was judged as likely to affect baseline assessments
- Subjects with a positive faecal occult blood test result between Visits 1 and 3.

- Subjects with clinically significant orthostatic changes in blood pressure or heart rate at Visit 3.

5.4.3. Predetermined Criteria for Subject Withdrawal

5.4.3.1. Subject withdrawal from the investigational product

Enrolment continued until approximately 800 subjects had been randomised. The double-blind medication assigned to withdrawn patient(s) was not to be re-used. Subjects who withdrew from the study were asked to return for scheduled visits for essential assessments (FEV_1, exacerbations, respiratory AEs and respiratory medications and GI AEs) even after study medication had been discontinued.

Subjects who terminated their participation in the study due to AEs were followed up as appropriate in order to determine the final outcome. Investigators made every effort to encourage subjects to remain in the study. For all subjects who withdrew or were withdrawn from the study prior to randomisation, pre-treatment early withdrawal assessments and procedures were completed, including Baseline Signs and Symptoms, changes or additions to concomitant medication, vital signs and respiratory examination. Laboratory tests and an ECG were performed if there were any abnormalities at the previous visit. Wherever possible, a follow-up visit was scheduled.

For all subjects who withdrew or were withdrawn from the study at a scheduled visit after randomisation, the assessments and procedures of the visit and any additional early withdrawal assessments and procedures were completed. Subjects who withdrew from the study between visits were asked to return within 24 hours of stopping study medication for an Early Withdrawal Visit.

CRFs of all subjects entered into the study were kept and the reason for withdrawal was noted on the Study Conclusion page for all enrolled subjects who did not complete the study. In addition, the date of last dose of study medication was recorded in the CRF for all subjects withdrawn from the study.

5.4.3.2. Subject withdrawal from the study

Subjects who completed the assessments scheduled for Week 52 (Visit 12) were defined as completing the study for the purposes of efficacy analyses.

Any patient who entered the study, (i.e., gave written informed consent) but did not, for any reason complete the study according to the definitions given above, were considered as a withdrawal, whether or not they had received any study medication.

Every effort was made by the Investigator to keep subjects in the study. However, a patient could be discontinued prior to completion of the study for the following reasons:

- Adverse event: This included deterioration in COPD or COPD exacerbation resulting in a patient being withdrawn.
- Lack of efficacy: This included a desire by the patient/Investigator that the patient be withdrawn from the study because of a lack of improvement in COPD symptoms. It

did not include a deterioration in COPD or COPD exacerbation which was regarded as an adverse event.

- Protocol Deviation: This included lack of compliance (dosing, visit schedule, diary criteria).
- Patient lost to follow-up
- Other: Reason documented in the CRF.

5.5. Investigational Product(s)

5.5.1. Description of Investigational Product(s)

Cilomilast was provided as a yellow, round, convex Tablet containing 15mg of cilomilast (SB 207499). Matching placebo Tablets were also provided. All drugs were supplied, packaged and labelled by International Clinical Supplies, GSK.

Metered Dose Inhalers (MDIs) of salbutamol (100 mcg/actuation, 200 actuations per canister) were provided for on-demand (prn) use during the study. A spacer was also supplied to each patient at Visit 1. Subjects could employ these for on-demand use if this was their customary inhalation method. Salbutamol was not considered study medication. Subjects in Denmark and the Netherlands were permitted salbutamol 200mcg **DISKUS** devices according to local preference.

Study medication details are show in Table 2.

Table 2 Study medication details

Drug and dose	Batch numbers	Date of manufacture	Expiry date
Cilomilast 15mg	[redacted]	10 Sept 2001	31 Aug 2005
Placebo Tablet	[redacted]	10 Sept 2001	31 Aug 2005
Placebo Tablet	[redacted]	09 Mar 1999	29 Feb 2004
Placebo Tablet	[redacted]	10 Sept 2001	31 Jul 2006

5.5.2. Dosages and Administration

Subjects who fulfilled the entry criteria entered a 4-week single-blind placebo run-in phase. During the run-in phase, subjects took one cilomilast-matched placebo Tablet twice daily, in the morning immediately after breakfast and in the evening immediately after a meal. Subjects did not take their study medication for at least 8 hours prior to attending clinic visits. On the day of a clinic visit, the post assessment dose of study medication administered in the clinic was administered with food.

Subjects who fulfilled the Randomisation Criteria entered a 52-week double-blind treatment phase. Subjects received either cilomilast 15mg or matching placebo bd. One Tablet of study medication was taken twice daily, in the morning immediately after breakfast and in the evening immediately after a meal. Subjects did not take study

medication for at least 8 hours before attending clinic visits. On the day of the clinic visit, the post assessment clinic dose of study medication was administered in the clinic with food.

5.5.3. Dose Rationale

The dose of cilomilast selected was based on results from the dose ranging studies (032 and 038). Four Phase III randomised, double-blind, placebo-controlled studies (studies 039, 042, 091 and 156) have recently been completed. In each of the phase III studies, subjects with COPD were randomised to receive cilomilast 15mg bd or placebo. A total of 1374 subjects were treated with cilomilast 15mg bd, which was the dose found to be efficacious in reducing exacerbations in subjects with COPD.

5.5.4. Blinding

All run-in medication was blinded to the patient, and all medication for randomised subjects was blinded to both the Investigator and the patient. The blind was maintained by GlaxoSmithKline (GSK) who maintained an updated copy of the master randomisation code.

Double-blind study medication was assigned to subjects through GSK's Registration and Medication Ordering System (RAMOS). The medication code for a particular patient could only be broken in the event of a serious adverse event which the Investigator felt could not be adequately treated without knowing the identity of the study medication. Every effort was made to contact the GSK Medical Monitor prior to breaking the code. If this was not possible and the situation was an emergency, the Investigator could break the code and contact the GSK Medical Monitor as soon as possible.

Individual Code breaks were provided to the Investigator and the participating local GSK office. Each code-break identified the container number and included an unblinding panel which could be removed by scratching with a coin to reveal the container contents.

The randomisation code was not disclosed to the Investigator or any personnel involved in the conduct of the study before the database was locked.

5.5.5. Treatment Assignment

Treatment allocation was made using GSK RAMOS. Subjects were randomised (and stratified according to their smoking status at Baseline) in a 1:1 ratio to cilomilast 15mg bd or placebo. To ensure balance with respect to the number of subjects assigned to each treatment group, the allocation schedule was generated in blocks using the GSK Coding Memo System. All trial medications were packaged to be indistinguishable irrespective of treatment. Randomised subjects were identified throughout the study by their CRF number.

The Investigator (or designee) phoned into RAMOS to register all subjects at the time they were initially dispensed a single bottle of 70 placebo run-in Tablets. Subjects were redispensed medication at visit 2 after drug accountability was undertaken. Subjects who were eligible to participate in the double-blind phase of the trial were randomised to

a treatment group through a call to RAMOS at Visit 3. During this call, a 6-digit container number was assigned to the patient from the Investigator's inventory which identified the container of double-blind medication to be dispensed. The container or containers assigned during the randomisation call contained sufficient double-blind study medication for the visit period. Although study medication was stored at each site, the Investigator (or designee) was required to phone into RAMOS to obtain a new study medication container number at each on-therapy visit (except Visit 4 where medication was counted and redispensed and Visit 12 where no medication was issued). All calls to RAMOS were confirmed with faxes which were sent to the Investigator upon completion of each call. Detailed RAMOS user instructions and worksheets were provided at study start. All RAMOS faxes and worksheets were retained in the Investigator's study file.

Counts of Tablets returned were made at the beginning of Visits 2 through 12. Compliance was calculated by using the formula below:

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

Compliance (%) was entered into the CRF.

If a patient shows < 80% or >120% compliance in taking study medication at any visit, the Investigator reminded the patient of the importance of adhering to the study medication procedures.

5.5.6. Treatment of Investigational Product Overdose

To date, there have been no cases of confirmed overdose with cilomilast. In the event of an overdose, general symptomatic and supportive measures were to be initiated promptly and maintained for as long as necessary.

Any instance of a suspected or confirmed overdose was required to be fully documented as a Serious Adverse Event and communicated to the GSK Medical Monitor within 24 hours.

5.6. Prior and Concomitant Medications and Non-Drug Therapies

5.6.1. Permitted Medications

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 salbutamol 100 mcg/actuation, MDI with or without a spacer for use on a prn basis was permitted throughout the study along with an alternative 200mcg **DISKUS** in Denmark and the Netherlands. Subjects used the inhaler and spacer (if customary) provided by GSK and not their own devices. The Investigator issued a new inhaler every 4 weeks or sooner, if necessary.

The use of anticholinergic medication by MDI was permitted during the study. Subjects could continue to use their regular single drug inhaler devices. Combined anticholinergic/β_2-agonists formulations were not permitted.

Between Visits 1 and 12, subjects were required not to use any additional bronchodilators that they possessed at home. If the patient experienced symptoms which did not respond adequately to rescue medication (e.g., salbutamol, two actuations every four hours), the patient contacted the Investigator. If a patient occasionally used salbutamol at an interval of less than every 4 hours during an exacerbation (not to exceed twice a day at the reduced interval), the patient remained in the trial at the discretion of the Investigator.

Table 3 Examples of permitted medications

Medication Class	Selected Trade Names
Selected short-acting inhaled β_2-agonists	VENTOLIN™ only
Inhaled anticholinergic agents	Atrovent
Nasal cromones	Rynacrom/Nasalcrom
Nasal steroids	BECONASE AQ™, FLIXONASE™, Nasalide, Nasacort, Rhinocort, Vancenase AQ
Antibiotics	AUGMENTIN™, Biaxin, Ceclor
Smoking cessation patches or gum	NICODERM™, Nicotrol, Habitrol, Nicorette

5.6.2. Prohibited Medications

Except in the short-term management of COPD exacerbations, the use of oral corticosteroids, combination short acting β_2-agonists and anticholinergics, inhaled long-acting β_2-agonists, inhaled short-acting β_2-agonists, oral β_2-agonists, nebulised β_2-agonists, nebulised anticholinergics, long acting anticholinergics, inhaled cromolyn sodium or nedocromil, xanthines, leukotriene modifiers and mucolytics were not allowed between Visits 1 and 12. Long-term oxygen therapy on anything other than an occasional use was also prohibited between Visits 1 and 12 unless subjects lived at altitude.

Table 4 provides a list of example prohibited medications along with Trade names.

Table 4 Prohibited medications

Medication Class	Selected Trade Names
Inhaled corticosteroids	Azmacort, BECOTIDE™, FLIXOTIDE™, Pulmicort, Syntaris
Oral corticosteroids	Prednisone, Medrol, Decadron, Sterapred
Combination of inhaled short-acting β_2-agonists & anticholinergics	Combivent, Duovent
Selected short-acting inhaled β_2-agonists	All except VENTOLIN
Long-acting inhaled β_2-agonists	SEREVENT™ Foradil
Oral β_2-agonists	VENTOLIN, VOLMAX™, Bricanyl
Nebulised $\beta_2$agonists	Salbutamol, metraproterenol, Alupent, Isuprel, VENTOLIN
Nebulised anticholinergics	Atrovent
Inhaled cromolyn sodium	Intal
Inhaled nedocromil	Tilade
Oral xanthines	Slo-Bid, Theo-Dur
Leukotriene antagonists	Accolate, Singulair
Long-term oxygen therapy (LTOT)*	n/a
Mucolytics (carbocysteine)	Mucodyne

Theophylline was not permitted at any time during the study. Use of theophylline for periods of more than 14 days would warrant withdrawal.

Treatment of COPD Exacerbations

Only if clinically indicated, oral steroids or antibiotics were administered for the short-term (<14 days) treatment of COPD exacerbations.

Subjects who took any corticosteroids or were hospitalised for the treatment of COPD exacerbations during the run-in phase were not eligible to be randomised to the double-blind phase.

Refer to Section 5.1 for definitions of the level of COPD exacerbations.

5.7. Study Assessments and Procedures

The study design has been presented in a schedule of time and events (Table 1).

5.7.1. Demographic and Baseline Assessments

The following demographic and baseline characteristics were recorded at visit 1 (screening).

- Demographic information including gender, ethnic origin, date of birth, height and weight.
- Medical and surgical history (including alcohol consumption) and physical examination (including respiratory examination).
- Cigarette smoking history and current smoking status.
- Pulmonary history and symptoms.
- Review of a current postero-anterior (PA) chest radiograph (performed within the 12 weeks prior to assessment). If such a radiograph was not available for review, a new radiograph was performed to be available for review at Visit 3.
- Assessment of COPD exacerbations.
- Concurrent COPD medication (and other concurrent medication).
- Influenza vaccinations within the past 12 months.
- 12-lead electrocardiogram (ECG)
- Vital signs
- Pulmonary function tests
- Haematology, biochemistry, (including beta-HCG for women of childbearing potential) and urinalysis details

Additional baseline data was recorded at Clinic Visit 2 at the end of the placebo run-in period (Table 1).

5.7.2. Efficacy Assessments

5.7.2.1. Primary efficacy endpoints

There were two primary efficacy endpoints:

- The mean change from baseline in trough pre-bronchodilator FEV_1 averaged over 52 weeks.
- The incidence rate of level II (moderate) and level III (severe) COPD exacerbations during the treatment period.

5.7.2.2. Secondary efficacy endpoints

There were five secondary endpoints in this study:

- The mean change from baseline in trough post-bronchodilator FEV_1 averaged over 52 weeks
- Time to first level II (moderate) or level III (severe) COPD exacerbation
- Time to first COPD exacerbation (all levels)
- Exacerbation incidence for all levels of COPD exacerbations

- Quality of life as determined using the St Georges Respiratory Questionnaire (SGRQ).

5.7.2.3. Other efficacy endpoints

The following tertiary endpoints were collected:

- Pulmonary function parameters (clinic FVC, clinic PEF, clinic FEF_{25-75}).
- Residual volume (body box)
- Morning PEF from DRCs
- Use of relief medication and percentage of days with no need for rescue medication (salbutamol)
- Duration of exacerbations
- Symptom scores and symptom free days from DRCs (24 hour period)
- Number of night-time awakenings
- Global subject assessment
- Global Investigator assessment
- Blood CD4+/CD8+ ratio
- Serum C reactive protein

5.7.2.3.1. Pulmonary function tests

At Clinic Visits post randomisation (3-12, except visit 4), pulmonary function tests (PFTs) were assessed at least 4 hours after the last dose of inhaled salbutamol or anticholinergic agent. Subjects were asked to refrain from smoking in the 2 hours prior to PFTs. PFTs were performed before and 30 minutes after the administration of 400 mcg salbutamol via metered dose inhaler (MDI) with spacer and were measured according to the BTPS (Body Temperature and Pressure Standard) convention using the spirometer provided by GSK.

Spirometers were supplied by Quantum Research Ltd, Welwyn Garden City and exceeded the criteria laid down in the ATS guidelines for research based spirometry. Spirometers were programmed with protocol specific software and calibrated prior to shipment. Calibration of the pneumotach was undertaken as a minimum on each clinic day via 3L syringe and more frequently if temperature varied significantly or the pneumotach was dropped. Calibration syringes were supplied to each site at study start and replaced annually with revalidated equipment. Site staff were all trained and certified on the equipment and standardized techniques on obtaining optimum quality spirometry before they were allowed to test subjects.

Pulmonary function tests could be repeated up to 8 times to obtain three acceptable readings according to ATS guidelines [ATS, 1995]. For each set of three FEV_1 measurements, one FEV_1 was within 10% of the highest.

During the baseline period Spirometry printouts were faxed to GSK on the day of testing and these were assessed by an independent consultant to assure optimization of data. Sites were asked to assure that the forced manoeuvre lasted at least 12 seconds or reached a clear plateau in order to ensure accurate FVC data. Subjects not meeting this standard were generally withdrawn prior to randomization were possible.

5.7.2.3.2. Exacerbations

Exacerbations were assessed by the Investigator as per the guidance and definitions laid out in Section 5.7.4.2.

5.7.2.3.3. Diary card data

Subjects were provided with paper DRCs for daily completion in order to compile much of the tertiary endpoint data. The subjects were shown how to complete the diaries and instructed to commence completion on the day after Visit 1 and to bring their completed diaries back to the next clinic visit.

Daily, during the study, the following were recorded each morning:

- Morning PEF (highest of three readings) measured by the subjects using a Mini-Wright peak flow meter before taking any salbutamol or anticholinergic medication
- Use of salbutamol during the previous 24 hours for symptomatic relief
- Night-time awakenings
- Time missed from work/usual activities (noted as half or full days)
- Assistance of caregiver
- Space was also provided on the diary to record adverse experiences contact with a healthcare professional and changes to medications.
- COPD symptoms experienced over the previous 24 hours (Cough, breathlessness, sputum production - volume, type (mucoid/purulent) and colour according to the scale in Table 5.

Table 5 COPD symptom scale

Variable	0	1	2	3	4
Breathlessness	Not breathless at rest or on exertion	Not breathless at rest, but breathless on moderate exertion (e.g. walking quickly)	Not breathless at rest, but breathless on mild exertion (e.g. walking on level ground)	Not breathless at rest, but breathless on minimal exertion (e.g. getting washed)	Breathless at rest
Cough	No cough	Mild cough (i.e. some, mostly morning)	Moderate cough (i.e. some morning and evening)	Severe cough	
Sputum production	None	Small amount of sputum	Moderate amount of sputum	Large amount of sputum	
Sputum colour	Colourless	White/grey	Light yellow/ green	Dark yellow/ green	

5.7.2.3.4. Residual Volume (selected centres only)

At selected centres Residual Volume (RV) was measured by body plethysmography at Baseline and Visits 9 and 12 (where RV = TLC – SVC (Total Lung Capacity - Slow Vital Capacity and Total Lung Capacity (TLC = TGVFRC+IC). These tests were conducted before and after administration of 400 mcg of salbutamol via MDI with a spacer.

Residual Volume was defined as the difference between the TLC and the maximum of the six collected SVC and FVC measurements.

$RV_{Box} = TLC_{Box} - \max(|SVC|, |FVC|)$

5.7.2.3.5. Patient and Investigator Global Assessments

Subjects were asked, "How do you feel now in comparison with when you started to take study medication"? Investigators were asked, "How do you assess the patient's COPD now in comparison to when they started to take study medication"? Both the patient and Investigator responded according to the following:

- Very much improved
- Much improved

- Minimally improved
- No change
- Minimally worse
- Much worse
- Very much worse

This was recorded at Visits 3, 9 and 12, Early Withdrawal.

5.7.2.3.6. CD4/CD8 lymphocyte ratio and Serum C Reactive Protein

Approximately 20 ml of blood was collected at Visits 3, 9 and 12, Early Withdrawal for analysis including CD4/CD8 lymphocyte ratio and Serum C Reactive Protein.

5.7.3. Health Outcome Assessments

5.7.3.1. Health outcome endpoints

- Resource utilisation and indirect co Disease-specific quality of life: SGRQ subscales (symptoms, activity and impact)
- Generic health status (EQ-5D)
- Time off work/normal activities due to COPD

5.7.3.2. Medical care utilisation data

Medical care utilisation data associated with COPD exacerbations was collected in the CRF which required healthcare professional or medical intervention. 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 or medical procedures used for the treatment of a COPD exacerbation.

5.7.3.3. Economic data collection

Subjects were asked to record in their diary card the amount of time missed from work or usual activities and if they required the assistance of a caregiver due to their COPD.

5.7.3.4. SGRQ

The SGRQ was administered at Baseline (Visit 3), at Visits 9 and 12. Any patient who withdrew from the study 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, 1991a]. 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 from baseline was considered to be clinically meaningful [Jones, 1991a].

5.7.3.5. EQ-5D

Quality of life was assessed with the EQ-5D at Baseline, Visits 9 and 12 and at Early Withdrawal in those countries where a validated translation was available. The EQ-5D is a standardised, self-administered, generic instrument which produces a single index value of the patient's current health status [Euroqol, 1990]. Subjects were asked to respond to five questions on different aspects of their health status that assessed mobility, usual activities, self-care, pain and depression. Answers to each question were responded to on a three-point scale which indicated the level of impairment (no problem; some or moderate problem(s); unable, or extreme problem). This generated a unique description of the subjects' health status which was valued between zero (representing death) and one (representing perfect health) according to the methodology developed by the authors [EuroQol].

As well as completing the five questions to generate a single health status index, subjects were asked to rate their current health status using the visual analogue scale 'Thermometer'. The 'Thermometer' had endpoints of 100 (best imaginable health state) and 0 (worst imaginable health state). The subject rated their current health state by drawing a line from the box marked 'Your health state today' to the appropriate point on the 'Thermometer' scale. If subjects were visually impaired it was appropriate for the Investigator to read aloud the instructions within the questionnaire and to record the responses on behalf of the patient.

5.7.4. Safety Assessments

5.7.4.1. Adverse events

It was the responsibility of the Investigator to detect and document all adverse events which occurred during the study and which fulfilled the definitions of an adverse event (AE) or serious adverse event (SAE). All SAEs which occurred up to and including 30 days after the last dose of double-blind study medication which were brought to the attention of the Investigator and were assessed as possibly drug related were recorded and forwarded to GSK.

Elective surgery or routine treatment/procedures related to a pre-existing condition that did not worsen were not recorded as AEs but were recorded in the medical/surgical procedures section of the CRF.

At each clinic visit, both spontaneously reported and elicited AEs and SAEs were documented in the subject's CRF and medical notes. In order to fulfil international safety reporting obligations, the Investigator included in his or her assessment any SAEs resulting from study participation (e.g. complications resulting from the taking of a blood sample). The Investigator attempted to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis was documented as the AE and/or SAE and not the individual signs/symptoms. If a diagnosis could not be reached it was permitted to record the symptoms as separate AE's. "Lack of efficacy" per se was not reported as an AE; the signs and symptoms or clinical sequelae resulting from lack of efficacy were to be reported if they fulfilled the AE or SAE definitions.

An AE was defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product which does not necessarily have to have a causal relationship with this treatment.

An AE could therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

AEs included:

- An exacerbation, or an unexpected increase in frequency or intensity of a pre-existing condition (other than COPD), including intermittent or episodic conditions.
- Significant or unexpected worsening or exacerbation of COPD
- A suspected drug interaction.
- An intercurrent illness.
- Any clinically significant laboratory abnormality.

An AE did not include:

- Anticipated day-to-day fluctuations of any pre-existing conditions, including the disease under study.
- Signs and symptoms of the disease under study that did not represent a significant worsening or exacerbation.
- Expected progression of the disease under investigation.

Gastrointestinal adverse events

Adverse events related to the gastrointestinal tract (GIAEs) were closely monitored during this study and treated appropriately. 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). The Investigator was asked to complete a clinical assessment of the GIAEs within 24 hours of occurrence. This assessment included a structured history of the AE 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. When the faecal occult blood test samples were returned for analysis, the Investigator questioned the patient to determine if the results had been affected by menstruation, bleeding haemorrhoids, blood in the urine, medications, vitamins, or foods. If a faecal occult blood test was positive at the time of a GIAE of concern or if the patient reported melaena during the randomised treatment phase of the study, the patient was referred to a gastroenterologist for evaluation and a complete colonoscopy requested that emphasises visualisation of the transverse colon. For instances of gross bleeding or melaena the patient was instructed to call the Investigator within 24 hours for a GIAE of concern assessment and was again Investigator referred to a gastroenterologist for evaluation and colonoscopy. Depending on the suspected site of bleeding an endoscopy was likely to be required in addition to the protocol requested colonoscopy. If all faecal occult blood samples were negative and the patient was clinically well the patient was still referred to a gastroenterologist for evaluation. The decision to undertake a colonoscopy was made on clinical grounds and subjects were allowed to remain in the study if this was not undertaken. If indicated, additional testing was performed at the discretion of the Investigator and reports faxed to the Sponsor as soon as available.

Within 24 hours of the first assessment, the Investigator reported these GIAE's to the GSK Medical Monitor.

The GIAE’s were followed to resolution and assessed at a frequency determined by the discretion of the Investigator. Any worsening of symptoms required reporting to the Investigator within 24hours and another assessment arranged. Assessments were performed by a qualified healthcare provider at the patient's home or at clinic visits. If the patient experienced symptoms which were severe or persistent and considered by the Investigator to be study-drug related, withdrawal of the patient was considered.

Note: All GIAE's of clinical concern were recorded in the GIAE section of the CRF. Any GIAE, regardless of intensity, that fulfilled the SAE criteria was recorded in the GIAE pages of the CRF.

5.7.4.2. Definition of a COPD exacerbation

An exacerbation of COPD was defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy. Exacerbations were categorised according to three levels of severity as detailed in Section 5.1.

The number and severity of COPD exacerbations was assessed by the Investigator at each clinic visit, by reviewing the diary card entries as well as specific questioning. Details of all exacerbations were recorded in the COPD Exacerbation Section in the CRF as follows: dates of onset and resolution; outcome, treatment and severity. In addition any information collected during the exacerbation was recorded in the CRF (e.g. Symptoms: breathlessness, cough, chest pain, sputum (volume and purulence); associated URTI (nasal congestion, sore throat, runny nose); sleep disturbance; confusion/alertness in case of pneumonia; oedema, ankle swelling; medications leading up to exacerbation; heart rate; respiratory rate; FEV_1; arterial blood gases/pulse oximetry; serum C Reactive Protein).

Note: Any exacerbation of COPD, regardless of level, that fulfilled the SAE criteria was recorded in the COPD SAE pages of the CRF.

If appropriate, courses of antibiotics were prescribed to treat an infection (Level I, II or III). Subjects who took any corticosteroids for the treatment of a COPD exacerbation during the run-in phase or who were hospitalised were not eligible to be randomised to the double-blind phase of the study.

Resolution of Exacerbations

The time of resolution of an exacerbation was determined by the Investigator and/or subject. However, some guidance for distinguishing recurrence of a single exacerbation from distinct exacerbation episodes was provided as follows.

- Level II exacerbations treated with oral corticosteroids were classified as separate exacerbations only if the courses of treatment were administered more than one week apart. A course of oral corticosteroids started within one week of finishing a previous course was considered a continuation of the exacerbation.
- Likewise hospitalisation for an exacerbation within a week of completing a course of oral corticosteroids or initiation of a course oral corticosteroids within a week of discharge from hospital for an exacerbation was considered a single continuous (Level III) exacerbation.

Where a Level I exacerbation was immediately preceded or followed (within 1 week) by an exacerbation of any level, the Investigator and/or subject considered the possibility that this represented a continuation of the exacerbation.

5.7.4.3. Serious adverse events

A serious AE (SAE) was any untoward medical occurrence which fulfilled the definition for an AE and in addition, was:

- Fatal
- Life threatening
- Disabling/incapacitating
- Resulted in hospitalisation or prolonged a hospital stay

- A congenital abnormality
- Any important medical occurrence which the Investigator regarded as serious based on appropriate medical judgement

This included events which occurred up to and including 30 days after the last dose of double-blind study medication which were brought to the attention of the Investigator and were assessed as possibly drug related.

In addition, GSK company policy dictates that the following events must be notified within 24 hours and must be documented and reported as for SAEs, on the SAE form:

- Cancer
- Overdose
- Pregnancy

A SAE did not include hospitalisation for:

- Elective surgery or routine treatment/procedures related to a pre-existing condition that did not worsen. Instead, these were recorded in the medical/surgical procedures section of the CRF.
- If anything untoward (i.e. complications) was reported during the procedure, these were reported as an AE, either 'serious' or 'non-serious' according to the usual criteria.
- A routine clinical procedure as stipulated by the protocol.
- Non-medical reasons (i.e. social admissions, hospitalisations for social, convenience or respite care).

5.7.4.4. Pregnancies

A pregnancy test for women of child-bearing potential was performed by a serum beta-HCG test at all visits except Visits 2, 4 and the Safety Follow-Up.

A urinary beta-HCG for women of child bearing potential was performed at the Safety Follow-up Visit.

Details of any pregnancies in subjects that occurred during the treatment and the follow-up period were documented and reported to GSK. In addition any pregnancies brought to the attention of the Investigator after this period, and where it was known that study medication was taken at the time of conception, were also reported.

Any pregnancies identified during the screening phase/prior to study medication administration did not need to be collected. All pregnancies were reported to GSK promptly. Although pregnancies are not generally serious AEs (and there is no serious criteria fulfilled) the Serious AE form was completed and forwarded to the GSK contact within 24 hours. All pregnancies were followed to term. Any premature terminations, including elective abortions were reported. The status of the mother and child was

forwarded to GSK after delivery. Subjects who became pregnant during the study discontinued the study immediately.

5.7.4.5. Clinical laboratory evaluations

Approximately 20 ml of blood was collected at each visit where blood was drawn for laboratory analyses (Visits 1, 3, 5, 6, 7, 8, 9, 10, 11, 12, Safety Follow-up and Early Withdrawal). Subjects who completed Visit 12 or who withdrew from the study had blood and urine samples collected at the Safety Follow-up Visit, only if abnormalities were observed at the last visit.

5.7.4.6. Other safety assessments

5.7.4.6.1. Physical/Respiratory Examination

A full physical examination (including respiratory examination) which consisted of measurement of height and body weight and full examination of major organ systems (Visit 1 only) was performed. At Visits 3, 12 and Safety Follow-up (if abnormal at the previous visit) or upon early withdrawal, the Investigator answered the following question "Has there been a clinically significant worsening since the last assessment in the patient's physical condition?" Any changes were documented as a Baseline Sign or Symptom at Visit 3 or an AE at Visit 12, Safety Follow-up or Early Withdrawal.

At visits required within 24 hours of the occurrence of GIAE's, a structured assessment of these AEs including a physical examination was performed.

5.7.4.6.2. Vital signs

Vital signs (blood pressure and heart rate) were measured at all visits after the patient had been sitting for 5 minutes. Measurements were made greater than 4 hours after the patient's last salbutamol administration.

At Visits 1, 3, 7, 9 and 12, Early Withdrawal and at visits associated with gastrointestinal adverse events, heart rate and blood pressure were measured after the patient had been supine for 5 minutes and then after the patient sat up with legs dependent for 1 minute. If this measurement showed a decrease in systolic blood pressure of ≥20 mmHg or a decrease in diastolic blood pressure of ≥10 mmHg or an increase in heart rate of ≥20 beats/minute at Visits 1 or 3, the patient was not eligible to participate in the study.

5.7.4.6.3. Chest radiograph

To exclude the possibility of any abnormality that may mimic or co-exist with COPD (e.g., pneumothorax, bronchial carcinoma, active pulmonary TB) a postero-anterior (PA) chest radiograph (X-ray) was performed at or within 12 weeks of Visit 1. The X-ray was required to be available to the Investigator by Visit 3 and subjects were excluded from the study as appropriate. A CT scan was permitted as a substitute for an X-ray, if one had been conducted within 12 weeks of Visit 1. Abnormal findings not consistent with the diagnosis of COPD were documented in the CRF and followed-up as appropriate.

5.7.4.6.4. ECG

A 12-lead ECG was performed at Visits 1, 3, 7, 9 and 12 and Safety Follow-up (if abnormal at the previous visit) or at Early Withdrawal. ECG's were conducted after the patient had been semi supine for 5 minutes but prior to salbutamol administration for pulmonary function reversibility testing. Each ECG recording was clearly labelled with patient initials, patient identification number, protocol number, centre number and date performed. They were reviewed by the Investigator for clinically significant abnormalities and details recorded in the CRF.

5.7.4.6.5. Faecal occult blood tests

Faecal occult blood tests were performed between Visits 1 and 3, immediately prior or post visit 11 (for those who consented for an additional test) and also after the final dose of double blind medication either at visit 12 or at the early withdrawal visit (three tests collected on consecutive bowel movements, if possible). The tests were 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 whilst 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 patient to determine whether the instructions were followed.

The test around visit 11 was conducted within14 days of visit 11, either pre or post visit. Samples were returned and tested within 14 days from the date of the first sample taken. Processing of test results outside this window was avoided as this reduced the sensitivity of the test.

Faecal occult blood was also tested in subjects who reported gastrointestinal symptoms that were of concern to them or interfered with daily activities. When the samples were returned for analysis, the Investigator questioned the patient to determine if the results had been affected by menstruation, bleeding haemorrhoids, blood in the urine, medications, vitamins, or foods.

5.8. Data Quality Assurance

Subject data was collected on NCR CRFs provided to the Investigator by GSK.

The Investigator or designee recorded all required subject data using the previously specified data collection method defined by GSK. An explanation had to be documented for any missing data. The Investigator signed and dated a declaration on the CRF attesting to his/her responsibility for the quality of all data recorded and that the data represented a complete and accurate record of each subject's participation in the study.

Monitors meetings were held to ensure that the data was captured correctly. Adherence to the protocol requirements and data accuracy was achieved through monitoring visits being carried out at each site.

The completed original CRFs were returned to GSK and tracked into Case Report Form Activity System (CRAMS).

Laboratory data was sent electronically to GSK by two central labs:

- Quest, UK for all participating countries except Australia and New Zealand
- Dorevitch, Australia.

The data was transferred electronically, in a specified format and loaded directly into the Clintrial 4.2 database.

The data recorded on the CRF was single entered directly into the Clintrial 4.2 database. The database was set-up and validated to GSK standards and tested using dummy data.

To ensure consistency and the reliability of the data, pre-review was carried out prior to entry and QC was carried out on the data entry of 10% of the CRF data and 20% of the diary card data. Computerised data validation was performed using Standard Query Logic (SQL) programmes. These programs checked for missing data, out of range values and cross checked data points for consistency.

Validation discrepancies were sent out for resolution to the relevant investigator in the form of DRQs (Data Resolution Query forms) only if they could not be resolved using the Standard Clarification Agreement or Data Validation Specification. The investigator signed and dated any explanation or correction. On return of the answered DRQ, the database and CRF were updated accordingly and the original DQ stored with the CRF.

Coding of Medical History, Adverse Experiences and Concomitant Medications were carried out using MedDra and GSK Drug.

Quality Control (QC) was carried out for the interim analysis as per the GSK SOP. 100% of the critical items were QCd for 10% of the subjects in the interim(10 subjects)

The final QC analysis was performed at a higher level than that stated in the GSK SOP to ensure the data standards. QC was carried out on 100% of the critical items for 10% of the subjects in the study (139 subjects).

The database for SB-207499_157 was released on 3rd March 2004. The datasets were then made available to Statistics and Programming for analysis.

5.9. Data Analysis Methods

5.9.1. Timings of Planned Analyses

5.9.1.1. Interim analyses and data monitoring

No interim analysis was performed for this study.

5.9.1.2. Changes in the conduct of the study or planned analyses

There were no changes in the conduct of the study. However, the summary of significant tests for prognostic factors affecting FEV_1 presented in Table 14.1O was undermined by the presence of co-linearity between factors in the model. Consequently, tests for prognostic factors were undertaken as a series of separate models with controls for treatment and visit. These are presented in Table 14.1O2 and Table 14.1O3.

5.9.2. Sample Size Considerations

In order to obtain 550 evaluable subjects, this study aimed to randomise a total of 800 subjects in a ratio of 1:1 for cilomilast (SB 207499) to placebo.

Sample size calculation for repeated measures analysis on FEV_1 was based on a compound symmetric correlation structure across double-blind visits. A sample size of 550 would have a greater than 90% power to detect a difference of 50ml in FEV_1 assuming a standard deviation of 210ml in the change from baseline, a correlation of 0.68 between visits and a significance level of 0.05.

Assuming a Poisson distribution for the number of COPD exacerbations (moderate and/or severe) during the treatment period and an exacerbation incidence of 0.8 per patient year for placebo group, a sample size of 550 would give greater than 90% power to detect a 30% reduction in exacerbation rate for cilomilast group compared with placebo group. The incidence of 0.8 per patient year was based on retrospective analysis of data from study 091 extrapolated to one year.

The superiority of cilomilast to placebo with regard to COPD exacerbations (moderate and/or severe) was further analysed by comparing exacerbation-free curves. Assuming 1) the censoring patterns for the observations were the same for the two independent treatment groups; 2) the exacerbation-free curves for the two treatment groups were $S_0(t)$ *and* $S_1(t)$ *and* $S_1(t) = [S_0(t)]^{\theta}$; 3) exacerbation-free rate for placebo group at one year was 42%, a sample size of 550 would give a greater than 90% power to detect a 15% difference (θ=0.65) in exacerbation-free rate for cilomilast group. The 42% exacerbation free rate was based on retrospective analysis of data from study 091 extrapolated to one year.

5.9.3. Sample size sensitivity

The power of the repeated measure analysis was affected by assumed mean difference in FEV_1, the assumed standard deviation and the correlation structure across the visits in the double-blind period. The following Table lists the statistical power at the stated sample size for mean treatment differences between 30 ml and 60 ml, standard deviations between 190 ml and 230 ml, and correlations between 0.60 and 0.80.

Table 6 Sample size sensitivity (sample size=275/arm)

		Statistical Power			
Standard Deviation	Correlation	Mean Difference (30ml)	Mean Difference (40ml)	Mean Difference (50ml)	Mean Difference (60ml)
190	0.70	58%	82%	95%	99%
190	0.80	53%	78%	92%	98%
210	0.60	55%	79%	93%	99%
210	0.70	50%	74%	90%	97%
210	0.80	45%	69%	87%	96%
230	0.60	47%	72%	89%	97%
230	0.70	43%	66%	84%	95%
230	0.80	39%	61%	80%	92%

5.9.4. Analysis Populations

5.9.4.1. Randomised population

This population consisted of all subjects who had a randomisation number assigned and were confirmed to receive at least one dose of double-blind study medication. All safety variables were analysed for this population.

5.9.4.2. Intent-to-treat population

The intent-to-treat (ITT) population for the analysis of FEV_1 included all subjects who had received at least one dose of double-blind medication and for whom a baseline and, at least, one on-therapy FEV_1 assessment were available. An on-therapy assessment was defined as any evaluation performed after the first dose and within one day after the last dose of study medication in the 52-week double-blind period. A similar ITT definition applied to all other continuous efficacy variables.

Analysis of number of COPD exacerbations during treatment period as well as time to the first COPD exacerbation included all randomised subjects.

5.9.4.3. Per-protocol (PP) population

The per-protocol population included all subjects who were in the Intent-To-Treat population and did not significantly violate the protocol. Details of protocol violations are found in Section 5.9.8.2.

Analyses for the per-protocol population were restricted to FEV_1 and exacerbation rate for Level II and III exacerbations.

5.9.5. Treatment Comparisons

5.9.5.1. Primary comparisons of interest

There were two primary comparisons of interest. The first was to compare the difference in change from baseline in pre-bronchodilator FEV_1 between the cilomilast group and the placebo treatment group (cilomilast – placebo) averaged over all double-blind visits in the intent-to-treat population. The second was to compare the exacerbation incidences (moderate or severe) during treatment period for cilomilast versus placebo. As statistical significance was demonstrated for both primary endpoints, each of the primary comparisons was performed at an alpha level of 0.05 without adjustment.

5.9.5.2. Other comparisons of interest

Time to first moderate or severe exacerbation during the treatment period was compared between treatment groups, stratified for smokers/ex-smokers.

The exacerbation free curves were compared between treatment groups, stratified for smokers/ex-smokers.

The incidence of all COPD exacerbations occurring during the treatment period was compared between treatment groups, stratified for smokers/ex-smokers.

The difference in change from baseline in post-bronchodilator FEV_1 averaged over all double-blind visits was also compared between the cilomilast group and the placebo treatment group (cilomilast – placebo), stratified for smokers/ex-smokers.

Additional comparisons between treatment groups, stratified for smokers/ex-smokers, was made for FEV_1 (both pre-bronchodilator and post-bronchodilator) at Weeks 4, 8, 12, 20, 28, 36, 44, 52 and endpoint in the double-blind period, where the endpoint was defined as the last on therapy evaluation.

5.9.6. General Considerations for Data Analyses

5.9.6.1. Multicentre studies

Centres were grouped by country for efficacy analyses.

5.9.6.2. Other strata and covariates

The impact of treatment-by-centre interaction and covariates (age, sex, disease severity and smoking status) was explored for the primary analyses of the primary endpoints. If evidence of a qualitative treatment-by-centre interaction was found, exploratory analyses was undertaken to further describe the interaction, and results presented by centre. Interaction terms were be tested at a significance level of 0.10.

5.9.6.3. Examination of subgroups

For each of the co-primary endpoints, the following sub-populations of interest were examined:

- Sex – [Males, Females]
- Percent Predicted FEV_1 – [<35% (severe), 35% to <50% (moderate), ≥50% (mild)]
- Smoking Status – There were two sets of categories for smoking status.
    1. Three categories [Non-smoker throughout, Smoker throughout, Smoker changed to non-smoker during the study and vice versa]
    2. Two categories [Non-smoker at baseline, Smoker at baseline]

In case there were discrepancies between the true smoking status recorded in CRF and one from RAMOS system, effort was made to make sure the CRF was correct. The one recorded in the CRF was used for analysis. If the number of discrepancies was large, analysis was performed both ways for FEV_1 and exacerbation.

5.9.6.4. Multiple comparison/multiplicity

As both FEV_1 and exacerbation incidence were required to be positive in this study no multiplicity adjustment was performed. The modified Bonferroni procedure of Hochberg was used to adjust for secondary endpoints. The procedure used the p-values from the five secondary endpoints.

5.9.7. Data Handling Conventions

5.9.7.1. Premature discontinuation and missing data

Missing data arising from subjects sporadically missing visits or assessments at visits was assumed missing completely at random. No attempts were made to assess the impact of missing data arising by this mechanism. Several analyses were performed to assess the impact of missing data arising from subjects withdrawing early from the study. In this regard withdrawals and completers were characterised both demographically and with regard to baseline disease characteristics.

Analyses was also performed to identify the pattern of dropouts and their impact on the assessment of FEV_1. The pattern of response was displayed graphically over time for completers and for early withdrawals. A graphical display of response over time was also displayed where the worst possible scores prior to withdrawal were imputed for subjects who withdrew due to insufficient therapeutic effects for both treatment groups.

In addition, for subjects who stopped their study medication and continued to come to the scheduled visits, graphical display of response over time (from baseline to the last visit, regardless of scheduled or not) were displayed to assess the withdrawal effects. Repeated measure analysis and analysis of variance (ANOVA) used for primary analysis were used for all subjects (regardless of withdrawal) and all visits (regardless of after withdrawal or not).

If evidence of informative censoring was observed then a pattern mixture model was used to estimate the treatment effect.

Exacerbation data after withdrawal was combined with on therapy data to analyse the level II and III exacerbation rate.

5.9.7.2. Derived and transformed data

5.9.7.2.1. Baseline

In general the last non-missing evaluation prior to the first dose was defined as baseline. However there were some exceptions to this. For all efficacy variables except exacerbation, and SGRQ and EQ-5D, observations within 10 minutes post first dose were considered for baseline. For exacerbation there was no 10-minute window and for SGRQ and EQ-5D baseline was defined as the observation at baseline (Visit 3).

For ECG and vital signs, evaluations which occurred within fifteen minutes post first dose of double-blind study medication were considered for baseline.

For laboratory evaluations, only date was compared. Laboratory samples collected in association with GIAE's of concern on the date of the randomisation visit or prior to the date of the randomisation visit were not considered for baseline.

For Orthostatic Vital Sign Change, as date and time were not available, all measurements collected on or prior to Visit 3 were considered for baseline.

5.9.7.2.2. Endpoint

Endpoint was defined as the last non-missing on-therapy assessment collected for a patient regardless of the type of visit the assessment was collected at. For SGRQ, Endpoint was defined as the assessment at the last on therapy visit no matter it was prior or post the last dose.

5.9.7.2.3. Duplicate or repeated observations

In cases where multiple observations were available or tests were repeated for a particular visit, the latest evaluation was used in the analysis. If a latest evaluation could not reasonably be determined based on date and/or time then the average of the multiple evaluations was taken.

5.9.7.2.4. Study Medication Record

Date of First Dose in the Double-blind Period

Date of first dose was the earlier of the date provided in the study medication record and the date provided for the in-clinic dose at Visit 3.

Date of Last Dose in the Double-blind Period

Date of the last dose was the later of the date provided in the study medication record, the date and time of the in-clinic dose at Visit 12 and the date provided on the study conclusion page of the CRF.

Exposure to Double-blind Study Medication

This was calculated according to the following:

(date of last dose in the double-blind period) – (date of first dose in the double-blind period) + 1

Randomised subjects whose date of first dose in the double-blind period was not available but was confirmed to have received a dose of double-blind study medication had an assumed exposure of one day. Relative Day

(date of assessment/event) – (date of first dose) + 1

Note: for assessments and events occurring prior to the date of first dose of double-blind study medication, "1" was not added when calculating the relative day.

5.9.7.2.5. Compliance

Number of Tablets consumed

n(Tablets dispensed) – n(Tablets returned) – n(Tablets lost)

Number of days between visits

(date of current visit) – (date of previous visit)

Visit Level Compliance

Overall Compliance

5.9.7.2.6. Visit dates

The date for each visit was defined as the date the patient presented to the clinic. If this date was not available, the date that standard vital signs were recorded was used.

5.9.7.2.7. Last study day

The last visit day regardless of withdrawal.

5.9.7.2.8. Prior, Concomitant and Post-therapy Medications

Prior medications

Any medication used prior to the date of the first dose including those which continued beyond the date of first dose of double-blind study medication.

Concomitant medications

Any medication initiated after the date of the first dose of double-blind study medication and prior to the last dose of double-blind study medication. Medications initiated prior to the date of the first dose of double-blind study medication and continued on or after the date of the first dose of double-blind study medication were also considered concomitant.

Post-therapy medications

Any medication initiated on or after the date of last dose of double-blind study medication. This did not include medications continuing from the double-blind period.

5.9.7.2.9. Pulmonary Function Tests (PFTs)

The flow loop with the highest FEV_1 value from a technically acceptable loop was used as the best flow loop. Values of FVC, PEF and FEF_{25-75} were all taken from the Investigator determined best loop.

5.9.7.2.10. COPD Exacerbation

Only those exacerbations with an onset date on or after the first dose of double-blind study medication were used in the analysis. For those exacerbations with an onset date on the date of first dose of double-blind study medication the onset time was compared to the dosing time to determine if the event was on-therapy. If an onset time was not available the event was classified as on-therapy. There were two types of censor in this study, censored by the end of double blind medication (no later than one day after the last dose of double-blind study medication) and by the last study day. A censored patient for an event was defined as any patient for whom the event was not observed during the time period of interest. For subjects who were censored, the time to event was defined as the total number of days of exposure to double-blind study medication or the number of days in study (visit clinic) depending on censor type used.

For the purpose of calculating the duration of an exacerbation with missing resolution date, duration was defaulted to the difference of the onset day and last study day if the difference was less than two weeks. Otherwise the duration was defaulted to two weeks. Duration of exacerbation on therapy was the number of days of exacerbation during the on therapy period.

5.9.7.2.11. St. George's Respiratory Questionnaire (SGRQ)

The SGRQ contains 76 weighted items grouped into three components, categorised as Symptoms, Activity and Impact. Each component score was calculated by summation of the weighted values within each category, divided by the maximum possible score for that category and multiplying by 100. The total score was calculated by aggregating the weighted scores from all 76 items and dividing by the maximum possible score for the SGRQ and multiplying by 100. This calculation was outlined in the developer's guide.

Treatment of Missing Values on SGRQ

If any questions in part 1 of the questionnaire (Symptoms Domain) were missed, then they were treated as having a negative response (i.e. 0). Up to 20% of questions may have been missed in part 2 of the questionnaire (Activity and Impact domain). If more

than 20% of questions were missing from a domain, then the domain total was set to missing. This equated to no more than 3 missed questions for the activity domain and no more than 6 missed questions for the impact domain. If there were more than 10 missed items in the whole of part 2 of the questionnaire, then the total score was set to missing. It was possible to have a domain total present with the total score missing.

Provided that fewer than 20% of questions were missing, they were dealt with by using the denominator which was made up of the maximum possible weights for the non-missing questions.

Multiple Responses on SGRQ

If multiple responses were available for a particular item, the average weight for that item was used in the analysis.

5.9.7.2.12. EQ-5D and Indirect Cost

EQ-5D

EQ-5D (EuroQoL) has been designed as an international, generic instrument for describing and quantifying health related quality of life. Data collected in this study consisted of 5 dimensions (mobility, self care, unusual activity, pain/discomfort, and anxiety/depression) and a thermometer score. Each dimension had three levels, level 0 (no problem), level 1 (some or moderate problems) and level 2 (unable or extreme problems) with scores 0, 1 and 2 respectively. Each level of five dimensions contributed a component of a five digit number and the five digit number corresponded to a score. The score was missing if one of the five dimensions was missing. There were in total 243 health states defined.

Valuations for the 243 health states defined by the EuroQoL classification have been calculated using a regression model. The following formula and worked example in Table 7 indicate how these coefficients were used so as to compute the estimated values for each state.

Table 7 Calculating EuroQoL state valuations

EuroQoL dimension	Level 1 coefficient	Level 2 coefficient
Mobility	0.069	0.314
Self care	0.104	0.214
Usual activity	0.036	0.094
Pain/discomfort	0.123	0.386
Anxiety/depression	0.071	0.236
	Constant = 0.081	N3 = 0.269

The arithmetic needed to recover the estimated value for any health state from this Table of decrements was given by

1- sum(level(where level>0)*coefficient)-constant*[at least one level 1]-N3*[at least one level 2]

Where [] was an indicator function with value 0 or 1.

A worked example: taking health state 0 0 1 1 2 for mobility, self care, unusual activity, pain/discomfort, and anxiety/depression

Full health (0 0 0 0 0) = 1.0

Constant term for level 1 (for any dysfunctional state)(subtract 0.081)

Mobility.. level 0(subtract 0)

Self-care.. level 0(subtract 0)

Usual activity.. level 1 (subtract 0.036)

Pain / discomfort.. level 1 (subtract 0.123)

Anxiety / depression.. level 2 (subtract 0.236)

Level 2 occurs within at least 1 dimension(subtract N3 parameter 0.269)

Hence the estimated value for state 0 0 1 1 2 is given by

1.0 - 0.081 - 0.036 - 0.123 - 0.236 - 0.269 = .255

Indirect Cost

Indirect costs were collected as time missed from work or usual activities due to COPD exacerbation problems and caregiver assistance. Time missed from work or usual activities were recorded as days and time receiving caregiver assistance were recorded as average weekly hours.

5.9.7.2.13. Patient and Physician's global Assessments

Two new categories were created, improvement and no improvement, as defined below,

Improvement = Very much improved, Much improved, Minimally improved

No improvement = No change, Minimally worse, Much worse, Very much worse

5.9.7.2.14. Diary Data

Several measures of efficacy were derived from patient diary data. All diary symptom assessments were recorded in the evening and based on observations over the course of the day. The Summary Symptom Score was calculated as the sum of cough, breathlessness, sputum production - volume and colour. If any of the four components were missing the Summary Symptom Score was also be set to missing.

The percentage of days symptom free was defined as the number of days during which the patient recorded no symptoms with respect to cough, sputum and breathlessness. A symptom free day equated to a Summary Symptom Score of 0. Percent of symptom-free days was calculated as 100 times the number of days symptom free divided by the total number days for which complete symptom data was available. Complete symptom data for a specific day was defined as a non-missing summary symptom score.

Baseline for the diary measures was defined as the average of all available data in the 14 days prior to Visit 3. The average over the 14 days immediately prior to the visit was calculated for each patient and used as the representative score for that visit. Subjects who had less than 10 days of diary data for a given visit were excluded from the analysis for that visit. For percentage of symptom-free days the score used for analysis was based on the percentage as calculated using all available days during the interval. Analyses was also performed on the percent of days symptom-free during the entire double-blind period.

5.9.7.2.15. Adverse Events

Baseline Signs and Symptoms

Any event with an onset date prior to the initial dose of double-blind study medication.

On-therapy Adverse Events

Any event with an onset date on or after the date of first dose of double-blind study medication and prior to two days after the last dose of double-blind study medication. For events occurring on the date of initial dose of double-blind study medication, the time of dosing was compared to the time of onset to determine if the event was categorised into the on-therapy or run-in period. If an onset time was not available the event was classified as on-therapy.

Post-therapy Adverse Event

A post-therapy adverse experience was defined as any event with an onset date at least two days after the last dose of study medication

Adverse Event Leading to Withdrawal

An adverse event leading to withdrawal was one where the "withdrawn" field in CRF was checked as "Yes".

Adverse Event with Missing Onset Date

Adverse events with a missing onset date were assumed to onset on Day 1 of the double-blind period.

5.9.7.2.16. ECGs / Clinical Laboratories / Sitting Vital Signs / Orthostatic Vital Signs

On-therapy assessments

Any assessments performed after the first dose of double-blind study medication and no later than one day after the last dose of double-blind study medication. Visit 3 labs associated with GIAE's of concern were also considered on-therapy.

Worst-case On-therapy Assessments

This was defined as the result with the highest concern level observed during the double-blind treatment period. Subjects who were beyond the normal range in both the high and low direction during the double-blind period were presented in both categories.

New-onset ECG Finding

An on-therapy finding that was not observed during the pre-therapy period (any of Visits 1, 2 or the Visit 3 assessments).

Calculation of Orthostatic Changes

The orthostatic change for a given vital sign measurement was calculated as the difference between the measurement taken with legs dependent and the measurement taken in the supine position:

Orthostatic Change = measurement dependent – measurement supine

5.9.7.3. Values of clinical concern

Table 8, Table 9 and Table 10 show the laboratory values, vital sign and ECG values of potential clinical concern in this study.

Table 8 Laboratory Values of Interest and 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	≤3.0 x 103/mm3	(3.0 x 103/mm3 – 1 x LLN)	(1 x ULN - 20.0 x $10^3/mm^3$)	≥ 20.0 x $10^3/mm^3$
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	not defined	not defined	(1 x ULN - 2 x ULN]	> 2 x ULN
Platelet Count	<100 x 109/L	[100 x 109/L – 1 x LLN)	(1 x ULN - 500 x 10^9/L]	> 500 x 10^9/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 ULN - 2.5 x ULN]	> 2.5 x ULN
Total Bilirubin	not defined	not defined	(1 x ULN - 1.5 x ULN]	> 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 ULN - 1.5 x ULN]	> 1.5 x ULN
Urea (SI Units)	not defined	not defined	(1 x ULN - 17.85 mmol/L]	> 17.85 mmol/L
Urea (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)	≤130 mmol/L	(130 mmol/L – 1 x LLN)	(ULN - 150 mmol/L)	≥ 150 mmol/L
Sodium (non-SI Units)	≤130 mEq/L	(130 mEq/L – 1 x LLN)	(ULN - 150 mEq/L)	≥ 150 mEq/L
Potassium (SI Units)	≤3.0 mmol/L	(3.0 mmol/L – 1 x LLN)	(ULN - 5.5 mmol/L)	≥ 5.5 mmol/L
Potassium (non-SI Units)	≤3.0 mEq/L	(3.0 mEq/L – 1 x LLN)	(ULN - 5.5 mEq/L)	≥ 5.5 mEq/L
Glucose (fasting / non-fasting)	<2.0 mmol/L	[2.0 mmol/L – 1 x LLN)	(ULN - 8.0 mmol/L]	> 8.0 mmol/L
Glucose (non-fasting)	<2.0 mmol/L	[2.0 mmol/L – 1 x 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

1. LLN = Lower Limit of Normal; ULN = Upper Limit of Normal

Table 9 Vital sign Values of Interest and Potential Clinical Concern

Parameter	Low Concern	Low	High	High Concern
Sitting Systolic BP	<75mmHg	75 – 89 mmHg	140 – 180 mmHg	>180 mmHg
Sitting Diastolic BP	<50 mmHg	50 – 59 mmHg	90 – 110 mmHg	>110 mmHg
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 mmHg	Decrease ≥ 20 mmHg
Orthostatic Change in Diastolic BP	not defined	not defined	not defined	Decrease ≥ 10 mmHg
Orthostatic Change in Heart Rate	not defined	not defined	not defined	Increase of ≥ 10 bpm

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

Table 10 ECG Values of Interest and Potential Clinical Concern

Parameter	Low Concern	Low	High	High Concern
QRS interval	not defined	not defined	120 – 199	≥ 200 msec
PR interval	not defined	not defined	200 – 249	≥ 250 msec
Atrial rate	(<50 bpm and 2 bpm lower than nadir from baseline) or (<45 bpm)	(45–<50 bpm and not less than 2 bpm nadir from baseline) or (50-55 bpm)	100 – 120 bpm	> 120 bpm
Ventricular rate	(<50 bpm and 2 bpm lower than nadir from baseline) or (<45 bpm)	(45–<50 bpm and not less than 2 bpm nadir from baseline) or (50-55 bpm)	100 – 120 bpm	> 120 bpm
QTc interval	Not defined	Not defined	430 – 450 msec (borderline, male); 450 – 470 msec (borderline, female)	> 450 msec (prolonged, male); >470 msec (prolonged, female)
QTc change from baseline	Not defined	Not defined	increase 30 – 60 msec	Increase > 60 msec
QRS axis	Not defined	Not defined	Not defined	Change from baseline by >±30 degrees, normal QRS axis at baseline (-30 to +90 degrees), and QRS interval at baseline <120msec

5.9.8. Study Population

5.9.8.1. Disposition of subjects

The distribution of time to withdrawal was estimated using the Kaplan-Meier product limit estimate.

Patient compliance was calculated at each visit. The number of subjects below 80% and above 120% were presented. Descriptive statistics were also presented.

Changes in smoking status were evaluated through a two-by-two contingency Table classifying subjects by their smoking status at baseline versus their status at a given visit.

5.9.8.2. Protocol deviations

5.9.8.2.1. Violations of Eligibility Criteria

For these violations all primary endpoint data were excluded from the per-protocol analysis.

- Subjects who had previously taken cilomilast
- Pre- salbutamol FEV_1/FVC ratio > 0.7 at Visit 1
- Increase in $FEV_1$of >15% absolute (pre Protocol amendment 2) and > 10% of predicted normal (post protocol amendment 2) and/or > 200 ml following salbutamol at Visit 1
- Post- salbutamol FEV_1 <30% or >70% of predicted value at Visit 1
- Participation in a pulmonary rehabilitation program (PRP) within 4 weeks prior to Visit 1
- Greater than a 20% change in pre- salbutamol clinic FEV_1between Visits 2 and 3

5.9.8.2.2. Excluded Medication Protocol Violations

Unless stated otherwise any primary endpoint data collected after the initiation of an excluded medication was excluded from per-protocol analysis.

- Concomitant oral or intravenous xanthine use within 2 weeks prior to Visit 3
- Concomitant oral or inhaled long-acting β_2- agonist use within 2 weeks prior to Visit 3
- Concomitant inhaled short acting β_2- agonist use other than salbutamol within 2 weeks prior to Visit 3
- Concomitant leukotriene modifiers use within 2 weeks prior to Visit 3
- Concomitant combined β_2- agonist /ipratropium use within 2 weeks prior to Visit 3
- Concomitant long term oxygen therapy use within 2 weeks prior to Visit 3
- Concomitant oral and/or inhaled corticosteroid within 2 weeks prior to Visit 3
- Nebulised or oral salbutamol or nebulised anticholinergics within 2 weeks prior to Visit 3
- Concomitant antibiotic use for COPD exacerbation within 2 weeks prior to Visit 3
- Concomitant use of nedocromil (bronchodilator and anti-inflammatory properties) within 2 weeks prior to Visit 3
- Anticholinergic use that was discontinued within 2 weeks prior to Visit 3
- Anticholinergics initiated after Visit 1
- Exclusionary medication use for the indication of COPD exacerbation for more than six weeks total exposure during the double-blind period (all data subsequent to six weeks exposure was excluded)

5.9.8.2.3. Visit Specific Protocol Violations

For these violations, primary efficacy data collected at the visit was excluded from the per-protocol analysis.

- Study medication compliance <80% or >120% during active, on-therapy dosing
- Salbutamol and/or anticholinergic medication within 4 hours of pulmonary function testing
- Entered a PRP during the study (all data collected excluded subsequent to entry)
- Use of study medication within 7 hours of first (trough) pulmonary function test

5.9.8.2.4. Conduct of Study Deviations

For these deviations, no data was excluded from the per-protocol analysis.

- Aged <40 or >80 years
- Cigarette smoking history <10 pack years
- Study medication compliance <80% or >120% during placebo run-in period (recorded at Visit 2 and Visit 3)
- Level 2 or level 3 exacerbation of COPD within 6 weeks prior to Visit 3
- Emergency room visit for treatment of COPD within 2 weeks prior to Visit 1
- Exclusionary medication used more than 2 weeks for COPD exacerbation (did not include subjects exceeding 6 weeks total exposure as described above)
- Exclusionary medication used for less than 2 weeks for indication other than COPD exacerbation
- Smoking within 2 hours of pulmonary function testing (at Visit 3 or later)

5.9.8.3. Demographic and baseline characteristics

Baseline and demographic characteristics were summarised using frequencies and percents as well as descriptive statistics. No hypothesis testing was performed for treatment differences in patient baseline characteristics, demography or patient disposition.

Concomitant and prior medications, post-therapy medications and concomitant medications given for COPD exacerbations were coded to generic terms using the GSK Drug dictionary. The number and percentage of subjects were summarised according to generic terms.

5.9.8.4. Treatment compliance

See Section 5.9.7.2.5.

5.9.9. Efficacy Analyses

All linear models to assess treatment effects for efficacy measures were performed using SAS procedure MIXED. Centres within countries were combined and used in the models.

5.9.9.1. Primary efficacy measure(s)

5.9.9.1.1. Primary Analysis of FEV_1

The primary assessment of treatment differences for mean change from baseline in FEV_1 (pre-bronchodilator) averaged over 52 weeks was based on a repeated measures model with fixed effects of treatment, time and country. Time was treated as a nominal variable in the analysis. A compound symmetric correlation structure was used. Least squares means along with 95% confidence intervals were calculated for each treatment group. Least squares means and 95% confidence intervals were also calculated for the treatment difference. Differences between treatment groups were assessed using t-tests on the least squares means.

5.9.9.1.2. Primary Analysis of Exacerbation Rate

The rate of a moderate or severe (level II or III) COPD exacerbations occurring during the treatment period was analysed using a maximum likelihood based analysis, assuming a Poisson distribution, with total duration on treatment as an offset variable. The mean rate per patient year has been presented for each treatment.

5.9.9.1.3. Sensitivity Analysis to Assess Impact on Primary Analysis

Sensitivity analyses was performed for FEV_1 to evaluate the impact of treatment-by-time interaction, normality of the underlying data and covariance structure of the underlying data on the inference drawn from the above repeated model. Sensitivity analyses was also performed for FEV_1 and exacerbation to evaluate the impacts of treatment-by-centre interaction and covariates (age, sex, disease severity and smoking status),

Treatment by Time Interaction

Treatment-by-time interaction was tested at a significance level of 0.10. The model for testing this interaction had all effects specified in the primary model with the addition of the interaction term. If evidence for a treatment-by-time interaction was observed then a repeated measures analysis was performed to estimate differences in the rate of change in FEV_1 between the two treatment groups. This model included all effects described for the primary model as well as a treatment-by-time interaction term. Time was treated as a continuous variable in this model. In addition, if the interaction occurred at the beginning of the study, the above repeated measure analysis was performed on the latter visits.

Normality of Underlying Data

The normality assumption of trough FEV_1 was explored through graphical examination of the residuals. The marginal residuals from each time point in the repeated measures analysis was plotted in a normal probability plot.

Treatment by Country Interaction

The impact of treatment-by-country interaction was explored for the primary analyses of the primary endpoints, FEV_1 and exacerbation. If evidence of a qualitative treatment-by-country interaction was found, exploratory analyses was undertaken to further describe the interaction and results presented by country. Treatment-by-country interaction was tested at a significance level of 0.10.

5.9.9.2. Secondary efficacy measures

Post-bronchodilator FEV_1 was analysed using the repeated measures model described above for pre-bronchodilator FEV_1. In addition to the repeated measures analysis, both pre-bronchodilator and post-bronchodilator FEV_1 was also analysed using an ANOVA model with fixed effects of treatment and country at each double-blind visit as well as at endpoint.

Time to the first moderate or severe COPD exacerbation (exacerbation-free curves) were estimated using Kaplan-Meier product limit method. The exacerbation-free rate at 52 weeks, and associated 95% confidence intervals, were estimated for each treatment group. A log-rank test was performed using SAS PROC LIFETEST® to compare the two curves between cilomilast and placebo groups.

The same analyses was performed for all levels of exacerbation.

Exacerbation was also presented by exacerbation level.

Total score of SGRQ was analysed using an ANOVA model with fixed effects of treatment and country at each double-blind visit as well as at endpoint.

Treatment-by-country interaction terms and distribution assumptions were not assessed for these endpoints.

5.9.9.3. Other efficacy measures

Change from baseline in FVC, PEF (clinic only) and FEF_{25-75} were analysed using the repeated measures model described above. All continuous variables (except ones mentioned below) were also analysed using an ANOVA model with fixed effects for treatment and country at each double-blind visit as well as at endpoint (based on change from baseline).

Use of relief medication, percentage of days with no need for rescue medication (salbutamol), number of night time awakenings and duration of exacerbation were tabulated using descriptive statistics and analysed using Wilcoxon rank sum test. All subjects should be included in the analysis with 0 or 100% as valid values, for example, patient without exacerbation will have 0 duration.

Global subject assessment and global Investigator assessment were tabulated using contingency Tables and improvement versus no improvement were tested using the chi square test.

5.9.10. Safety Analyses

5.9.10.1. Adverse event

All AEs in the double-blind period have been presented for both treatment groups by body system, severity level (mild, moderate and severe), time of initial onset and action taken. Time to onset was assessed for AEs using a life-Table analysis. This was done for AEs with a 5% or greater incidence in the cilomilast group. In addition, the cumulative incidence of nausea, abdominal pain, diarrhoea and vomiting by time was estimated using the Kaplan-Meier product limit estimate. This methodology was also used to assess cumulative incidence of GIAE's of concern and DI AE body system. No formal statistical hypothesis testing was performed for AEs.

5.9.10.2. Clinical Laboratories

Descriptive statistics for blood chemistry and haematology by visit/week and treatment group have been provided. Transitions from baseline in blood chemistry and haematology parameters have been presented. The number and percent of subjects with a concern have been presented by baseline concern category. A summary over the entire double-blind period was performed using the "worst-case" for each patient. A summary was also performed at endpoint for each patient. Endpoint was defined as the last on-therapy evaluation. Faecal occult blood measurements was summarised for all subjects and separately for the population of subjects with GIAE's of concern. The number and percentage of subjects with positive results have been presented.

5.9.10.3. Vital Signs

Vital signs, heart rate, systolic blood pressure and diastolic blood pressure have been summarised similarly as for clinical laboratory variables.

Orthostatic vital signs have been summarised as above for all subjects and separately for the population of subjects with GIAE's of concern.

5.9.10.4. ECGs

ECG variables atrial rate, ventricular rate, PR interval, QRS interval and axis, uncorrected QT interval and corrected QT interval using Bazett formula (QTc) have been summarised the same as for clinical laboratory variables with the addition that new-onset ECG findings based on cardiologist interpretation of the tracings have been presented by SNOMED terminology

5.9.11. Health Outcomes Analyses

The number of healthcare resource utilisations during the treatment period were analysed using a poisson regression model. SGRQ sub scores, EQ-5D dimension score and thermometer score, and indirect cost were analysed the same way as the total SGRQ score (ANOVA).

The mean days missed and assistance needed , mean days in the study and their ratio are displayed.

6. STUDY POPULATION RESULTS

6.1. Disposition of Subjects

Table 13.1A and Table 11 summarise data on patient numbers in this study. The total number of subjects recruited into the study was 1390 of which 907 (65.3%) were randomised to receive treatment. 479 (34.5%) subjects were withdrawn during the single-blind run-in period prior to randomisation, of which 271 (19.5%) did not fulfil the entry criteria (Table 13.3). There were 288 (31.8%) patient withdrawals during the double-blind period, mainly due to an AE (Table 13.4).

Recruitment details per country are detailed in Table 13.1B. Germany was the highest recruiting country with 151 subjects randomised to treatment. Patient attendance at each Clinic Visit is presented in Table 13.2 and details of time of withdrawal during the double-blind period in Table 13.5.

Table 11 Number of subjects who completed each phase of the study

	Placebo (n)	Cilomilast (n)	Total (n)
Total population			1390
Randomised	452	455	907
Withdrawn during single-blind			479
Completed single-blind			911*
Withdrawn during double-blind due to:	121	167	288
Adverse event	46	80	126
Insufficient efficacy	18	8	26
Protocol deviation	8	16	24
Lost to follow-up	10	32	42
Other	39	31	70
Completed double-blind	331	288	619

1. Data Source: Table 13.1A, Table 13.3, Table 13.4
2. *four subjects completed the single-blind period but were not randomised

6.2. Protocol Deviations

There were a total of 192 protocol deviations related to conduct of the study, 105 (24%) in the placebo group and 87(21%) in the cilomilast group (Table 13.6C). The most common deviation was smoking within 2 hours of pulmonary function testing which occurred in 63 (15%) subjects in the placebo group and 48 (12%) in the cilomilast group. A summary of conduct of study deviations is shown in Table 12.

Table 12 Summary of conduct of study deviations

Deviation	Placebo n (%)	Cilomilast n (%)
Study compliance <80% during placebo run-in	19 (4.4)	21 (5.1)
Level II or III exacerbation of COPD within 6 weeks of Visit 3	4 (0.9)	2 (0.5)
Exclusionary medication used more than 2 weeks for COPD exacerbation	17 (3.9)	15 (3.6)
Exclusionary medication used less than 2 weeks for indication other than COPD exacerbation	11 (2.5)	9 (2.2)
Exclusionary medication used more than 2 weeks for indication other than COPD exacerbation	2 (0.5)	3 (0.7)
Oxygen therapy	0	1 (0.2)
Smoking within 2 hours of pulmonary testing function	63 (14.5)	48 (11.7)
TOTAL:	105 (24.2)	87 (21.1)

1. Data Source: Table 13.6C

6.3. Populations Analysed

All efficacy measures were analysed for the ITT population defined as all subjects who received randomised study medication and had a baseline evaluation and at least one on-therapy efficacy evaluation during the 52 week treatment period. This consisted of 845 subjects (433 in placebo group; 412 in cilomilast group) (Table 13.1A). This number was reduced from the 907 randomised by the requirement to have at least one primary efficacy measurement post randomisation and the removal of the efficacy data from all 28 patients from centre [redacted] Efficacy data from centre [redacted] was removed after concerns over the integrity of endpoints subsequent to irregularities detected at audit. Safety data from this site has remained in the safety analysis which remains at 907 subjects.

All safety analyses were carried out in the randomised population consisting of 452 subjects in the placebo group and 455 in the cilomilast group.

The primary efficacy endpoints were also analysed in the PP population (defined as all patient in the ITT population who did not significantly violate the protocol) which comprised 375 subjects in the placebo group and 345 subjects in the cilomilast group. A summary of the protocol violation which resulted in exclusion from the PP analysis is presented in Table 13.6A and the time point during the study when the violation occurred in Table 13.6B.

The most common reason for exclusion from the PP population was due to a visit specific violation including study medication compliance <80% or >120% by 93 (22%) subjects in the placebo group and 106 (26%) subjects in the cilomilast group and use of study

medication within 7 hours of the trough lung function measurement by 31 (7%) subjects in the placebo group and 20 (5%) subjects in the cilomilast group. A summary of the protocol violations resulting in partial or total exclusion from the PP population is shown in Table 13. Partial exclusion from the PP population resulted in the exclusion of data from the time of the violation through all subsequent data and complete exclusion resulted in total exclusion from the PP analysis.

Table 13 Summary of protocol violations resulting in exclusion from the Per Protocol population

Type of Violation	Placebo n (%)	Cilomilast n (%)
Violation of eligibility criteria	24 (5.5)	20 (4.9)
Exclusionary medications	48 (11.1)	52 (12.6)
Visit specific violations	58 (13.4)	67 (16.3)
All violations: Partial exclusion	119 (27.5)	114 (27.7)
Complete exclusion	58 (13.4)	67 (16.3)
All violations: At least one protocol violation	117 (40.9)	181 (43.9)

1. Data Source: Table 13.6A

A summary of the patient populations is given in Table 14.

Table 14 Study populations

	Placebo (n)	Cilomilast (n)	Total (n,%)
Safety analysis	452	455	907 (100)
ITT population	433	412	845 (93)
Per protocol (PP) population	375	345	720 (79)
Partial exclusion from PP population	119	114	233 (26)
Total exclusion from PP population	58	67	125 (14)

1. Data Source: Table 13.1A. % calculated as the % of randomised subjects.

6.4. Demographics and Other Baseline Characteristics

6.4.1. Demographic Characteristics

Demographic details at baseline of the randomised population are summarised in Table 13.7A and Table 15. The treatment groups were well matched with respect to the demographic parameters of age, race, height and weight. There were slightly more females in the placebo group (27%) than the cilomilast group (22%). Demographic details of the PP population are presented in Table 13.7B and were also well matched

between the treatment groups. A summary of the demographic characteristics split by current smokers and previous smokers is also found in s 13.7C and 13.7D respectively.

Table 15 Summary of demographic characteristics at screening - all randomised subjects

	Placebo (n,%)	Cilomilast	Total (n,%)
Sex: Female	122 (27)	98 (22)	220 (24)
Male	330 (73)	357 (79)	687 (76)
Race: Caucasian	433 (96)	436 (96)	869 (96)
Mean Age (years): <50	34 (8)	20 (4)	54 (6)
50-65	215 (48)	213 (47)	428 (47)
>65	203 (45)	222 (49)	425 (47)
Mean (sd) Weight (kg)	74.3 (15.2)	74.3 (14.7)	74.3 (14.9)
Mean (sd) Height (cm)	168.9 (8.4)	169.3 (8.3)	169.1 (8.4)

1. Data Source: Table 13.7A. % calculated as the % of randomised subjects.

6.4.2. Baseline Characteristics

Details of lung function parameters measured at screening for the randomised population are presented in Table 13.9A and for the PP population in Table 13.9B. The smoking history, duration of COPD and alcohol intake for the randomised population are summarised in Table 13.12A and for the PP population in Table 13.12B.

Table 16 summarises some of the key baseline characteristics of the randomised population. The treatment groups were well matched for baseline lung function and smoking status, although subjects in the cilomilast group had a slightly decreased lung function compared to subjects receiving placebo. The mean duration of COPD was also similar between the treatment groups.

Table 16 Baseline characteristics - randomised population

Variable	Placebo N=452	Cilomilast N=455
Mean FEV_1 (L) pre-salb	1.42	1.36
Mean % predicted FEV_1 post-salb	52.7	50.4
Salbutamol reversibility (%)	5.6	5.6
Volume reversibility (ML)	67.69	65.04
Ipratropium reversibility (%)	9.9	9.6
FVC (L)	2.86	2.78
FEV_1:FVC	0.50	0.49
PEF (L/min)	194.8	191.6
Mean Duration of COPD (years)	7.8	7.9
Smoking status, n (%)		
Current smoker	188 (42)	196 (43)
Ex smoker	264 (58)	259 (57)
Mean Pack years	43.8	44.8
Mean Cigarettes/day	16.9	17.0

1. Data Source: Table 13.9A, 13.12A

6.4.3. Other Current Medical Conditions

A summary of the prior medical conditions recorded at screening are summarised in Table 13.13A for the randomised population. In the placebo group, 267 (59%) subjects reported at least one prior condition and in the cilomilast group, 262 subjects (58%) reported a condition. The most common prior medical conditions were related to surgical and medical procedures with 120 (27%) subjects in the placebo group and 95 (21%) in the cilomilast group reporting a procedure, the most common of which was an appendicectomy.

All subjects reported a current medical condition at screening (Table 13.13B) which included COPD. The most common group of conditions reported were related to infections and infestations, which were reported by 213 (47%) subjects in the placebo group and 184 (40%) subjects in the cilomilast group. This category included chronic bronchitis, which was reported by 199 (44%) subjects in the placebo group and 169 (37%) subjects in the cilomilast group. Other conditions reported by greater than 5% of the randomised population included hypertension by 33% of subjects in both groups, hypercholesterolaemia by 7.3% and 6.8% in the placebo and cilomilast group and diabetes mellitus by 7.5% and 4.2% respectively.

6.4.4. Previous Medications

A summary of prior medications which were taken by randomised subjects including those that were discontinued prior to randomisation and those that continued post-randomisation is presented in Table 13.15A.

Table 17 summarises the most common medications which were taken by >10% of subjects in any treatment group and were discontinued upon entry into the study. The

most common medication which was discontinued was the long-acting β_2-agonist salmeterol by 23% of subjects randomised to receive placebo and 29% subjects randomised to receive cilomilast. Former cumulative long acting beta2 agonist use (Salmeterol, formoterol, eformoterol fumarate and fenoterol hydrobromide) reached 44.5% and 53.2% in placebo and cilomilast groups respectively. Former inhaled corticosteroid use (including fluticosone propionate and budesonide) were used by a total of 34% and 41% of placebo and cilomilast patients.

Table 17 Most common (>10% of subjects in any treatment group) medication discontinued at screening - all randomised subjects

Medication	Placebo, n (%)	Cilomilast, n (%)
Salmeterol/salmeterol xinafoate	103 (23)	131 (29)
Fluticasone propionate	92 (20)	116 (26)
Theophylline	67 (15)	76 (17)
Budesonide	61 (14)	67 (15)
Acetylsalicyclic acid	64 (14)	56 (12)
Fenoterol hydrobromide	43 (9)	50 (11)
Eformoterol fumarate	41 (9)	47 10)

1. Data Source: Table 13.15A

6.4.5. Other Factors Affecting Response to Therapy

There were no other factors recorded which could affect the response to therapy.

6.5. Concomitant Medications

A summary of medications which were taken by randomised subjects which included those that were continued from pre-randomisation and those that were initiated post-randomisation is presented in Table 13.15B. Table 18 summarises the five most common medications taken during the study. The most common medication taken in both the placebo and cilomilast group was salbutamol.

Table 18 Five most common medications taken during the study - all randomised subjects

Medication	Placebo n (%)	Cilomilast n(%)
Salbutamol	439 (97.1)	440 (96.7)
Ipratropium bromide	230 (50.9)	208 (45.7)
Paracetamol	89 (19.7)	79 (17.4)
Acetetylsalicyclic acid	77 (17.0)	69 (15.2)
Amoxicillin	37 (8.2)	48 (10.5)

1. Data Source: Table 13.15B

A summary of medications which were prescribed to randomised subjects for exacerbations of COPD during the study is presented in Table 13.15D.

Table 19 summarises the most common medications which were taken by >5% of subjects in any treatment group for an exacerbation. The most common medication prescribed by Investigators was the antibiotic amoxicillin/amoxicillin trihydrate.

Table 19 Most common (>5% subjects in any treatment group) medication given for a COPD exacerbation - all randomised subjects

Medication	Placebo n (%) n=452	Cilomilast n (%) n=455
Total medications	179 (39.6)	175 (38.5)
Amoxicillin / Amoxicillin trihydrate	45 (9.9)	62 (13.6)
Prednisolone	46 (10.2)	37 (8.1)
Prednisone	32 (7.1)	45 (9.9)
Ipratropium bromide	34 (7.5)	29 (6.4)
Clavulanate potassium	17 (3.8)	28 (6.2)

1. Source Table: 13.15D.

6.6. Treatment Compliance

Details of compliance with study medication is summarised in Table 13.6A with descriptive statistics presented in Table 13.6B. Compliance with taking study medication was high with a mean compliance during the double blind period in the placebo group of >96% at all visits. In the cilomilast group the mean compliance was >94% at all visits.

7. EFFICACY RESULTS

7.1. Primary Efficacy Results

The primary measures of efficacy were the mean change from baseline in trough pre-bronchodilator FEV_1 averaged over 52 weeks and the incidence rate of level II (moderate) and level III (severe) COPD exacerbations during the treatment period.

7.1.1. Pre-bronchodilator trough FEV_1

7.1.1.1. ITT population

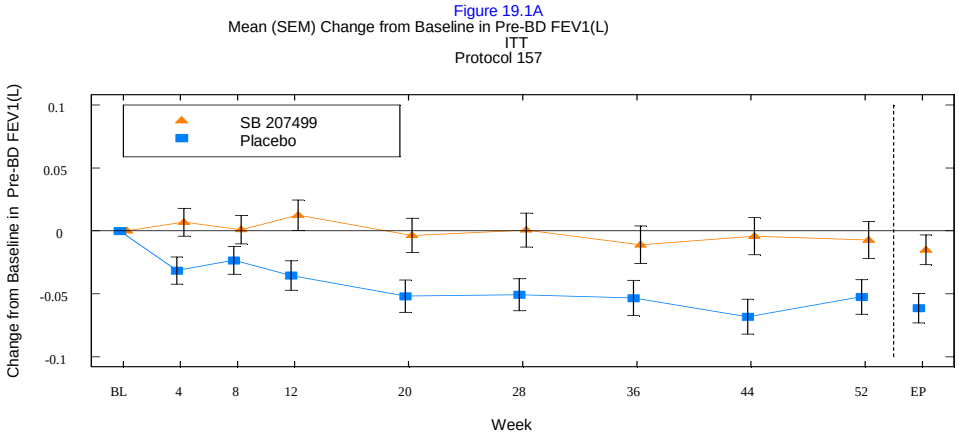
Trough FEV_1 was measured at every scheduled clinic visit except visit 4 and at any unscheduled visit as a result of a COPD exacerbation. For all subjects in the ITT population, the average change from baseline over 52 weeks in trough FEV_1 was significantly greater in subjects receiving cilomilast compared to placebo. Table 20 summarises the difference in pre-bronchodilator trough FEV_1 between subjects receiving cilomilast and placebo over 52 weeks. These data are presented graphically in Figure 1.

Table 20 Mean difference between treatment groups in change from baseline in pre-bronchodilator trough FEV_1 over 52 weeks - ITT population

Treatment	N	Change from baseline (L)		Comparison with placebo (L)			
		Mean	SEM	Mean difference	Lower 95% CI	Upper 95% CI	P value
Placebo	416	1.421	0.024				
Cilomilast	395	1.340	0.025	0.041	0.019	0.063	0.000*

1. Data source: Table 14.1A: * significantly different from placebo. Means adjusted for baseline, country and

Figure 1 Mean Change from baseline in Pre-bronchodilator FEV_1 ITT population



Graphical presentations of the mean change from baseline in pre-bronchodilator trough FEV_1 in the ITT completers, ITT withdrawals and ITT (withdrawals due to lack of efficacy imputed with worst score) by treatment group are shown in Figure 19.1B, Figure 19.1C and Figure 19.1D respectively. Results demonstrated in these figures do not markedly differ from the all patient data presented above. The ITT withdrawals group show a slight decline in FEV_1 at week 44 although the very low numbers of subjects withdrawing at this late stage restrict the significance of these data. Analyses to assess the impact of withdrawals on the change from baseline in trough FEV_1, with missing values for withdrawn subjects imputed with the worst value prior to withdrawal, provided no evidence to suggest that the observed treatment effect on FEV_1 was being significantly impacted by the withdrawn subjects

Graphical presentations of the mean change from baseline in pre-bronchodilator trough FEV_1 averaged over 52 weeks in the ITT, ITT completers and at ITT endpoint by treatment group are shown in Figure 19.1F, Figure 19.1G and Figure 19.1H respectively.

The summary statistics for the change from baseline in pre-bronchodilator trough FEV_1 at each clinic visit/week for the ITT population are presented in Table 14.1B. The difference between the groups in change from baseline in favour of cilomilast was significant as early as 4 weeks after the start of treatment and was maintained throughout the 52 week period (except for a non-significant difference at week 8). The largest difference between the groups was seen at week 44 where a difference of 0.064L was observed. Treatment by week is summarised in Table 21 and presented graphically in Figure 19.1E.

Table 21 Mean difference between treatment groups in change from baseline in pre-bronchodilator trough FEV_1 by week in the ITT population

Time from randomisation	Comparison with placebo (L)			
	Mean difference	Lower 95% CI	Upper 95% CI	P value
Week 4	0.038	0.011	0.066	0.006*
Week 8	0.024	-0.003	0.052	0.083
Week 12	0.048	0.019	0.077	0.001*
Week 20	0.048	0.016	0.081	0.003*
Week 28	0.051	0.019	0.083	0.002*
Week 36	0.042	0.007	0.078	0.018*
Week 44	0.064	0.029	0.099	0.000*
Week 52	0.045	0.011	0.080	0.010*
Endpoint	0.046	0.017	0.076	0.002*

1. Data source: Table 14.1B
2. * significantly different from placebo. Means adjusted for baseline value and country.

Descriptive statistics for the change from baseline by week and treatment group for the ITT population is presented in Table 14.1C.

Descriptive statistics for the change from baseline at study endpoint (week 52) by country is presented in Table 14.1I.

7.1.1.2. Results of Covariate Analyses

Sensitivity analyses was performed to evaluate the impacts of treatment-by-time, treatment by country interaction and covariates (age, sex, disease severity and smoking status) on pre-bronchodilator trough FEV_1.

A summary of tests of significance for interaction terms for change from baseline in pre-bronchodilator FEV_1 in the ITT population is presented in Table 14.1N and shows that there was no significant treatment by country (p=0.7755) or treatment by visit interaction (p=0.5414).

A summary of significance tests for prognostic factors effecting the change from baseline in trough FEV_1 in the ITT population is presented in Table 22. These were undertaken as a series of separate models of covariance of analysis with controls for treatment and visit. An initial model with more extensive elements was undermined by co-linearity between factors within the model.

Table 22 Summary of tests of significance for prognostic factors affecting the change from baseline in trough FEV_1

	Covariate				
	AGE	BASELINE	Predicted FEV1	SEX	SMOKING STATUS
P value	0.6424	0.0001	0.6842	0.0941	0.8863
Estimate	-0.0003	-0.0494	-0.0002	0.0227	-0.0016

1. Data source: Ad hoc Table 14.1O2 and Table 14.1O3. Age unit 1 year; baseline unit L; FEV1 unit 1% SEX represents change from male to female, Smoking status represents change from smoking to non-smoking

Baseline FEV_1 is the only covariant which has a statistical significant prognostic effect on change from baseline in FEV_1. This suggests that for every 1L increase in baseline FEV_1 there is a decrease in change from baseline of 0.0494 L.

The relationship of smoking status suggests that baseline smokers will have a 0.0016L increase in change from baseline over non-smokers and that females will have an advantage of 0.0227 L over males although neither of these are statistically significant (P values of 0.8863 and 0.0941 respectively). Increasing age and predicted FEV_1 at baseline would result in a lower FEV_1 change from baseline although these again are not significant.

7.1.1.3. Per-protocol population

In the PP population, the difference between the cilomilast and placebo groups in the mean change from baseline in trough FEV_1 averaged over 52 weeks was the same as seen in the ITT population (0.041L; $p<0.001$) (Table 14A.1A). Summary statistics for the change from baseline by week in pre-bronchodilator trough FEV_1 is presented in Table 14A.1B and summarised in Table 23. The difference between the groups in change from baseline in favour of cilomilast was significant at 4, 12, 20, 28, 44, 52 weeks and study endpoint. The largest difference between the groups was seen at week 20 where a difference of 0.057L was observed.

Table 23 Mean difference between treatment groups in change from baseline in pre-bronchodilator trough FEV_1 by week in the PP population

Time from randomisation	Comparison with placebo (L)			
	Mean difference	Lower 95% CI	Upper 95% CI	P value
Week 4	0.043	0.015	0.072	0.003
Week 8	0.017	-0.013	0.047	0.258
Week 12	0.046	0.015	0.077	0.003
Week 20	0.057	0.022	0.092	0.002
Week 28	0.052	0.016	0.087	0.004
Week 36	0.022	-0.017	0.061	0.267
Week 44	0.054	0.016	0.093	0.006
Week 52	0.045	0.007	0.082	0.019
Endpoint	0.047	0.017	0.077	0.002

1. Data source: Table 14.A1B: * significantly different from placebo. Means adjusted for baseline value and country.

Graphical presentations of the mean change from baseline in pre-bronchodilator trough FEV_1 averaged over 52 weeks in the PP population is shown in Figure 19A.1A and averaged over 52 weeks in the PP population in Figure 19A.1F.

Results of the mean change from baseline in pre-bronchodilator trough FEV_1 in sub-populations of subjects split by smoking status, gender, % predicted FEV_1 at entry and reversibility at baseline are found in Section 7.4.

7.1.2. Incidence rate of level II/III COPD exacerbations

7.1.2.1. All randomised subjects

A summary of level II/III COPD exacerbation rates per treatment year is presented in Table 24. There was no significant difference between the treatment groups over 52 weeks of treatment. The rate per patient year in the placebo group was 0.447 compared to 0.500 in the cilomilast group (p=0.384).

Table 24 Summary of level II/III COPD exacerbation rates per patient year - all randomised subjects

Treatment	N	Rate per patient year	95% CI	Incidence density ratio	95% CI	p value
Placebo	437	0.448	0.357, 0.563			
Cilomilast	442	0.483	0.384, 0.608	1.0776	0.827, 1.405	0.5804

1. Data source: 14.7A. Incidence density ratio is cilomilast relative to placebo.

A graphical representation of the mean (95% CI) rate of level II/III exacerbations per patient year in the ITT is shown in Figure 19.7K.

7.1.2.2. Per-protocol population

A summary of the level of II/III exacerbations in the PP population is presented in Table 25. There was no significant difference observed between the treatment groups over 52 weeks of treatment. The rate per patient year in the placebo group was 0.430 compared to 0.462 in the cilomilast group (p=0.6134).

Table 25 Summary of level II/III COPD exacerbation rates per patient year - PP population

Treatment	N	Rate per patient year	95% CI	Incidence density ratio	95% CI	p value
Placebo	414	0.431	0.339, 0.545			
Cilomilast	422	0.474	0.362, 0.588	1.0737	0.815, 1.415	0.6134

1. Data source: Table 14A.7A. Incidence density ratio is cilomilast relative to placebo.

7.2. Secondary Efficacy Results

7.2.1. Mean change from baseline in trough post-bronchodilator FEV_1

For all subjects in the ITT population, the average change from baseline over 52 weeks in trough post-bronchodilator FEV_1 was significantly greater in subjects receiving cilomilast compared to placebo as summarised in Table 26. Over 52 weeks the mean difference between the groups was 0.034L.

Table 26 Mean difference between treatment groups in change from baseline in post-bronchodilator trough FEV_1 over 52 weeks - ITT population

Treatment	N	Change from baseline (L)		Comparison with placebo (L)			
		Mean	SEM	Mean difference	Lower 95% CI	Upper 95% CI	P value
Placebo	411	-0.002	0.009				
Cilomilast	390	0.032	0.010	0.034	0.011	0.057	0.004*

1. Data Source: Table 14.3A: * significantly different from placebo. Means adjusted for baseline, country and week.

Table 27 presents the change from baseline in post-bronchodilator trough FEV_1 at each clinic visit/week. The difference between the groups in favour of cilomilast was significant at week 12 (0.051L; p=0.001), which was maintained until the end of the 52 week treatment period. The largest difference between the groups was seen at week 44 with a difference of 0.072L observed.

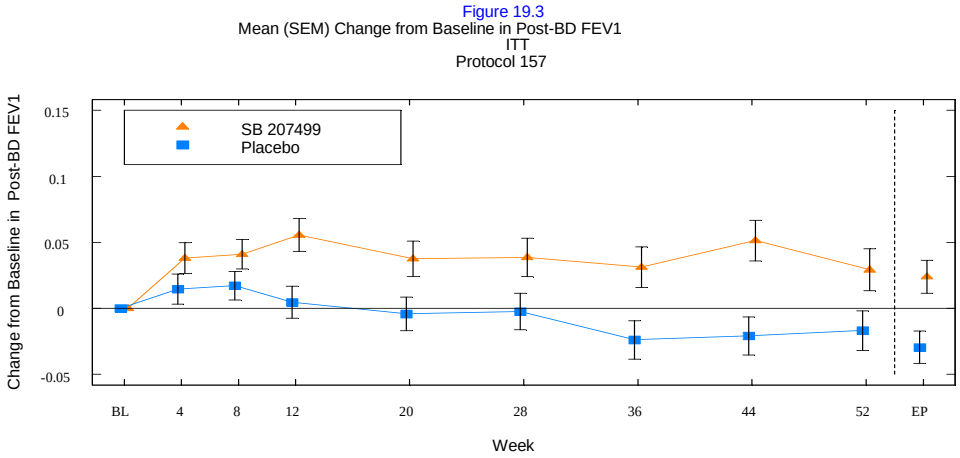
Table 27 Mean difference between treatment groups in change from baseline in post-bronchodilator trough FEV_1 by week in the ITT population

Time from randomisation	Comparison with placebo (L)			
	Mean difference (L)	Lower 95% CI	Upper 95% CI	P value
Week 4	0.024	-0.005	0.052	0.106
Week 8	0.024	-0.003	0.051	0.086
Week 12	0.051	0.021	0.081	0.001
Week 20	0.042	0.010	0.073	0.010
Week 28	0.041	0.006	0.076	0.021
Week 36	0.055	0.018	0.092	0.003
Week 44	0.072	0.035	0.109	0.000
Week 52	0.046	0.009	0.083	0.016
Endpoint	0.053	0.023	0.084	0.001

1. Data Source: Table 14.3B: * significantly different from placebo. Means adjusted for baseline value and country.

Descriptive statistics for the change from baseline by week and treatment group for the ITT population is presented in Table 14.3C. Graphical representation of the mean (sem) change from baseline in post-bronchodilator trough FEV_1 in the ITT population is shown in Figure 2.

Figure 2 Mean change from Baseline in Post Bronchodilator FEV_1 ITT population



7.2.2. Time to first level 2 (moderate) or level 3 (severe) COPD exacerbation

7.2.2.1. All randomised subjects

A summary of level II/III exacerbation-free survival is presented in Table 28. There was no significant difference in the survival rate between the treatment groups. The exacerbation-free survival has been estimated using Kaplin-Meier estimate of time to first exacerbation.

Table 28 Summary of level II/III exacerbation-free survival - all randomised subjects

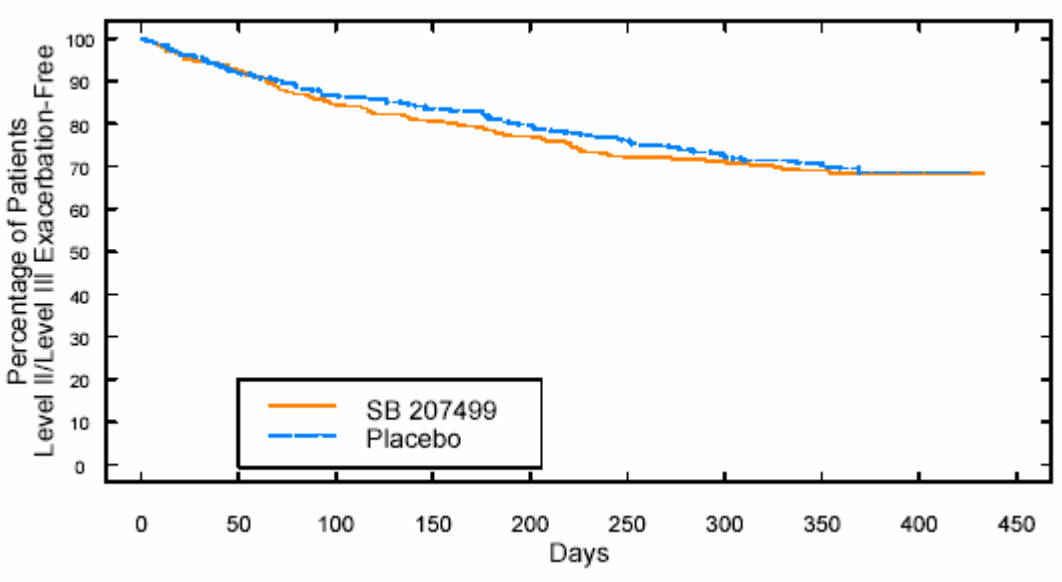
Treatment group	No. of subjects exacerbation free	% of subjects exacerbation free	95% CI	p value
Placebo	318	69.6	65.0 74.2	
Cilomilast	329	68.4	63.5, 73.3	0.637

1. Data source: 14.7C

The distribution of level II/III exacerbations by treatment group is presented graphically in Figure 19.7C and a Kaplin-Meier estimate of % of subjects who were level II/III exacerbation free in Figure 3. Graphical representations of the mean cumulative function for level II/III exacerbations for all randomised subjects and the distribution of all level II/III exacerbations is shown in Figure 19.7E and Figure 19.7C respectively. A Kaplin-

Meier estimate of the percentage of subjects which remained level II/III exacerbation free is also shown in Figure 19.7A.

Figure 3 Kaplan-Meier Estimates of Percentage of subjects who are level II/Level III Exacerbation-free ITT population



A summary of the poisson regression of prognostic factors for a level II/III exacerbation for all randomised subjects is presented in Table 14.7E. The percent predicted FEV_1 at study entry was a significant risk for COPD exacerbation ($p<0.001$) as was age ($p=0.0091$) and gender ($p=0.0335$). Neither smoking status ($p=0.7147$) or treatment ($p=0.7621$) proved to be a significant risk factor for a level II/III exacerbation.

7.2.2.2. Per-protocol population

A summary of level II/III exacerbation-free survival is presented in Table 29. There was no significant difference in the survival rate between the treatment groups. The exacerbation-free survival has been estimated using Kaplin-Meier estimate of time to first exacerbation.

Table 29 Summary of level II/III exacerbation-free survival - PP population

Treatment group	No. of subjects exacerbation free	% of subjects exacerbation free	95% CI	P value
Placebo	304	70.6	65.9, 75.3	
Cilomilast	316	69.4	64.4, 74.3	0.645

1. Data source: 14A.7C

A Kaplin-Meier estimate of % of subjects who were level II/III exacerbation free is presented in Figure 19A.7A.

A summary of the poisson regression of prognostic factors for a level II/III exacerbation for subjects in the PP population is presented in Table 14A.7E. The percent predicted FEV_1 at study entry was the only factor which was a significant risk for COPD exacerbation (p=0.0010). The effect of age (p=0.0073), gender (p=0.0424), smoking status (p=0.7475) and treatment (p=0.7512) did not prove to be a significant risk factor for a level II/III exacerbation.

7.2.3. Time to first COPD exacerbation (all levels)

7.2.3.1. All randomised subjects

A summary of exacerbation-free survival for all exacerbations is presented in Table 30. There was no significant difference in the survival rate between the treatment groups. The exacerbation-free survival has been estimated using Kaplin-Meier estimate of time to first exacerbation.

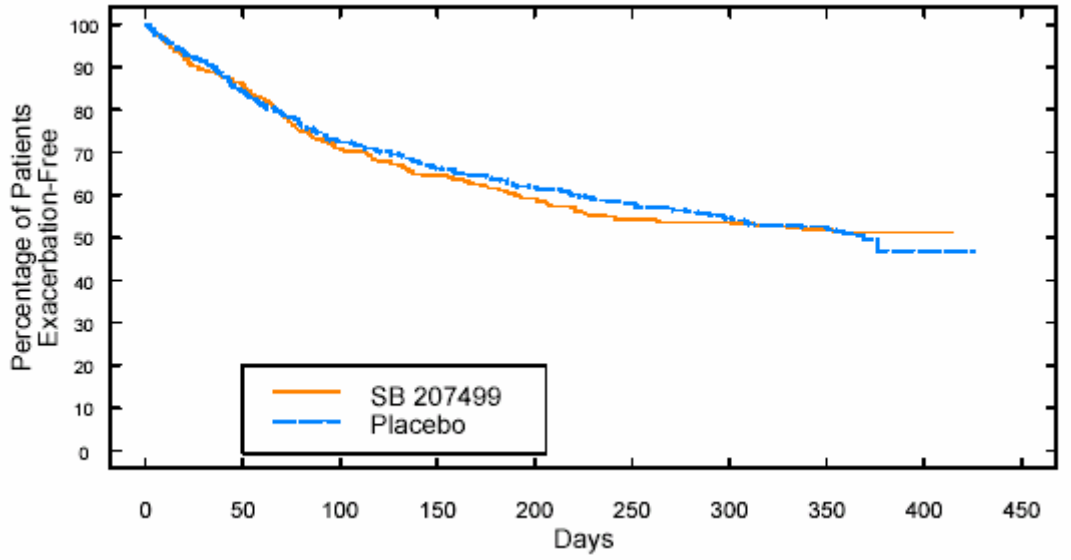
Table 30 Summary of exacerbation-free survival - all randomised subjects

Treatment group	No. of subjects exacerbation free	% of subjects exacerbation free	95% CI	P value
Placebo	240	50.7	45.7, 55.7	
Cilomilast	263	51.2	46.0, 56.5	0.952

1. Data source: 14.7D

The distribution of exacerbations by treatment group is presented graphically in Figure 19.7D and a Kaplin-Meier estimate of % of subjects who were exacerbation free in Figure 4. Graphical representations of the mean cumulative function for all exacerbations for all randomised subjects and the mean (95% CI) rate of all exacerbations per patient year in the ITT is shown in Figure 19.7F and Figure 19.L respectively.

Figure 4 Kaplan-Meier Estimates of Percentage of subjects who are Exacerbation-free – ITT population



A summary of the poisson regression of prognostic factors for time to first exacerbation for all exacerbations for randomised subjects is presented in Table 14.7F. The percent predicted FEV_1 at study entry was the only factor which was a significant risk for COPD exacerbation ($p<0.001$). The effect of age ($p=0.7171$), gender ($p=0.1636$), smoking status ($p=0.3055$) and treatment ($p=0.2040$) did not prove to be a significant risk factor for an exacerbation.

7.2.3.2. Per protocol population

A summary of exacerbation-free survival for all exacerbations is presented in Table 31. There was no significant difference in the survival rate between the treatment groups. The exacerbation-free survival has been estimated using Kaplin-Meier estimate of time to first exacerbation.

Table 31 Summary of exacerbation-free survival - PP population

Treatment group	No. of subjects exacerbation free	% of subjects exacerbation free	95% CI	P value
Placebo	229	51.6	46.5, 56.7	
Cilomilast	252	52.0	46.6, 57.3	0.945

1. Data source: 14A.7D

A Kaplin-Meier estimate of % of subjects who were exacerbation free is presented in Figure 19A.7B.

A summary of the poisson regression of prognostic factors for time to first exacerbation for subjects in the PP population showed that % predicted FEV_1 was the only factor which was a significant risk ($p<0.001$) (Table 14A.7F). The effect of age ($p=0.7818$), gender ($p=0.2507$), smoking status ($p=0.4070$) and treatment ($p=0.2321$) were not significant risk factors.

7.2.4. Incidence for all COPD exacerbations

7.2.4.1. All randomised subjects

A summary of the COPD exacerbation rate per patient year for all randomised subjects is presented in Table 32. There was no significant difference between the groups for the exacerbation rate per patient year. A rate of 0.909 per patient year was seen in subjects receiving placebo and 0.867 per patient year in subjects receiving cilomilast.

Table 32 COPD exacerbation rates per patient year - all randomised subjects

Treatment	Rate per patient year	95% CI	Incidence density ratio	95% CI	P value
Placebo	0.909	0.745, 1.110			
Cilomilast	0.867	0.712, 1.057	0.9537	0.775, 1.173	0.6541

1. Source Table: 14.7B Incidence density ratio is cilomilast relative to placebo.

The frequency of exacerbations of all levels is shown in Table 33. There were fewer subjects experiencing level I exacerbations (mild) in subjects receiving cilomilast. The number of subjects experiencing level II and III exacerbations was the same between the treatment groups.

Table 33 Frequency of COPD by exacerbation level - all randomised subjects

	No. of subjects (no. of exacerbations)					
	Placebo			Cilomilast		
	I	II	III	I	II	III
All subjects	120 (237)	110 (190)	17 (18)	95 (176)	108 (172)	15 (18)

1. Data Source: Table 14.7H. Levels are not mutually exclusive across subjects. Each exacerbation has one unique level but subjects can have multiple exacerbations of the same level.

A summary of the marginal regression analysis of time to multiple exacerbations in all randomised subjects gave a relative risk value of 1.0032 (p=0.9753). This relative risk was calculated based on the first four exacerbations per patient (Table 14.7R).

7.2.4.2. Per-protocol population

A summary of the COPD exacerbation rate per patient year in the PP population is presented in Table 14A.7B. There was no significant difference in the incidence density ratio as summarised in Table 34. A rate of 0.917 per patient year was seen in subjects receiving placebo and 0.872 per patient year in subjects receiving cilomilast.

Table 34 COPD exacerbation rates per patient year - PP population

Treatment	N	Rate per patient year	95% CI	Incidence density ratio	95% CI	P value
Placebo	414	0.905	0.739, 1.109			
Cilomilast	422	0.859	0.701, 1.052	0.9487	0.766, 1.176	0.6305

1. Data Source: Table 14A.7B. Incidence density ratio is cilomilast relative to placebo.

A summary of the COPD exacerbation rate per patient year by country is given in Table 14.7I. There were no significant differences between the treatment groups observed in any country.

7.2.5. Quality of life (SGRQ)

7.2.5.1. Total score

A summary of the average change from baseline over 52 weeks in the total score of the SGRQ in the ITT population is presented in Table 14.2A. When averaged over 52 weeks, there were mean decreases from baseline of -1.5 points in the placebo group and -1.3 points in the cilomilast group indicating an improvement relative to baseline in both groups. The mean difference between subjects receiving cilomilast and subjects receiving placebo was 0.202 points which was not significant (p=0.835).

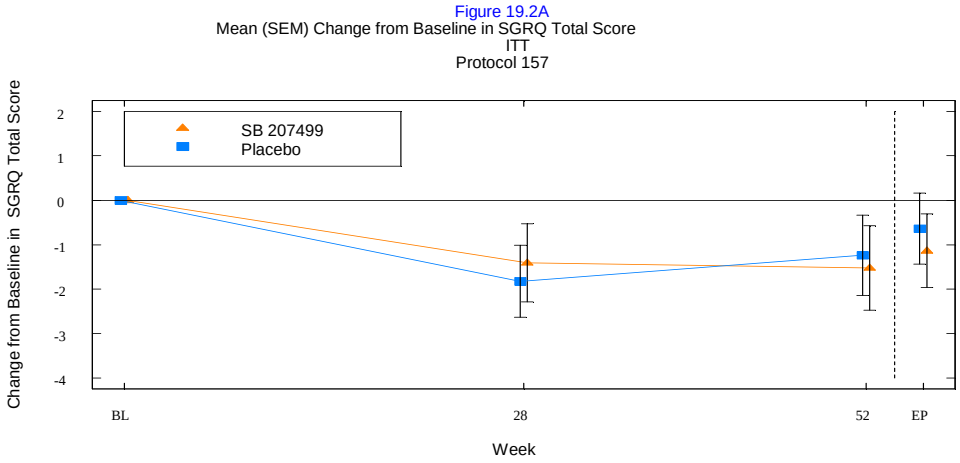
Summary statistics for the change from baseline in total score by week is presented in Table 14.2B. At week 28, 52 and study endpoint the mean difference between the two treatment groups in change from baseline was not significant. Analysis of change by week shows that placebo subjects reach maximum benefit at week 28 with a declining effect at week 52 and endpoint (-1.235 and -0.637 respectively). Alternatively the cilomilast group demonstrate an increasing effect towards week 52 (-1.522) with maximum differentiation over placebo at endpoint -0.499 although this is neither clinically of statistically significant at this point (p=0.627).

Descriptive statistics for the change from baseline in total score by week is presented in Table 14.2C.

Descriptive statistics for the change from baseline in total score at study endpoint by country and treatment group is presented in Table 14.2I.

A graphical representation of the mean (sem) change from baseline in total score of the ITT is presented in Figure 5. The ITT completers do not differ markedly from the ITT population and these are shown in Figure 19.2B.

Figure 5 Mean (SEM)Change from Baseline in SGRQ Total Score ITT population



7.2.5.2. Per-protocol population

No Per protocol analysis was undertaken for SGRQ endpoints.

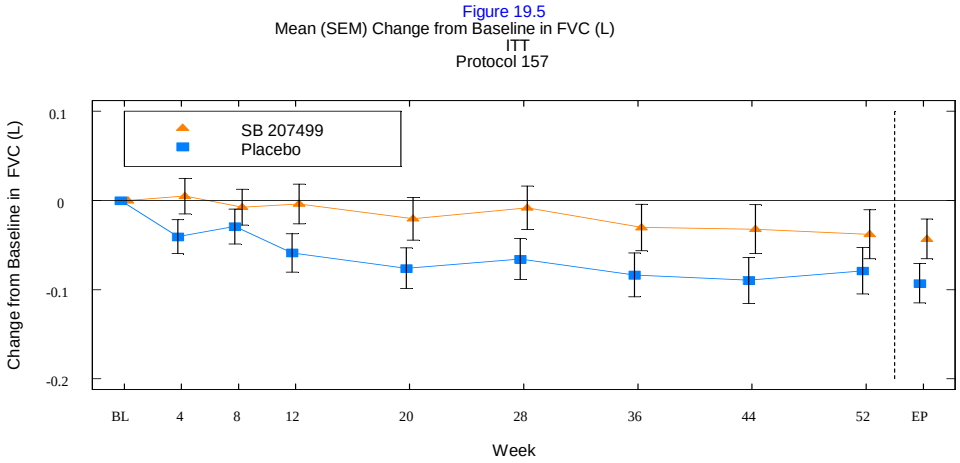
7.3. Other Efficacy Results

7.3.1. Pulmonary function parameters

7.3.1.1. Clinic FVC

A summary of the average change from baseline over 52 weeks in clinic visit trough FVC in the ITT population is presented in Table 14.5A. The mean change from baseline in FVC was larger in the placebo group (-0.068L) compared to the cilomilast group (-0.026L) with a mean difference in change from baseline between the groups of 0.042L which was significant (p=0.037). Summary statistics and descriptive statistics for the change from baseline and the change from baseline in comparison with placebo by week are presented in Table 14.5B and Table 14.5C. A graphical presentation of the mean (sem) change from baseline in trough FVC is shown in Figure 6.

Figure 6 Mean (SEM) Change from baseline in FVC (L) ITT population



7.3.1.2. Clinic PEF

A summary of the average change from baseline in trough clinic PEF over 52 weeks showed a mean change from baseline of -4.38L/min in the placebo group and 1.12L/min in the cilomilast group. This resulted in a mean treatment difference between the groups of 5.5L/min which was significant (p=0.023) (Table 14.9A). A summary of the change from baseline by week is summarised in Table 35. A significant difference between the groups in favour of cilomilast was seen at week 44, week 52 and at study endpoint.

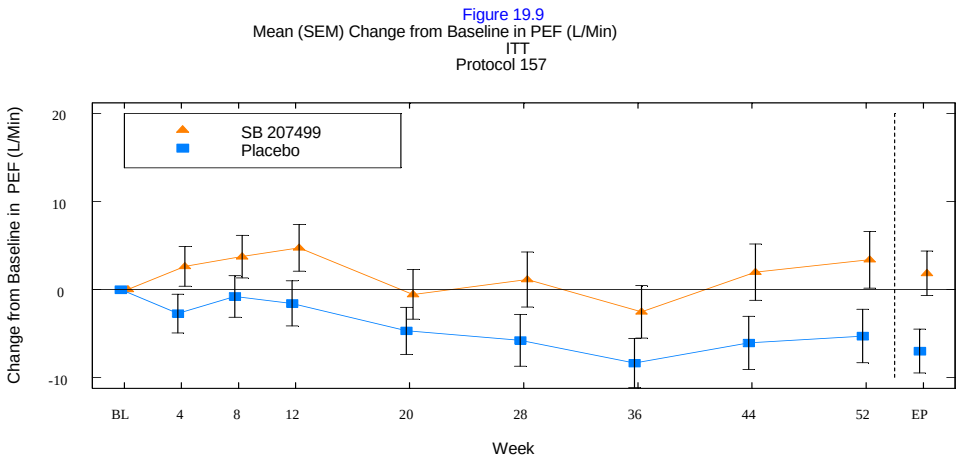
Table 35 Change from baseline in trough PEF by week - ITT population

Time from randomization	Comparison with placebo (L/min)			
	Mean difference	Lower 95% CI	Upper 95% CI	P value
Week 4	5.361	-0.105	10.826	0.055
Week 8	4.522	-1.362	10.407	0.132
Week 12	6.312	-0.091	12.716	0.053
Week 20	4.139	-2.537	10.814	0.224
Week 28	6.900	-0.525	14.325	0.068
Week 36	5.812	-1.259	12.884	0.107
Week 44	8.032	0.422	15.642	0.039*
Week 52	8.667	1.123	16.210	0.024*
Endpoint	8.840	2.627	15.054	0.005*

1. Data Source: Table 14.9B: * significantly different from placebo. Means adjusted for baseline value and country.

Descriptive statistics for the mean change from baseline in trough PEF by week and treatment group in the ITT population is presented in Table 14.9C. A graphical presentation of the mean (sem) change from baseline in trough PEF is shown in Figure 7.

Figure 7 Mean (SEM) Change in Baseline in PEF (L/min) ITT population



7.3.1.3. Clinic FEF_{25-75}

A summary of the average change from baseline in trough FEF_{25-75} in the ITT population over 52 weeks is summarised in Table 36. A summary of the change from baseline by week and change in comparison with placebo by week is presented in Table 14.24B. There was no statistical difference between the groups at any time point during the study.

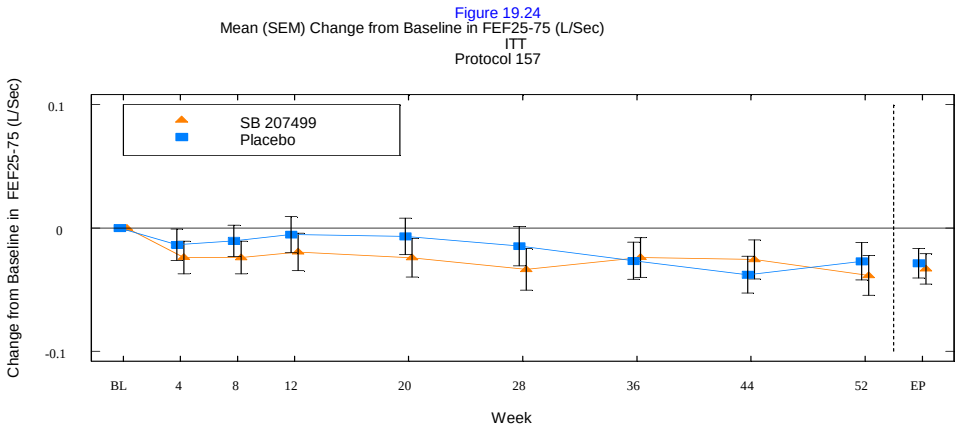
Table 36 Change from baseline over 52 weeks in trough FEF_{25-75} - ITT population

	Comparison with placebo (L/sec)			
	Mean difference	Lower 95% CI	Upper 95% CI	P value
Over 52 weeks	-0.010	-0.037	0.017	0.468

1. Data Source: Table 14.24A

Descriptive statistics for the mean change from baseline in trough FEF_{25-75} by week and treatment group in the ITT population is presented in Table 14.24C and a graphical presentation of the mean (sem) change from baseline in trough FEF_{25-75} is shown in Figure 8.

Figure 8 Mean (SEM) Change from Baseline in FEF25-75 (Lsec) ITT population



7.3.2. Residual volume

A summary of the change from baseline in residual volume by week is summarised in Table 37. No significant difference was seen between placebo and cilomilast groups. Total subject numbers were low (n = 23 and 21 for placebo and cilomilast respectively)

which precluded meaningful results. Descriptive statistics for the change from baseline in residual volume by week and treatment group is presented in Table 14.15C.

Table 37 Change from baseline in residual volume by week - ITT population

Week	Comparison with placebo (L)			
	Mean difference	Lower 95% CI	Upper 95% CI	P value
Week 28	0.379	-0.172	0.930	0.171
Week 52	0.304	-0.174	0.782	0.204
Endpoint	0.199	-0.329	0.727	0.450

1. Data Source: Table 14.15B.

7.3.3. Morning PEF from DRC

A summary of the average change from baseline in domiciliary PEF over 52 weeks showed a mean change from baseline of 3.2L/min in the placebo group and 3.3L/min in the cilomilast group. This resulted in a mean treatment difference between the groups of 0.304L/min which was not significant (p=0.831) (Table 14.10A). Summary statistics of the change from baseline by week and treatment group are presented in Table 14.10B. At no time point was the difference between the groups significant. Descriptive statistics are presented in Table 14.10C and a graphical presentation of mean (sem) change from baseline in domiciliary PEF in Figure 19.10.

7.3.4. Use of relief medication and % of days with no rescue medication

A summary of the average daily salbutamol inhaler use by week is presented in Table 38. Although there is a small reduction in inhaler use, this only reaches statistical significance at week 36 (-0.16, p=0.009). The percentage of days with no rescue medication is presented in Table 14.31. There is no difference between treatment groups at endpoint and no statistical difference between treatment groups at any time on therapy.

Table 38 Average daily inhaler use ITT population

time from randomization	Comparison with placebo (% days)	
	Mean	P value
Week 2	-0.59	0.068
Week 4	-0.11	0.232
Week 8	-0.04	0.149
Week 12	-0.13	0.105
Week 20	0.11	0.118
Week 28	-0.05	0.522
Week 36	-0.16	0.009
Week 44	-0.07	0.318
Week 52	-0.10	0.166
Endpoint	-0.55	0.144

1. Data Source: Table 14.31. Data are the % of the last 14 days prior to the visit without inhaler use.

7.3.5. Duration of exacerbations

The mean duration (days) of an exacerbation is given in summary in Table 39. The mean difference in duration between the groups was 8.35 days which was not statistically significant (p=0.325).

Table 39 Duration (days) of an exacerbation - all randomised subjects

			Comparison with placebo (days)	
Treatment	N	Mean ± SD	Mean ± SD	P value
Placebo	197	44.25 ± 65.1		
Cilomilast	179	35.90 ± 52.0	8.3 ± 59.2	0.325

1. Data Source: Table 14.7S

7.3.6. Symptom scores and symptom free days

A summary of the average change from baseline in the ITT population over 52 weeks of treatment in the summary symptom score is given in Table 14.4A. A mean improvement from baseline of -0.15 and -0.12 was seen in the placebo and cilomilast treatment groups respectively which resulted in a mean difference in change from baseline of 0.029 between cilomilast and placebo which was not significant (p=0.733). Summary statistics for the change from baseline in summary score by week and treatment groups are

presented in Table 14.4B and descriptive statistics for the change from baseline by week are presented in Table 14.4C.

A summary of the average change from baseline over 52 weeks of % symptom-free days is given in Table 14.6A in the ITT population. A mean improvement from baseline in % symptom free days of 0.018 and 0.009 was seen in the placebo and cilomilast treatment groups respectively. The mean difference in change from baseline of -0.008 between cilomilast and placebo was not significant (p=0.395). Summary statistics and descriptive statistics for the change from baseline by week in percent of symptom free days is presented in Table 14.6B and Table 14.6C. At no time point was the difference between the groups significant.

7.3.7. Diary card parameters

A summary of the average change from baseline over 52 weeks in diary card measured parameters in the ITT population is shown in Table 40. Over 52 weeks there was no statistical difference between the groups in cough, sputum and breathlessness. Summary statistics for the change from baseline by week showed that there was no statistical difference between the groups at any time point during the study for any of the measured parameters (Table 14.25B, Table 14.26B, Table 14.27B). Descriptive statistics for the change from baseline for cough, sputum and breathlessness are presented in Table 14.25C, Table 14.26C and Table 14.27C respectively.

The average daily breathlessness score, coughing score, sputum quantity and sputum colour by week showed that at no time point was there any statistical significance between placebo and cilomilast (Table 14.33, Table 14.34, Table 14.35, Table 14.36).

Table 40 Average change from baseline over 52 weeks in diary card measured parameters - ITT population

Parameter	Comparison with placebo (score)			
	Mean difference	Lower 95% CI	Upper 95% CI	P value
Cough	0.018	-0.038	0.073	0.531
Sputum	0.023	-0.028	0.074	0.371
Breathlessness	-0.042	-0.105	0.022	0.199

1. Data Source: Table 14.25A, Table 14.26A, Table 14.27A

Graphical presentation of the mean (sem) change from baseline in domiciliary cough, sputum and breathlessness are show in Figure 19.25, Figure 19.26 and Figure 19.27 respectively.

7.3.8. Night-time awakenings

A summary of the average number of night-time awakenings by week showed that there was no statistical difference between the groups at any time point (Table 14.32). At study

endpoint the mean difference between placebo and cilomilast was -0.53 which was not significant (p=0.786). The average number of night-time awakenings by week is shown in summary in Table 41.

Table 41 Average number of night-time awakenings - ITT population

Week	Comparison with placebo (awakenings)	
	Mean	P value
Week 2	-0.56	0.407
Week 4	-0.00	0.452
Week 8	0.01	0.903
Week 12	0.00	0.403
Week 20	0.01	0.379
Week 28	0.05	0.173
Week 36	0.06	0.890
Week 44	0.02	0.692
Week 52	0.02	0.583
Endpoint	-0.56	0.908

1. Data Source: Table 14.32. Data are the no. of awakenings averaged over the last 14 days prior to the visit.

7.3.9. SGRQ subscales (symptoms, activity and impact)

A summary of the average change from baseline in the ITT population in the individual SGRQ domains over 52 weeks is presented in Table 42. There was no statistical difference between the groups for any domain over 52 weeks or at week 28,week 52 and study endpoint (Table 14.21B, Table 14.22B, Table 14.23B).

Table 42 Average change from baseline over 52 weeks in individual domains of the SGRQ - ITT population

Week	Comparison with placebo (points)			
	Mean difference	Lower 95% CI	Upper 95% CI	P value
Activity	0.385	-2.058	2.828	0.757
Impact	0.387	-1.653	2.426	0.710
Symptoms	-0.549	-3.152	2.054	0.679

1. Data Source: Table 14.21A, Table 14.22A, Table 14.23A. Means are adjusted for baseline value, country and week.

Descriptive statistics for the change from baseline by week and treatment group is presented in Table 14.21C, Table 14.22C and Table 14.23C for the activity, impact and symptom scores respectively. A graphical representation of the mean change (sem) from

baseline in activity score, impact score and symptom score is also presented in Figure 19.21, Figure 19.22 and Figure 19.23 respectively.

7.3.10. Global subject assessment

A summary of the Investigator global assessment of efficacy is summarised in Table 43. At week 28, 52 and study endpoint, the number of subjects who had at least improved was greater in the cilomilast group compared to placebo.

Table 43 Patient global assessment of treatment efficacy - ITT population

			% subjects (score)								
Week	Treat-ment	n	Very much improved	Much improved	Improved	No change	Worse	Much worse	Very much worse	At least improved	P value
28	Placebo	364	3.8	17.3	28.3	39.3	7.7	2.5	0.3	49.5	0.1445
	Cilomilast	321	5.6	16.3	33.3	34.9	7.8	1.6	0.3	55.5	
52	Placebo	323	4.3	24.5	26.3	36.2	5.0	1.9	0.3	55.1	0.0609
	Cilomilast	279	6.8	23.7	32.6	28.3	6.1	1.8	0.0	63.1	
End	Placebo	390	4.1	21.8	24.1	35.4	6.9	5.1	1.0	50.0	0.2232
	Cilomilast	355	5.6	20.0	29.0	32.4	7.0	3.9	0.8	54.6	

1. Data Source: Table 14.42. p value analyses at least improved vs. no better

7.3.11. Global Investigator assessment

A summary of the Investigator global assessment of efficacy is summarised in Table 44. At week 28, 52 and study endpoint, the number of subjects who had at least improved was greater in the cilomilast group compared to placebo. At week 52 and study endpoint the number of subjects who had improved was significantly greater in the cilomilast group than the placebo group.

Table 44 Investigator global assessment of treatment efficacy - ITT population

			% subjects (score)								
Week	Treat-ment	n	Very much improved	Much improved	Improved	No change	Worse	Much worse	Very much worse	At least improved	P value
28	Placebo	365	1.4	11.5	29.6	47.1	7.1	1.4	0.0	42.5	0.1146
	Cilomilast	321	2.2	12.8	33.6	40.8	7.8	0.9	0.3	48.6	
52	Placebo	324	1.5	16.4	29.0	42.0	6.8	1.9	0.0	46.9	0.0077
	Cilomilast	279	3.2	17.9	37.3	33.7	5.4	1.4	0.0	58.4	
End	Placebo	390	1.3	14.4	27.2	41.0	9.2	4.1	0.5	42.8	0.0363
	Cilomilast	356	2.8	14.6	33.4	36.2	7.6	3.4	0.6	50.8	

1. Data Source: Table 14.41. p value analyses at least improved vs. no better

7.3.12. Blood CD4+/CD8+ ratio

There was no statistical difference between the groups for the change from baseline in blood CD4+/CD8+ ratio at either week 52 or study endpoint in the ITT population. A mean difference between the groups in change from baseline in favour of cilomilast of -0.029 (p=0.566) and -0.037 (p=0.450) was seen at week 52 and study endpoint respectively (Table 14.14B). Descriptive statistics of the change from baseline by week and treatment group is presented in Table 14.14C.

7.3.13. Serum C reactive protein

A summary of the change from baseline in serum C reactive protein at week 52 and study endpoint in the ITT population is summarised in Table 45. The change from baseline was not significant between the treatment groups at week 52 or study endpoint. Descriptive statistics for the change from baseline by week and treatment group is presented in Table 14.16C.

Table 45 Change from baseline in serum C reactive protein - ITT population

Week	Comparison with placebo (mg)			
	Mean difference	Lower 95% CI	Upper 95% CI	P value
Week 52	0.008	-0.007	0.023	0.315
Endpoint	0.000	-0.018	0.018	0.991

1. Data Source: Table 14.16B

7.4. Subgroup Analyses

7.4.1. Gender

7.4.1.1. Pre-bronchodilator trough FEV_1

Descriptive statistics for the change from baseline in pre-bronchodilator trough FEV_1 at study endpoint by gender is presented in Table 46. The increase in FEV_1 in females receiving cilomilast was higher than in males.

Table 46 Descriptive statistics for pre-bronchodilator FEV_1 at study endpoint by gender - ITT population

Gender	Treatment group (n)		Mean (SD) change from baseline (L)	
	Placebo	Cilomilast	Placebo	Cilomilast
Females	108	80	-0.017 (0.193)	0.016 (0.154)
Males	312	317	-0.072 (0.229)	-0.014 (0.223)

1. Data source: Table 14.1J.

7.4.1.2. COPD exacerbation rate

A summary of the COPD exacerbation rate per patient year by gender is given in Table 14.7J. There was no significant difference between the treatment and placebo in either gender group although the incidence density ratio (cilomilast relative to placebo) in females was more favourable at 0.8471 (p=0.4072) relative to the effect in Males 0.9530 (p=0.7081).

7.4.2. Percent Predicted FEV_1

7.4.2.1. Pre-bronchodilator trough FEV_1

Descriptive statistics for the change from baseline in pre-bronchodilator trough FEV_1 at study endpoint by COPD severity according to the ATS classification is presented in Table 47. Difference over placebo reaches a maximum in the moderate subjects (74mls). Mild subjects show a difference of 42mls and severe subjects -9mls.

Table 47 Descriptive statistics for pre-bronchodilator FEV_1 at study endpoint by ATS severity - ITT population

Severity	Treatment group (n)		Mean (SD) change from baseline (L)	
	Placebo	Cilomilas	Placebo	Cilomilast
Mild	258	209	-0.059 (0.245)	-0.017 (0.224)
Moderate	139	148	-0.059 (0.180)	0.015 (0.196)
Severe	21	44	-0.028 (0.152)	-0.037 (0.200)
Unknown	2	2	-0.205 (0.219)	0.010 (-0.085)

1. Data source: Table 14.1K.

7.4.2.2. COPD exacerbation rate

A summary of the COPD exacerbation rate per patient year by ATS severity is given in Table 14.7K. Exacerbation rates increased with FEV_1 severity. There were no significant differences between the treatments in any of the subgroups observed for any severity, although the incidence density ratio (cilomilast relative to placebo) for most favourable in the severe group (mild 0.8509 (p=0.3051), moderate 0.9398 (p=0.7073) and severe 0.7190 (p=0.3454).

7.4.3. Smoking Status

7.4.3.1. Pre-bronchodilator trough FEV_1

7.4.3.1.1. ITT Population

For all subjects in the ITT population, the average change from baseline over 52 weeks in trough FEV_1 was significantly greater in subjects receiving cilomilast compared to placebo for all subjects irrespective of their smoking history. Table 48 summarises the difference in the mean change from baseline in pre-bronchodilator trough FEV_1 between subjects receiving cilomilast and placebo over 52 weeks by smoking status. A significant difference in the change from baseline was seen in subjects who were both smokers and non-smokers at baseline and throughout the study. The largest difference was however seen in subjects who were smokers. For subjects who changed their smoking status during the study, a non significant increase in trough FEV_1 was seen over 52 weeks in subjects receiving cilomilast compared to placebo.

Table 48 Mean difference between treatment groups in pre-bronchodilator trough FEV_1 over 52 weeks in the ITT population by smoking status

Smoking status			Comparison with placebo (L)			
	Placebo N	Cilomilast N	Mean difference	Lower 95% CI	Upper 95% CI	P value
Smokers at baseline:	180	179	0.049	0.014	0.083	0.006*
Non-smokers at baseline	236	216	0.038	0.009	0.066	0.011*
Smokers throughout	143	148	0.046	0.007	0.085	0.021*
Non-smokers throughout	216	205	0.037	0.007	0.067	0.016*
Changed status during	57	42	0.028	-0.030	0.086	0.344

1. Data Source: Table 14.1A: * significantly different from placebo. Means adjusted for baseline, country and week.

Summary statistics for the change from baseline in pre-bronchodilator FEV_1 by week in subjects by smoking status throughout the study is presented in Table 14.1BS through to Table 14.1BW.

Summary statistics for the change from baseline in pre-bronchodilator FEV_1 by week in subjects who were smokers at baseline is presented in Table 14.1BS. A significant difference between cilomilast and placebo in favour of cilomilast was seen at week 4, 12, 20, 28 and 44. The largest difference between the groups was seen at week 28 where a difference of 0.067L was observed (p=0.009). A significant difference was also seen between the groups at the same time points for subjects who were smokers throughout the study (Table 14.1BU). The largest difference between the groups was seen at week 44 where a difference of 0.083L was observed (p=0.008). At endpoint the difference of 0.046L showed a trend towards significant (P= 0.0051).

Summary statistics for the change from baseline in pre-bronchodilator FEV_1 by week in subjects who were non-smokers at baseline is presented in Table 14.1BT. A significant difference between cilomilast and placebo in favour of cilomilast was seen at week 12, 20, 44 and 52. The largest difference between the groups was seen at week 44 where a difference of 0.082L was observed (p=0.009). A significant difference was also seen between the groups at week 12, 28 and 44 for subjects who were non-smokers throughout the study (Table 14.1BV). The largest difference between the groups was seen at week 44 where a difference of 0.054L was observed (p=0.019).

For the small number of subjects (n=99) who changed their smoking status from baseline during the treatment period, there was no significant difference between the groups at any time point (Table 14.1BW). Change at endpoint was 0.038L (p=0.128).

Descriptive statistics for the change from baseline by week and treatment group for the ITT population is presented in Table 14.1C. Descriptive statistics for the change at each

visit split into smokers at baseline (Table 14.1CS) and non-smokers (Table 14.1CT) and for those subjects who were smokers throughout the study (Table 14.1CU), non-smokers throughout the study (Table 14.1CV) and those that changed smoking status during the study (Table 14.1CW) are presented.

7.4.3.1.2. Per protocol population

For all subjects in the PP population, the average change from baseline over 52 weeks in trough FEV_1 was significantly greater in subjects receiving cilomilast compared to placebo for all subjects irrespective of their smoking history. The change was slightly greater than in the ITT in all sub-populations of subjects categorised by smoking status.

Table 49 summarises the difference in the mean change from baseline in pre-bronchodilator trough FEV_1 between subjects receiving cilomilast and placebo over 52 weeks by smoking status. A significant difference in the change from baseline was seen in subjects who were both smokers and non-smokers at baseline and throughout the study. The largest difference was however seen in subjects who were smokers. For subjects who changed their smoking status during the study, a non significant increase in trough FEV_1 was seen over 52 weeks in subjects receiving cilomilast compared to placebo.

Table 49 Mean difference between treatment groups in pre-bronchodilator trough FEV_1 over 52 weeks in the PP population by smoking status

Smoking status			Comparison with placebo (L)			
	Placebo N	Cilomilast N	Mean difference	Lower 95% CI	Upper 95% CI	P value
Smokers at baseline:	164	157	0.048	0.013	0.083	0.007*
Non-smokers at baseline	194	174	0.039	0.010	0.068	0.009*
Smokers throughout	130	129	0.046	0.007	0.086	0.023*
Non-smokers throughout	179	167	0.040	0.010	0.070	0.009*
Changed status during	49	35	0.031	-0.031	0.094	0.324

1. Data Source: Table 14A.1A: * significantly different from placebo. Means adjusted for baseline, country and week.

Summary statistics for the change from baseline in pre-bronchodilator FEV_1 by week in subjects who were smokers at baseline is presented in Table 14A.1BS. A significant difference between cilomilast and placebo in favour of cilomilast was seen at week 4, 20, 28, 44 and 52, although when adjusted for multiplicity data at weeks 20, 44 and 52 fail to reach statistical significant levels of $P<0.025$. The largest difference between the groups was seen at week 28 where a difference of 0.066L was observed ($p=0.019$). A significant difference was also seen between the groups at weeks 4, 20 and 44 for subjects who were

smokers throughout the study (Table 14A.1BU). The largest difference between the groups was seen at week 44 where a difference of 0.081L was observed (p=0.022).

Summary statistics for the change from baseline in pre-bronchodilator FEV_1 by week in subjects who were non-smokers at baseline is presented in Table 14A.1BT. A significant difference between cilomilast and placebo in favour of cilomilast was seen at week 4, 12, 20, 44 and endpoint, although when adjusted for multiplicity weeks 44 and endpoint do not reach the required level of p=0.025. The largest difference between the groups was seen at week 12 where a difference of 0.053L was observed (p=0.007). A significant difference was also seen between the groups at week 12 and 20 for subjects who were non-smokers throughout the study (Table 14A.1BV). The largest difference between the groups was seen at week 20 where a difference of 0.058L was observed (p=0.011).

For the small number of subjects who changed their smoking status from baseline during the treatment period (n=84), there was no significant difference between the groups at any time point (Table 14A.1BW).

Descriptive statistics for the change from baseline by week and treatment group for the PP population is presented in Table 14A.1C. Descriptive statistics for the change at each visit split into smokers at baseline (Table 14A.1CS) and non-smokers (Table 14A.1CT) and for those subjects who were smokers throughout the study (Table 14A.1CU), non-smokers throughout the study (Table 14A.1CV) and those that changed smoking status during the study (Table 14A.1CW) are presented.

7.4.3.2. COPD exacerbation rate level II/III

7.4.3.2.1. All randomised subjects

A summary of level II/III exacerbation rates per patient year by smoking status is given in Table 50 and level II/III exacerbation free survival in Table 14.7C. Former smokers had both higher rate of exacerbations and a lower exacerbation free survival although Smoking status did not significantly impact the treatment effect on exacerbations.

Table 50 Summary of smoking status on the exacerbation rate of level II/III exacerbations - all randomised subjects

Smoking status	Placebo Rate per year	Cilomilast Rate per year	Incidence density ratio	P value
Smoker at baseline	0.537	0.487	0.9076	0.6555
Non-smoker at baseline	0.581	0.641	1.1044	0.5945
Smoker throughout study	0.437	0.469	1.0730	0.7879
Non-smoker throughout study	0.622	0.636	1.0230	0.9053
Changed status	0.659	0.587	0.8915	0.7555

1. Data Source: Table 14.7T; Incidence density ratio is cilomilast relative to placebo

7.4.3.2.2. Per protocol population

A summary of level II/III exacerbation-free survival by smoking status at 52 weeks in the PP population is presented in Table 14A.7C. The number of subjects who remained exacerbation free was similar between placebo and cilomilast in each smoking status sub-group, with no significant differences observed between the groups.

7.4.3.3. Post-bronchodilator trough FEV_1

For all subjects in the ITT population, the average change from baseline over 52 weeks in trough post-bronchodilator FEV_1 was significantly greater in subjects receiving cilomilast compared to placebo (Table 14.3A). A significant treatment difference was also seen in subjects who were non-smokers at baseline and were either smokers or non-smokers during the double-blind period (mean difference 0.037L: 95% CI, 0.007, 0.068; p=0.017). For subjects who were non-smokers throughout the study, the mean difference between the groups was statistically significant (difference 0.033L; 95% CI, 0.001, 0.065; p=0.041). For subjects who were smokers throughout the study or who changed their smoking status during the study, the difference between the groups was not significant (difference 0.030L; 95% CI, -0.010, 0.070; p=0.145 and 0.026L; 95% CI -0.041, 0.094; p=0.444 respectively). Summary statistics for the change from baseline in post-bronchodilator FEV_1 in the ITT population by week in subjects by smoking status throughout the study is presented in Table 14.3BS to Table 14.3BW.

Descriptive statistics for the change from baseline by week and treatment group for the ITT population is presented in Table 14.3CS to Table 14.3CW.

7.4.3.4. Time to first level 2 (moderate) or level 3 (severe) COPD exacerbation

7.4.3.4.1. All randomised subjects

A summary of level II/III exacerbation-free survival by smoking status is presented in Table 51. There was no significant treatment difference in the survival rate within any of the populations. The exacerbation-free survival has been estimated using Kaplin-Meier estimate of time to first exacerbation.

Table 51 Summary by smoking status of number (%) of subjects which remained exacerbation-free of level II/III exacerbations at 52 weeks

Smoking status	Placebo N (%)	Cilomilast N (%)	P value
All subjects	318 (70)	329 (68)	0.637
Smoker at baseline	136 (70)	145 (69)	0.869
Non-smoker at baseline	182 (69)	184 (68)	0.619
Smoker throughout study	114 (75)	116 (69)	0.293
Non-smoker throughout study	158 (67)	166 (69)	0.939
Changed status	38 (63)	29 (66)	0.846

1. Data Source: Table 14.7C

7.4.3.5. Time to first COPD exacerbation (all levels)

7.4.3.5.1. All randomised subjects

A summary of exacerbation-free survival by smoking status is presented in Table 52. There was no significant treatment difference in the survival rate within any of the populations. The exacerbation-free survival has been estimated using Kaplin-Meier estimate of time to first exacerbation.

Table 52 Summary by smoking status of number (%) of subjects which remained exacerbation-free of all exacerbations at 52 weeks

Smoking status	Placebo N (%)	Cilomilast N (%)	P value
All subjects	240 (51)	263 (51)	0.952
Smoker at baseline	99 (49)	112 (51)	0.707
Non-smoker at baseline	141 (52)	151 (52)	0.677
Smoker throughout study	83 (53)	88 (50)	0.730
Non-smoker throughout study	119 (49)	136 (53)	0.728
Changed status	31 (51)	22 (49)	0.847

1. Data Source: Table 14.7D

7.4.3.5.2. Per protocol population

A summary of exacerbation-free survival for all exacerbations by smoking status is presented in Table 14A.7D. There was no significant difference in the survival rate between any of the populations.

7.4.3.6. Incidence for all COPD exacerbations

7.4.3.6.1. All randomised subjects

A summary of annual exacerbation rate for all exacerbations by smoking status is given in Table 53. Continuous smokers and baseline smokers had higher exacerbation rates within the placebo arm and similar rates in the active treatment arm. This resulted in a marginally more favourable incidence density ratio in smokers. However, the treatment difference was not significant in any of the subgroups.

Table 53 Summary of smoking status on the exacerbation rate of all exacerbations per patient year - all randomised subjects

Smoking status	Placebo Rate per year	Cilomilast Rate per year	Incidence density ratio	P value
Smoker at baseline	1.351	1.078	0.7981	0.1561
Non-smoker at baseline	1.084	1.115	1.0284	0.8495
Smoker throughout study	1.333	1.112	0.8341	0.3213
Non-smoker throughout study	1.145	1.104	0.9638	0.8079
Changed status	1.050	0.979	0.9323	0.8007

1. Data Source: Table 14.7U; Incidence density ratio is cilomilast relative to placebo

The frequency of all levels of exacerbations by smoking status is summarised in Table 54. Subjects receiving cilomilast had a small reduction in the number of subjects experiencing a level I exacerbation and the number of level I exacerbations in all populations when compared to placebo. The number of subjects of level II and III exacerbations was similar between the subgroups.

Table 54 Frequency and rate of COPD by exacerbation level and smoking status - all randomised subjects

	No. of subjects (no. of exacerbations)					
	Placebo			Cilomilast		
	I	II	III	I	II	III
All subjects	120 (237)	110 (190)	17 (18)	95 (176)	108 (172)	15 (18)
Smokers at baseline	57 (132)	47 (77)	9 (10)	47 (91)	48 (70)	5 (5)
Non-smokers at baseline	63 (105)	63 (113)	8 (8)	48 (85)	60 (102)	10 (13)
Smokers throughout study	46 (117)	32 (54)	3 (3)	41 (81)	39 (55)	4 (4)
Non Smokers throughout study	60 (100)	62 (112)	7 (7)	45 (80)	55 (96)	10 (13)
Changed status	13 (19)	16 (24)	7 (8)	8 (14)	13 (20)	1 (1)

1. Data Source: Table 14.7H. Levels are not mutually exclusive across subjects. Each exacerbation has one unique level but subjects can have multiple exacerbations of the same level.

7.4.3.6.2. Per-protocol

A summary of exacerbation-free survival by smoking status at 52 weeks in the PP population is presented in Table 14A.7D. The number of subjects who remained exacerbation free was similar between placebo and cilomilast in each smoking status sub-group, with no significant differences observed between the groups.

7.4.3.7. Quality of life (SGRQ) - total score

The mean treatment difference in SGRQ total score fails to reach statistical significance at any point during the study within any of the smoking subgroups. Improvement from baseline is more notable in the smokers than non-smokers. Smokers show an increased treatment effect with time due to a decline in the placebo group over weeks 24 to 52 and a maximum treatment effect relative to placebo at week 52(-1.079 p=0.539). Non smokers show limited change from baseline in either placebo or cilomilast subjects with a maximum effect seen at endpoint for consistent non smokers of -1.145 (p=0.437). This is summarised in Table 55. Descriptive statistics for the effect of smoking status on the change from baseline in total SGRQ at week 28, 52 and study endpoint are presented in Table 14.2C, Table 14.2CS, Table 14.2CT, Table 14.2CU, Table 14.2CV and Table 14.2CW.

Table 55 Change from baseline in total SGRQ score by smoking status - comparison with placebo

Subjects	Comparison with placebo (points)	
	Mean difference	P value
All subjects average over 52 weeks	0.202	0.835
All subjects study endpoint	-0.499	0.627
Baseline Smokers study endpoint	-0.325	0.832
Baseline non-smokers study endpoint	-0.698	0.622
Smokers throughout study- study endpoint	0.104	0.952
Non-smokers throughout study - study endpoint	-1.145	0.437
Change in smoking status during study-study endpoint	-0.837	0.822

1. Data Source: Table 14.2A, Table 14.2B, Table 14.2BS, Table 14.2BT, Table 14.2BU, Table 14.2BV, Table 14.2BW

7.5. Efficacy Conclusions

- The average change from baseline over 52 weeks in pre-bronchodilator trough FEV_1 was significantly greater in subjects receiving cilomilast (0.041L) compared to placebo. The difference between the groups in change from baseline was clinically significant as early as 4 weeks after the start of treatment and was maintained

throughout the 52-week period (0.045L at week 52 p=0.010) in this population of poorly reversible subjects.

- A significant difference in the change from baseline in pre-bronchodilator trough FEV_1 was seen in subjects who were both smokers and non-smokers at baseline and throughout the study. However, the largest difference was seen in subjects who were smokers at baseline (0.049L mean change over 52 weeks, p=0.006).
- Subjects treated with cilomilast broadly maintained FEV_1 at baseline levels until endpoint, with the treatment difference (0.046L) produced by a more rapid decline in the placebo group (-0.061 vs. -0.015L on cilomilast at endpoint).
- There was no significant difference between the treatment groups over 52 weeks of treatment for level II/III COPD exacerbation rates per treatment year in the ITT or PP population.
- Exacerbation rates were significantly lower than predicted for both treatment arms 0.448 and 0.483 for placebo and cilomilast respectively compared with an estimated placebo group rate of 0.8 used to power the study.
- There was a significant improvement in the average change from baseline over 52 weeks in trough post bronchodilator FEV_1 (0.034L, p=0.004) which was maintained at endpoint (0.053L, p=0.001)
- There was also significant differences between cilomilast and placebo in improving clinic visit PEF (5.5L/min, p=0.023) and FVC (0.042L, p=0.037) both averaged over 52 weeks.
- No significant difference was seen in FEF_{25-75} or RV.
- At week 52, both the patient and Investigator global assessment of efficacy resulted in more subjects being categorised as improved in the cilomilast group compared to the placebo group.
- There was no statistical difference between cilomilast and placebo for any domain of the SGRQ, symptoms (cough, sputum, breathlessness), use of relief medication and night-time awakenings.
- There was also no statistical difference observed in the ratio of blood CD4+/CD8+ and serum C reactive protein between cilomilast and placebo.

8. SAFETY RESULTS

8.1. Extent of Exposure

The extent of exposure to study medication is summarised in Table 15.1A. and Table 56. A total of 907 subjects received study medication. The mean treatment exposure was higher in the placebo group (309.5 days) compared to cilomilast (275.4 days) (Table 15.1B).

A similar proportion of subjects in each treatment group received study medication for the entire treatment period, with 165 subjects (36%) in the placebo group and 155 subjects (34%) in the cilomilast group receiving study medication for more than 364 days.

Table 56 Summary of Exposure to study medication

Days exposure	Placebo (n=452)	Cilomilast (n=455)
Mean (SD)	309.5 (112.5)	275.4 (137.6)
Median (range)	364 (1 - 426)	363 (1 - 433)
< 14 days (%)	14 (3.1)	22 (4.8)
15-28 (%)	8 (1.8)	21 (4.6)
29-84 (%)	26 (5.8)	44 (9.7)
85-196 (%)	27 (6.0)	44 (9.7)
197-308 (%)	31 (6.9)	25 (5.3)
309-364 (%)	181 (40)	144 (31.6)
>364 (%)	165 (36.5)	155 (34.1)

1. Data Source: Table 15.1B, Table 15.1A

8.2. Adverse Events

8.2.1. On-therapy Adverse Events

Table 15.2A to Table 15.2B summarise the on-therapy AEs by preferred term and by MeDRA preferred term.

Overall, 343 (76%) subjects in the placebo group and 351 (77%) in the cilomilast group reported an AE that started on-therapy. Table 57 gives an overall summary of the numbers of AEs that occurred on-therapy.

Table 57 Number of subjects with Adverse Events on-therapy - safety population

Event	Placebo, N (%) N=452	Cilomilast, N (%) N=455
Any AE	343 (75.9)	351 (77.1)
Any SAE	55 (12.2)	53 (11.6)
Drug-related AE	47 (10.4)	98 (21.5)
Withdrawn due to AE	40 (8.8)	75 (16.5)
Any AE requiring a change in medication	288 (63.7)	285 (63.2)

1. Data Source: Table 15.2A, Table 15.3, Table 15.7, Table 15.8B, Table 15.9A

The most commonly reported AE on-therapy was exacerbation of COPD in both treatment groups (46% placebo vs. 42% cilomilast). As expected, the body system with the highest number of AEs reported was the Respiratory, Thoracic and Mediastinal disorder system (53% placebo, 48% cilomilast) (Table 15.2B). AEs related to Infections and Infestations were the second most commonly reported AEs in both treatment groups (29% placebo, 28% cilomilast) followed by events related to the Gastrointestinal body system (15% placebo, 28% cilomilast).

Events of the GI system display a two fold increase in prevalence between cilomilast and placebo. This is largely driven by increases in abdominal pain/discomfort, diarrhoea, dyspepsia, nausea and vomiting. Events of the GI system are investigated specifically within this protocol and are reference in more detail in following sections.

The most commonly reported events occurring in >4% of subjects in either treatment group are summarised in Table 58.

Table 58 Most commonly (reported by >4% of subjects) in either treatment group reported Adverse Events on-therapy - safety population

Event	Placebo N (%) N=452	Cilomilast N (%) N=455
Any AE	343 (75.9)	351 (77.1)
Exacerbation of COPD	209 (46.2)	191 (42.0)
Nasopharyngitis	54 (11.9)	43 (9.5)
Nausea	14 (3.1)	44 (9.7)
Headache	22 (4.9)	35 (7.7)
Diarrhoea	13 (2.9)	33 (7.3)
Hypertension	18 (4.0)	13 (2.9)
Vomiting	8 (1.8)	21 (4.6)
Back pain	20 (4.4)	6 (1)
Dyspepsia	6 (1.3)	18 (4.0)
Anorexia	1 (0.2)	18 (4.0)

1. Source Data: Table 15.2A.

8.2.1.1. Drug-related Adverse Events

A summary of on-therapy AEs considered by the Investigator to be related to study medication is presented in Table 15.3. There were twice as many events reported in the cilomilast group, the majority of which were related to the GI body system. The incidence of other drug-related AEs was similar between the two treatment groups. The most common drug-related AEs were nausea, headache and diarrhoea. Table 59 summarises the most common events occurring in >1% of subjects in any treatment group.

Table 59 Most common (reported by >1% of subjects in either treatment group) Adverse Events assessed as related to study medication - safety population

Event	Placebo N (%) N=452	Cilomilast N (%) N=455
Any drug related AE	47 (10.4)	98 (21.5)
Nausea	5 (1.1)	33 (7.3)
Diarrhoea	6 (1.3)	20 (4.4)
Headache	6 (1.3)	12 (2.6)
Vomiting	3 (0.7)	11 (2.4)
Dyspepsia	2 (0.4)	10 (2.2)
Exacerbation of COPD	6 (1.3)	8 (1.8)
Upper abdominal pain	2 (0.4)	9 (2.0)
Abdominal pain	1 (0.2)	8 (1.8)
Anorexia	0	7 (1.5)
Dizziness	0	7 (1.5)

1. Data Source: Table 15.3

8.2.1.2. Intensity of Adverse Events

The incidence of AEs by Investigator-determined intensity is presented in Table 15.4. The incidence of events determined as being of severe intensity was similar between the groups with 50 subjects (11%) in the placebo group and 49 subjects (11%) in the cilomilast group with an event determined as severe. The only events which were classified as severe in >1% of subjects in either treatment was an exacerbation of COPD in 15 subjects (3.3%) receiving placebo and 17 subjects (3.7%) receiving cilomilast and nausea in 6 subjects (1.3%) receiving cilomilast. Severe gastrointestinal disorders totalled 1.1% in the placebo group and 3.1% in the cilomilast group.

8.2.1.3. Time to onset

The incidence of AEs (which have been experienced by ≥ 2% of subjects in any treatment group) by initial time of onset is shown in Table 15.5. The most common AEs experienced within one day of study treatment with cilomilast were nausea, dyspepsia and headache and headache with placebo (Table 60).

Table 60 Incidence of on-therapy experiences experienced by >= 4 subjects in any treatment group by time of onset within the first 28 days of treatment- Safety population

	Days relative to first study medication dose				
	1	2-7	8-14	15-21	22-28
Placebo	N (%)	N (%)	N (%)	N (%)	N (%)
Total with AEs	13 (2.9)	37 (8.2)	36 (8.1)	32 (7.3)	31 (7.1)
COPD	0	11 (2.4)	12 (2.7)	9 (2.1)	4 (0.9)
Nasopharyngitis	0	4 (0.9)	1 (0.2)	3 (0.7)	3 (0.7)
Headache	1 (0.2)	2 (0.4)	2 (0.4)	3 (0.7)	0
Cilomilast					
Total with AEs	25 (5.5)	62 (13.7)	46 (10.4)	47 (10.9)	39 (9.4)
COPD	1 (0.2)	10 (2.2)	13 (2.9)	12 (2.8)	9 (2.2)
Nausea	4 (0.9)	18 (4.0)	3 (0.7)	4 (0.9)	1 (1.2)
Diarrhoea	3 (0.7)	10 (2.2)	3 (0.7)	2 (0.5)	4 (1.0)
Headache	4 (0.9)	9 (2.0)	3 (0.7)	4 (0.9)	2 (0.5)
Dyspepsia	4 (0.9)	4 (0.9)	2 (0.5)	2 (0.5)	2 (0.5)
Vomiting	2 (0.4)	1 (0.2)	0	4 (0.9)	1 (0.2)
Anorexia	0	4 (0.9)	3 (0.7)	1 (0.2)	0
Dizziness	0	4 (0.9)	0	2 (0.5)	1 (0.2)

1. Data Source: Table 15. 5

Within the placebo group the highest percentage of new AEs occurred in week one (11.1%) with a total of 33.4% of subjects experiencing an AE in the first 28 days. This compares with 19.3 % of cilomilast subjects with an AE within the first week and 49.4% of patient experiencing an AE in the 28 days. Post day 28 the AE rates are more similar between the two arms and showed a decline with time of 24.7% declining to 12.3% between day 29-56 and 141-168 in the placebo arm and 21.8% declining to 13.0% over the same period of time in the cilomilast arm. Post day 168 AEs were seen in 46.9% of placebo subjects and 43.9% of cilomilast subjects. GIAE's had reduced to 1.8% in the placebo group and 2.7% in the cilomilast group within the post day 168 interval.

8.2.1.4. Adverse Events leading to an interruption in study medication

The AEs which resulted in an interruption in study medication are summarised in Table 15.6. In the placebo group, a total of 24 events (5.3%) resulted in an interruption in medication compared to 40 events (8.8%) in the cilomilast group. Three events occurred in >1% of subjects in any treatment group; nausea in 4 subjects (0.9%) receiving placebo and 6 subjects (1.3%) receiving cilomilast, exacerbation of COPD by 4 subjects (0.9%) and 6 subjects (1.3%) and headache by 3 subjects (0.7%) and 5 subjects (1.1%) respectively.

8.2.1.5. Post-treatment Adverse Events

A summary of AEs reported post-treatment is presented in Table 15.10 and is summarised in Table 61 for AEs occurring in three or more subjects in any treatment group. The most common event was pneumonia reported by seven subjects (3 subjects placebo; 4 subjects cilomilast).

Table 61 Most common(reported by >= 3 subjects in either treatment group) Adverse Events Post-treatment - safety population

Event	Placebo N (%) N=452	Cilomilast N (%) N=455
Total post-treatment events	55 (12.2)	67 (14.7)
Pneumonia	3 (0.7)	4 (0.9)
Nausea	2 (0.4)	3 (0.7)
Hypertension	5 (1.1)	1 (0.2)
Headache	3 (0.7)	1 (0.2)
Back pain	3 (0.7)	0

1. Data Source: Table 15.10

8.3. Serious Adverse Events

8.3.1. Fatal Events

A fatal outcome was reported in twelve subjects during the study period (eight receiving placebo and four receiving cilomilast), all of which were assessed as unrelated to study medication (Table 15.8B). Narratives are provided for all deaths in Section 16.3.

8.3.2. Non-Fatal Events

8.3.2.1. Run-in

The incidence of SAEs, which occurred during the run-in period are summarised in Table 15.8A. There were no SAEs reported in subjects who were subsequently randomised to receive placebo. In subjects who were subsequently randomised to receive cilomilast, 3 subjects had a total of 4 SAEs which included chronic respiratory failure,

secondary polycythaemia, upper abdominal pain and dysthymic disorder. A total of 11 subjects who were not randomised had a SAE, of which all were exacerbations of COPD.

8.3.2.2. On-therapy

The incidence of SAEs which occurred on-therapy are summarised in Table 15.8B. A similar number of subjects developed a SAE in each treatment group with 55 subjects (12.2%) of subjects receiving placebo and 53 subjects (11.6%) receiving cilomilast experiencing a SAE. The most common SAE reported in both groups was an exacerbation of COPD, involving 18 subjects (4%) in the placebo group and 19 subjects (4%) in the cilomilast group. Details of events which occurred in two subjects or more are summarised in Table 62.

Five subjects experienced a SAE which was assessed as possibly or probably related to study medication. All subjects received cilomilast. These are summarised in Table 63.

Table 62 Most common (reported by >=2 subjects in either treatment group) Serious Adverse Events reported on-therapy - safety population

Event	Placebo N (%) N=452	Cilomilast N (%) N=455
Any SAE	55 (12.2)	53 (11.6)
Exacerbation of COPD	18 (4.0)	19 (4.2)
Atrial fibrillation	1 (0.2)	3 (0.7)
Myocardial ischaemia	2 (0.4)	2 (0.4)
Pneumonia	2 (0.4)	2 (0.4)
Coronary artery disease	1 (0.2)	2 (0.4)
Atrial flutter	0	2 (0.4)
Duodenal ulcer	0	2 (0.4)
Syncope	2 (0.4)	1 (0.2)
Tachycardia	2 (0.4)	0

1. Data Source: Table 15.8B.

Table 63 Serious adverse events assessed as related to study medication - safety population



1. Data Source: Case Narratives Section 16.2.

8.3.2.3. Post-treatment

The incidence of SAEs which occurred post-treatment are summarised in Table 15.8C. In the placebo group, 15 subjects (3.3%) developed such an event compared with 11 subjects (2.4%) receiving cilomilast. Events that occurred in ≥ 2 subjects in either treatment group were pneumonia (placebo 3 subjects, cilomilast 1 patient), exacerbation of COPD (2 subjects each group) and neoplasms (placebo1 patient, cilomilast 2 subjects).

8.4. Adverse Events Leading to Premature Discontinuation of Investigational Product and/or Study

The incidence of new onset AEs on-therapy leading to patient withdrawal from therapy is summarised by MedDRA preferred term by descending order of frequency in the cilomilast group in Table 15.9A and by MedDRA preferred term grouping in Table 15.9B. On-therapy AEs which lead to withdrawal were reported by 40 subjects (8.8%) in the placebo group and 75 subjects (16.5%) in the cilomilast group. The most common AEs leading to withdrawal were exacerbation of COPD, nausea, diarrhoea and vomiting. Apart from exacerbation of COPD, there were more subjects reporting events which lead to withdrawal in the cilomilast group. All other AEs leading to withdrawal were reported by three subjects or less. A summary of the events which lead to withdrawal of ≥ 2 subjects in either treatment groups is summarised in Table 64.

Total numbers of patients withdrawing from the study due to AEs are marginally higher as reflected in Table 13.4 (46 and 80 placebo and cilomilast respectively) than presented in Table 15.9A. The discrepancy in numbers relates to subjects withdrawn due to adverse events with onset dates prior to therapy (9 placebo and 10 cilomilast) and subjects with an adverse event on-therapy which is associated with withdrawal but classification for the main reason for withdrawal by the investigator as insufficient therapeutic effect, another reason or protocol deviation (3 placebo and 5 cilomilast).

Table 64 Most common (reported by >= 3 subjects in either treatment group) Adverse Events leading to patient withdrawal - safety population

Event	Placebo N (%) N=452	Cilomilast N (%) N=455
Total AEs leading to withdrawal	40 (8.8)	75 (16.5)
Exacerbation of COPD	17 (3.8)	12 (2.6)
Nausea	1 (0.2)	16 (3.5)
Diarrhoea	2 (0.4)	11 (2.4)
Vomiting	0	7 (1.5)
Abdominal pain	0	5 (1.1)
Dyspepsia	0	5 (1.1)
Upper abdominal pain	0	4 (0.9)
Dizziness	0	4 (0.9)
Headache	1 (0.2)	3 (0.7)
Anorexia	0	3 (0.7)
Exacerbation of dyspnoea	0	3 (0.7)
Atrial fibrillation	0	2 (0.4)
Duodenal ulcer	0	2 (0.4)
Dyspnoea	2 (0.4)	0
Fatigue	0	2 (0.4)
Lung disorder	2 (0.4)	0

1. Data Source: Table 15.9A.

8.5. Other Relevant Adverse Events

8.5.1. Gastrointestinal Adverse Events of concern

A summary of the incidence of GIAEs of concern, those that lead to patient withdrawal from the study and Investigator determined intensity of the events are presented in Table 15.11A, Table 15.11B and Table 15.11C respectively. A summary of the events which resulted in 2 or more subjects being withdrawn from the study is presented in Table 65. There were more GIAEs of concern and subsequent withdrawals reported in subjects receiving cilomilast than placebo (Table 65). Individual narratives for patients with GIAEs of concern are presented in Section 16.4.

Table 65 GI Adverse Events (reported by >= 2 subjects in either treatment group) which lead to patient withdrawal - safety population

Event	Placebo N (%) N=452	Cilomilast N (%) N=455
Total GI events of concern	11 (2.4)	30 (6.6)
Total GI events that lead to withdrawal	1 (0.2)	17 (3.7)
Diarrhoea	0	6 (1.3)
Abdominal pain	0	3 (0.7)
Nausea	0	4 (0.9)
Vomiting	0	3 (0.7)

1. Data Source: Table 15.11A and Table 15.11B

The number of subjects with GI events that were assessed by the Investigator to be of severe intensity was 2 (0.4%) in the placebo group and 6 (1.3%) in the cilomilast group. In the placebo group, one subject had upper abdominal pain and one had iron deficiency anaemia. In the cilomilast group six subjects developed AEs of severe intensity including ileus and reflux oesophagitis, upper abdominal pain and gastritis, blood in stool, nausea and two cases of diarrhoea (Table 15.11C). These were generally considered probably or of suspected relationship to study drug apart from ileus and reflux oesophagitis and blood in stool which were both considered to be of unlikely relationship to study drug.

A summary of the routine faecal occult blood measurements for all subjects on-therapy is presented in Table 15.12A. Results of FOB testing at the time of a GIAE of concern are presented in Table 15.12B. The number of subjects with positive results at baseline was zero in both treatment groups as this was a randomisation criterion.

A total of nine subjects who were tested on-therapy at the specified visit interval displayed a transition from a negative FOB test at baseline to a positive result on therapy. These included five subjects (3.5%) from the placebo group and four subjects (3%) from the cilomilast group (Table 15.12A). In subjects with GIAEs of concern, the number of subjects who shifted from a negative result at baseline to a positive result during the double-blind treatment period was three in the placebo group and two in the cilomilast group (Table 15.12A). In addition to this there were eight subjects where frank blood was seen at the time of the GIAE or was the main reason for the GIAE and where a test for occult blood was not undertaken. Two additional cilomilast group subjects had positive FOB tests either as part of the Visit 12 procedures post therapy or at a GIAE event but tested post withdrawal of therapy.

In total 15 subjects developed a combination of the above criteria and were investigated for a GIAE of concern plus the presence of blood in the stools (either frank or occult) on therapy or immediately post therapy. These are presented in Table 66 and brief narratives are also presented below.

For patients who developed a GIAE of concern in association with a positive faecal occult blood test the protocol defined that a colonoscopy was required to fully investigate the condition. Of the 15 subjects investigated 8 had colonoscopy, 1 subject refused colonoscopy, 2 investigators did not consider endoscopic evaluation necessary, 1 subject had a sigmoidoscopy and 3 had gastroscopy only as this was indicated from the symptoms presented.

Details of orthostatic vital signs for GIAE subjects are described in Section 8.8.1.1. Only one subject taking cilomilast displayed any element of concern in orthostatic vital signs. However, there were no clinical signs of blood loss.

8.5.1.1. Narratives for GIAEs of concern plus frank melaena or positive faecal occult blood

Placebo group subjects

[redacted] No FOB testing was undertaken. [redacted] The investigator considered these events probably related to study medication, corrective therapy was given and these resolved on day 166. The patient continued on the study without further GIAE.

[redacted] These tests were conducted as part of the routine visit 12 and were not the result of a specific GIAE. However the positive FOB results prompted a GIAE assessment. No additional symptoms were recorded, orthostatic vital signs and labs were normal. The investigator considered the positive FOB not to be related to study medication. [redacted]

[redacted] The patient continued on therapy until study end and the investigator did not consider this event related to study medication. FOB tests at study end were negative.

[redacted] Assessment revealed no other symptoms, a negative FOB test and normal orthostatic vital signs and labs. [redacted]

[redacted] No colonoscopy was undertaken as the symptoms did not reoccur. The FOB results at study end were negative and the investigator did not consider the event related to study medication.

[redacted] The patient continued on the study until completion.

[redacted]

Cilomilast group subjects

[redacted] The investigator considered this of unlikely relationship to study drug, no new therapy was prescribed and the patient continued to study end without further GI event.

[redacted] The event was considered to be of unlikely relationship to study medication and the event did not result in patient withdrawal although the patient was withdrawn on day 254 as a result of investigator decision.

[redacted] Labs and orthostatic vitals signs were normal throughout the study and at a GIAE assessment visit. The patient was referred to a GI specialist for colonoscopy. Normal findings were observed in the entire colonic area up to the caecum.

[redacted]

[redacted] The investigator considered this probably related to study medication and the subject was withdrawn on day 256. No colonoscopy was undertaken for this second event

[redacted] Both events were moderate in intensity and considered by the investigator to be probably related to study medication. FOB testing on day 62 at a follow up assessment were positive for three consecutive samples. Orthostatic vital signs and lab results remained normal. [redacted] Medication was stopped on day 58 and the patient withdrawn from the study.

[redacted] A further moderate episode was noted on day 33 which lasted for 6 days was considered to be of probable relationship to study drug by the investigator. This resulted in the subjects' withdrawal. [redacted] This was considered of unlikely relationship to study drug by the investigator.

[redacted] The event was considered to be of unlikely relationship to study medication by the investigator and the patient remained on therapy until completion without recurrence.

[redacted] No other abnormality was noted at this time. [redacted]

[redacted] The investigator did not consider this event related to study medication and the patient remained in the study to completion. No further events were noted and FOB testing at visit 12 was normal.

[redacted] The investigator undertook a full assessment on day 6. Orthostatic vital signs were normal, no other symptoms were noted at the time of the blood in stool event or on full examination. The patient was referred to a gastrointestinal specialist. [redacted]

Table 66 Summary of results for subjects investigated for GIAEs of concern plus frank or occult blood



ND refers to not done

a. Drug-related refers to investigator opinion of relationship of AE to study drug. No=not related/unlikely to be related. Yes=Suspected/Probably related.
b. Faecal occult blood test result taken at time of GIAE of concern
c. sBP=systolic blood pressure, dBP=diastolic blood pressure, HR= heart rate. Values of concern are decrease of ≥20 for sBP, decrease of ≥10 for dBP and increase of ≥10 for HR.
d. Hb=haemoglobin. 'Worst case' result from any blood test during treatment. Value of low concern is <0.8xLLN (lower limit of normal), low value is 0.8-1xLLN, high value is 1-1.2xULN (upper limit of normal)
* Positive FOB post therapy

Graphical representations of the cumulative incidence of nausea, abdominal pain, diarrhoea and vomiting by time of initial onset are shown in Figure 19.15, Figure 19.16, Figure 19.17 and Figure 19.18 respectively. Graphical representations of the cumulative incidence of GI AEs of concern and all GI AEs by time of initial onset are shown in Figure 19.19 and Figure 19.20 respectively. GIAEs of concern and other GI events show

a sharp increase at the onset of treatment (first 28days) which is still significant up to 50 days post onset of therapy. Cilomilast GIAE rates decline towards a placebo rate with time although the time taken to achieve this varies. Abdominal pain is quickest to recede at approximately 50 days, nausea settles to a similar rate to placebo by day 75 and vomiting (driven by very small numbers) takes up to 175 days. Post day 168 all GIAE's had reduced to 1.8% in the placebo group and 2.7% in the cilomilast group.

8.5.2. Adverse Events Requiring Concomitant Therapy

Adverse events requiring corrective therapy are presented in Table 15.7 and summarised in Table 67. The most common event was an exacerbation of COPD in both treatment groups which occurred in 169 subjects (37%) receiving placebo and 161 subjects (35%) receiving cilomilast.

Table 67 Most common (reported by >2% of subjects in either treatment group) Adverse events requiring a change in medication - safety population

Event	Placebo N (%) N=452	Cilomilast N (%) N=455
Any AE requiring a change	288 (63.7)	285 (62.6)
Exacerbation of COPD	169 (37.4)	161 (35.4)
Nasopharyngitis	29 (6.4)	26 (5.7)
Headache	16 (3.5)	21 (4.6)
Influenza	12 (2.7)	12 (2.6)
Hypertension	14 (3.1)	10 (2.2)
Dyspepsia	4 (0.9)	14 (3.1)
Back pain	14 (3.1)	4 (0.9)
Rhinitis	8 (1.8)	11 (2.4)
Cough	6 (1.3)	11 (2.4)
Nausea	4 (0.9)	13 (2.9)
Urinary tract infection	12 (2.7)	2 (0.4)
Upper respiratory tract infection	6 (1.3)	10 (2.2

1. Data Source: Table 15.7.

8.6. Pregnancies

There were no pregnancies reported in this study.

8.7. Clinical Laboratory Evaluations

8.7.1. Laboratory Values Over Time

A summary of the descriptive statistics for clinical laboratory evaluations over time (by visit/week) is presented in Table 15.14.

8.7.2. Individual Subject Changes

A summary of the transition from baseline for each haematology analyte measured is presented in Table 15.15. Table 68 details the shift in any haematology analyte which was not of concern at baseline and changed to a value of either low or high concern at any time on-therapy. Values of concern are detailed in Section 5.9.7.3.

Table 68 Transition from baseline to a value of concern for haematology analytes on-therapy

Parameter	Baseline	No. of subjects with value of concern on-therapy			
		Low concern		High concern	
		Placebo N (%)	Cilomilast N (%)	Placebo N (%)	Cilomilast N (%)
Haemoglobin	Low (0.8 x LLN - < 1xLLN)	3 (16.7)	1 (5.3)	0	0
	Normal (1 x LLN - 1 x ULN)	1 (0.3)	1 (0.3)	1 (0.3)	0
Haematocrit	Low (0.8 x LLN - < 1xLLN)	1 (7.1)	0	0	0
	Normal (1 x LLN - 1 x ULN)	2 (0.5)	1 (0.3)	1 (0.3)	1 (0.3)
RBC		0	0	0	0
WBC	Normal (1 x LLN - 1 x ULN)	5 (1.2)	1 (0.3)	0	0
Platelets	Low (100 billion/L - <1 x LLN)	2 (66.7)	2 (66.7)	0	0
	Normal (1 x LLN - 1 x LLN)	1 (0.2)	2 (0.5)	5 (1.2)	1 (0.2)
	High (>1 x ULN - 500 billion/L)	0	0	2 (13.3)	0

1. Data Source: Table 15.15. Percentages are based on the number of subjects tested within each baseline category

A summary of the transition from baseline for each biochemistry analyte measured is shown in Table 15.15 and Table 69 below details the shift in any biochemistry analyte which was not of concern at baseline and changed to a value of either low or high concern at any time on-therapy. Values of concern are detailed in Section 5.9.7.3.

Subjects who had values missing at baseline but had a value of concern on therapy have not been included in this summary Table. There was no significant difference observed between the groups for any parameter although there were more changes to a value of concern in subjects receiving placebo than cilomilast.

Table 69 Transition from baseline to a value of concern for biochemistry analytes on-therapy

		No. of subjects with value of concern on-therapy			
Parameter	Baseline	Low concern		High concern	
		Placebo N (%)	Cilomilast N (%)	Placebo N (%)	Cilomilast N (%)
Sodium	Low (>130 mmol/l - <1 x LLN) Normal (1 x LLN - 1 x ULN)	2 (25.0) 5 (1.2)	3 (42.9) 1 (0.3)	0 5 (1.2)	0 2 (0.5)
Potassium	Low (>3.0 mmol/L x < 1 x LLN) Normal (1 x LLN - 1 x ULN) High ((>1 x ULN - < 5.5 mmol/L)	0 1 (0.2) 0 (14.3)	1 (33.3) 1 (0.3) 0	0 33 (7.8) 0	0 27 (6.8) 2 (33.3)
Chloride		0	0	0	0
Blood urea nitrogen	High (> 1 x ULN - 17.85 mmol/l)	0	0	0	1 (7.7)
Creatinine	Normal (1 x LLN - 1 x ULN) High (> 1 x ULN - 1.5 x ULN)	0 0	0 0	4 (1.0) 1 (20.0)	3 (0.8) 0
Uric acid	High (> 1 x ULN - 1.4 x ULN)	n/a	n/a	4 (20.0)	2 (15.4)
Alkaline phosphatase	Normal (≤ 1 x ULN)	n/a	n/a	1 (0.2)	0
AST	Normal (≤ 1 x ULN) High (> 1 x ULN - 2 x ULN)	n/a	n/a	5 (1.2) 4 (33.3)	2 (0.5) 4 (26.7)
ALT	Normal (≤ 1 x ULN) High (> 1 x ULN - 2 x ULN)	n/a	n/a	8 (1.9) 4 (30.8)	0 5 (22.7)
Total Bilirubin	Normal (≤ 1 x ULN) High (> 1 x ULN - 1.5 x ULN)	n/a	n/a	2 (0.5) 2 (15.4)	0 1 (10.0)
Fasting Glucose	Normal (1 x LLN - 1 x ULN) High (> 1 x ULN - 8.0 mmol/L)	0 0	0 0	6 (5.7) 4 (50.0)	5 (4.2) 4 (44.4)
Random glucose	Low (2.0 mmol/L - < 1 x LLN) Normal (1 x LLN - 1 x ULN) High (> 1 x ULN - 8.0 mmol/L)	0 1 0	0 1 0	4 44 13	1 37 12
GGT	Normal (≤ 1 x ULN) High (> 1 x ULN - 2.5 x ULN)	n/a	n/a	8 11	4 8

1. Data Source: Table 15.15. Percentages are based on the number of subjects tested within each baseline category
2. n/a=not applicable as no lower level of concern defined

8.7.3. Abnormalities of Potential Clinical Concern

There were no abnormalities observed which were considered to be clinically significant.

8.8. Other Safety Evaluations

8.8.1. Vital signs

A summary of the transitions from baseline in orthostatic vital signs for all subjects and separately for the population of subjects with GI AEs of concern is presented in Table 15.13B and Table 15.13A respectively.

8.8.1.1. Subjects with GI AEs of concern

Details of summary statistics for orthostatic vital signs measured during GIAEs of concern are presented in Table 15.13A. The number of subjects with a systolic BP value of concern on-therapy and at study endpoint was zero in both treatment groups. For diastolic BP, two subjects in the placebo group had a decrease of ≥ 10mm Hg on-therapy one of which had resolved by study endpoint. No cilomilast subjects had values of concern on therapy or at endpoint. For heart rate, three subjects in the placebo group and one patient in the cilomilast group had an increase from < 10bpm at baseline to levels of concern (>10bpm) on-therapy. [redacted] This subject had no other indicators of clinical concern. Haematology values were normal and FOB tests at endpoint were negative.

8.8.1.2. All subjects

The number of subjects with an orthostatic vital sign value of concern on-therapy and at study endpoint is summarised in Table 70.

There was no noticeable difference between the groups with similar numbers of subjects transferring from normal baseline readings to a reading of concern on-therapy or at endpoint.

The numbers of subjects who presented with levels of concern at baseline consistently reduced when tested again on therapy and at endpoint in both groups.

Table 70 Transition from baseline to values of concern on-therapy and at study endpoint in orthostatic vital signs: Safety population

Parameter	Baseline measurement	No. of subjects with value of concern			
		On-therapy		Study endpoint	
		Placebo N (%)	Cilomilast N (%)	Placebo N (%)	Cilomilast N (%)
Systolic BP	Normal (decrease < 10mmHg)	11 (2.8)	11 (3.0)	4 (1.0)	4 (1.1)
	High (decrease 10-19 mmHg)	1 (3.1)	2 (9.1)	0	0
Diastolic BP	Normal (decrease < 10mmHg)	27 (6.5)	32 (8.3)	7 (1.7)	11 (2.8)
	Concern (decrease ≥ 10mmHg)	1 (33.3)	1 (14.3)	1 (33.3)	0
Heart rate	Normal (Increase < 10 bpm)	44 (11.3)	39 (10.2)	14 (3.6)	13 (3.4)
	Concern (Increase ≥ 10 bpm)	9 (31.0)	3 (25.0)	4 (13.8)	3 (25.0)

1. Data Source: Table 15.13B. Percentages are based on the number of subjects tested within each baseline category
2. Values of concern are decrease of ≥20 for systolic BP, decrease of ≥10 for diastolic BP and increase of ≥10 for Heart Rate.
3. Percentages are based on the number of patients tested within each baseline category.

8.8.1.3. Standard and sitting vital signs

A summary of descriptive statistics for standard vital signs by visit is presented in Table 15.16. The transition from baseline in sitting vital signs is presented in Table 15.17.

A summary of the shift in sitting vital signs to a value of high clinical concern or low concern is given in Table 71. Values of concern are detailed in Section 5.9.7.3. There is no significant difference between treatment groups in the transition from baseline parameters either on-therapy or at endpoint to a value of high or low concern.

Table 71 Transition from baseline to values of concern on-therapy and at study endpoint in sitting vital signs: safety population

		No. of subjects with transition to value of high concern or low concern			
Parameter	Baseline measurement	low concern on-therapy: endpoint		High concern On-therapy : endpoint	
		placebo N (%)	cilomilast N (%)	Placebo N (%)	cilomilast N (%)
Heart rate	Normal (60-99 bpm) High (100-120 bpm) Low (50-59bpm)	1 (0.2) : 0 0 : 0 1 (9.1) : 1(9.1)	3 (0.7) : 2(0.5) 0 : 0 1(11.1) : 1(11.1)	1 (0.2) : 0 2 (14.3) : 0 0 : 0	2 (0.5) : 1(0.2) 1 (9.1) : 0 0 : 0
Diastolic BP	Normal (60-89 mm Hg) High (90-110 mm Hg) Low concern (<75mm Hg)	02(0.6) : 0 0 : 0 0 : 0	2(0.5) : 0 0 : 0 0 : 0	0 : 0 2(2.2) : 0 0 : 0	0 : 0 1(1.6) : 0 0 : 0
Systolic BP	Normal (90-139 mm Hg) High (140 - 180 mm Hg) High Concern (>180 mm Hg)	0 : 0 0 : 0 0 : 0	0 : 0 0 : 0 0 : 0	0 : 0 10 (5.1) : 3 (1.5) 1(100) : 1 (100)	0 : 0 4 (2.4): 0 2(66.6) : 1 (33.3)

1. Data Source: Table 15.17. Percentages are based on the number of subjects tested within each baseline category
2. Values given are on therapy: endpoint

8.8.2. ECG

A summary of the descriptive statistics for ECG data (by visit/week) is presented in Table 15.18 and transitions from baseline for each ECG parameters at each visit/week in Table 15.19A.

Mean change from baseline at week 52 is minimal and very similar between treatment groups. Table 72 details the shift in any ECG parameter which was not of concern at baseline and changed to a value of concern at any time on-therapy and at study endpoint. Values of concern are detailed in Section 5.9.7.3. There is no significant difference between treatment groups in transition to values of concern on-therapy or at endpoint.

Table 72 Transition from baseline to a value of concern for ECG parameters on-therapy and at study endpoint

Parameter	Baseline	No. of subjects with value of concern			
		On-therapy		Study endpoint	
		Placebo N (%)	Cilomilast N (%)	Placebo N (%)	Cilomilast N (%)
QRS interval	Normal (<120 msec)	0	2 (0.6)	0	1 (0.3)
	High (120-199 msec)	0	2 (4.7)	0	1 (2.3)
PR interval	Normal (200 msec)	3 (0.9)	4 (1.2)	2 (0.6)	4 (1.2)
	High (200-249 msec)	0	2 (5.6)	0	1 (2.8)
	Concern (≥ 250msec)	3 (75.0)	3 (75.0)	1 (50.0)	2 (50.0)
Ventricular rate	Normal (56-99 bpm)	2 (0.5)	1 (0.3)	0	1 (0.3)
	High (100-120 bpm)	0	1 (4.8)	0	0
Atrial rate	Normal (56-99 bpm)	3 (0.8)	0	1 (0.3)	0
Uncorrected QT	Normal (<500msec)	1 (0.2)	3 (0.8)	1 (0.2)	1 (0.3)
	Concern (≥ 500 msec)	0	1 (33.3)	0	1 (33.3)
Corrected QT (Bazett method)	Normal (<430 msec male; < 450 msec female)	50 (14.9)	33 (11.5)	24 (7.1)	19 (6.6)
	High (43-450 msec male; 450-470 female)	11 (33.3)	14 (26.9)	7 (21.2)	9 (17.3)
	Concern (>450 msec male; > 470 msec female)	24 (64.9)	30 (68.2)	14 (37.8)	25 (56.8)

1. Data Source: Table 15.19A. Subjects who had values missing at baseline but had a value of concern during the study have not been included in this summary Table. Percentages are based on the number of subjects in each subgroup at baseline rather than total population.

8.8.2.1. Change from baseline in corrected QT interval

A summary of the calculated change from baseline in corrected QT interval (Bazett) at each clinic visit/week is presented in Table 15.19B.

The QTc change of concern (> 60 msec) from baseline occurred in 55 subjects receiving placebo and 43 subjects receiving cilomilast on-therapy in patients who demonstrated a normal QTc value at baseline. A large proportion of subjects had a high QTc value (430-450msec male: 450-470msec female) at baseline (33 placebo; 52 cilomilast) which changed by a value of concern in 2 subjects receiving placebo and 4 subjects receiving cilomilast. At study endpoint, concern values of QTc change from baseline were present

in 33 and 25 subjects who had normal QTC values at baseline and 1 and 3 subjects who had high values in the placebo and cilomilast groups respectively. There is no apparent treatment difference in QT change from baseline based on these observations.

8.8.2.2. Incidence of new-onset ECG abnormalities

A summary of the incidence of new onset abnormalities in ECG parameters is presented in Table 15.20. All abnormalities which occurred in ≥ 2% of subjects in any treatment group are shown in Table 73. A similar incidence of new-onset abnormalities was seen in each treatment group. The most common abnormality presented in each group was sinus tachycardia which occurred in a higher percentage of subjects receiving placebo.

Table 73 Most common (reported by >=2% of subjects in either treatment group) new-onset ECG abnormalities on-therapy

ECG abnormality	Placebo (n=411) N (%)	Cilomilast (n=387) N (%)
Sinus tachycardia	22 (5.6)	15 (4.1)
S-T changes non-specific	15 (3.9)	13 (3.5)
Premature atrial contractions	10 (2.5)	12 (3.2)
Left axis deviation EKG	9 (2.3)	11 (3.0)
Sinus bradycardia	9 (2.3)	9 (2.4)
T-wave flat	7 (1.8)	8 (2.1)
Sinus arrhythmia	4 (1.0)	8 (2.1)
Premature ventricular contractions unifocal	4 (1.0)	8 (2.1)
Incomplete bundle branch block	3 (0.8)	8 (2.1)
Right bundle branch block	6 (1.5)	7 (2.0)

1. Data Source: Table 15.20.

Atrial fibrillation and atrial flutter occurred in marginally higher numbers in the cilomilast group subjects. Atrial Fibrillation as a new onset AE on-therapy was seen in 2 (0.4%) vs. 4 (0.9%) subjects taking placebo vs. cilomilast and as a new finding not present at baseline on ECG's in 2 (0.5%) vs. 6 (1.6%) placebo vs. cilomilast subjects. Not all the abnormalities noted in the ECG findings have been recorded as on-therapy AE's. Two cilomilast subjects were taking medication for atrial fibrillation at baseline although their baseline ECG did not show the condition. Overall numbers of subjects suffering from atrial fibrillation are low in relation to baseline values of 14 (3.6%) and 15 (3.3%) subjects in placebo and cilomilast groups with either prior or current atrial fibrillation at screening.

Atrial flutter occurred as a new AE on-therapy in 1 (0.2%) and 2 (0.4%) of placebo and cilomilast subjects respectively and was not seen in any subjects either as a past or ongoing condition at baseline.

8.9. Safety Conclusions

- The overall incidence of AEs and SAEs was similar between the placebo and cilomilast treatments groups. The majority of adverse events were mild or moderate in intensity.
- There were more events assessed as drug-related and leading to withdrawal or interruption of study drug in the cilomilast group which were mainly due to events associated with the GI system.
- Cilomilast group AE rates were highest over the first 28 days of treatment and reduced to levels similar to, or slightly raised from placebo over the subsequent study period.
- Routine orthostatic vital signs testing and FOB testing introduced to monitor potential silent GI bleeding showed no difference between placebo and cilomilast treatment groups.
- Intensive monitoring of GIAE's of concern revealed 15 subjects (6 placebo, 9 cilomilast) with a GIAE of concern plus frank or occult blood on examination.
- Colonoscopy associated with GIAE's of concern demonstrated no evidence of ischaemic vasculopathy of the colon. The majority of GI pathophysiology related to polyps, diverticular disease and haemorrhoids in the colon and gastritis, duodenitis or oesophagitis in the upper GI tract.
- Both placebo and cilomilast had a minimal effect on vital signs, mean ECG parameters, transition from baseline to ECG values of concern to new onset ECG abnormalities.
- There was no difference between placebo and cilomilast in the transition to a value of either low or high concern in haematology and biochemistry analytes or vital signs and new-onset ECG changes.
- Cilomilast was well-tolerated in the majority of subjects over 52 weeks of treatment.

9. HEALTH OUTCOMES RESULTS

9.1. EQ-5D

EQ-5D thermometer of health scale shows increase in health status by week with time in both overall effect and relative to placebo. The maximum difference over placebo is achieved at endpoint (2.488) which reaches the level required for statistical significance (p=0.044). A trend towards significance is seen at week 52 (2.226, p=0.094).

There is no real difference in heath status as assessed by the EQ-5D heath state tariff with both treatment arms broadly unchanged at endpoint.

EQ-5D tariff health state and EQ-5D thermometer health scale are presented in Table 14.11B and Table 14.12B. Descriptive statistics are presented in Table 14.11C and Table 14.12C respectively.

9.2. Resource utilisation and indirect costs

A summary of the average daily caregiver assistance in the ITT population by week is presented in Table 14.38. Levels for both groups were low and there was no statistical difference between the treatment groups at any time point.

9.3. Time off work/normal activities due to COPD

A summary of the average daily missed time from work or usual activities in the ITT population by week is presented in Table 14.37. A minimal difference was seen at any timepoint throughout the study in either treatment arm and no statistical difference was seen.

9.4. Health Outcomes Conclusion(s)

- The effect of cilomilast on health outcomes as measured in this study is limited to the visual analogue health scale thermometer. Improvements over baseline increase with time and reach statistical significance at week 52 and are retained at endpoint.

10. DISCUSSION

This study was designed to evaluate the efficacy, safety and tolerability of cilomilast 15mg bd as a maintenance therapy in subjects with COPD. A total of 1390 subjects were recruited into the study and after a 4 week, single-blind, placebo run-in phase 907 eligible subjects were randomised to receive either double-blind cilomilast 15mg bd (455 subjects) or placebo (452 subjects) for 52 weeks. During the run-in phase 479 subjects were withdrawn mainly due to AEs or a failure to meet entry criteria. A further 288 subjects withdrew during the double-blind treatment period leaving 619 patients who completed the study as planned.

The intention to treat (ITT) population consisted of 845 subjects. This number was reduced from the 907 randomised by the requirement to have at least one primary efficacy measurement post randomisation and the removal of the efficacy data from all 28 patients from centre [redacted]. Efficacy data from centre [redacted] was removed after concerns over the integrity of endpoints subsequent to irregularities detected at audit. Safety data from this site has remained in the safety analysis which remains at 907 subjects.

The two treatment groups in the randomised patient population were well matched for demographic characteristics in relation to age, race, height and weight. There were more females in the placebo group (27% vs. 22%) and subjects in the cilomilast group had marginally more severe disease (mean FEV_1 1.42L vs. 1.36L pre bronchodilator; predicted FEV_1 of 52.7 vs. 50.4% post bronchodilator, placebo vs. cilomilast respectively). Chronic bronchitis was present in 63.3% of the placebo group subjects and 57.1% of the cilomilast patients. Other than this the groups were reasonably well matched for reversibility (5.6% in both groups), $FEV_{1.}$ FVC ratio (0.50 vs. 0.49), active smoking status (42% vs. 43%) mean pack years (43.8 vs. 44.8) and current cigarette consumption (16.9 vs. 17 cigarettes per day) placebo vs. cilomilast respectively.

All patients reported current conditions at entry. The most common were chronic bronchitis (47% and 40%), hypertension (33% in both groups), hypercholesterolaemia (7.3% and 6.8%) and diabetes mellitus (7.5 and 4.2%) for placebo and cilomilast respectively. Gastrointestinal disorders existed in 16.2% and 18.7% of placebo and cilomilast subjects.

Subjects were provided with salbutamol metered dose inhalers for use on an ‘as-needed’ basis although the option to use a diskus device was permitted in three countries in a proportion of patients. Subjects were permitted to continue inhaled anticholinergic medication at a stable dose throughout the study although no other COPD medications were allowed except for the short-term treatment of exacerbations. Prior medications stopped included long-acting beta agonists such as Salmeterol and fenoterol (in 44.5% vs. 53.2% of placebo/cilomilast subjects), inhaled steroids including fluticasone and budesonide (34% vs. 41%) and theophylline (15% vs. 17%) of placebo and cilomilast subjects respectively.

Subjects used salbutamol (on a PRN basis) in 98.2% 98.9% of cases and ipratropium bromide in 53.8% and 53.6% of cases for placebo and cilomilast respectively.

During exacerbations the most common medications used were antibiotics with amoxicillin/amoxicillin trihydrate the most commonly used in 9.9% and 13.6% of subjects. Prednisonole, prednisone and methylprednisolone was used in 20.2% and 19.8% of placebo and cilomilast patients respectively.

Compliance with study medication was good with more than 96% of subjects in the placebo group and 94% of patients in the cilomilast group between 80 and 120% compliant during the 52-Week double-blind phase. The mean duration of exposure to double-blind study medication was 309.5 and 275.4 days for placebo and cilomilast subjects respectively.

The primary efficacy variables were mean change from baseline in clinic FEV_1 (measured pre-bronchodilator) at trough drug levels, and the incidence rate of level II/III exacerbations during the treatment period.

The treatment difference in FEV_1 (at trough plasma levels) averaged over 52 weeks was 0.041L $p<0.0001$. The difference over placebo reached statistical significance from week 4 which was maintained for the duration of the treatment period (difference at endpoint 0.046L $p=0.006$ and at week 52 of 0.045L $p=0.010$). In the per protocol (PP) population, the mean change over 52 weeks for FEV_1 was the same as the ITT population (0.041L $p<0.001$) and equivalent with time, endpoint difference 0.047L, $p=0.002$ and at week 52 0.045L $p=0.010$.

FEV_1 at endpoint demonstrated an average decline within the cilomilast group of 0.015L relative to a predicted normal decline of 0.025-0.029L for healthy individual males and females respectively [ECCS, 1983] or 0.053L for a COPD patient [Calverley, 2003]. The placebo group demonstrated a decline of 0.061L.

Tests of significance were undertaken to evaluate treatment by country and visit whilst covariates for age, sex, FEV_1 baseline, % predicted FEV_1 and baseline smoking status were undertaken to look for prognostic relationships. There was no significant treatment by country or treatment by time interactions. Tests for significance of prognostic factors only revealed baseline FEV_1 as a significant prognostic element on treatment effect. For every 1L rise in FEV_1 treatment effect decreased by 0.0494L.

FEV_1 was maintained in both current non-smokers and smokers although the largest mean difference was seen in current smokers (0.049L $p=0.006$). Gender also showed an effect on FEV_1 with males demonstrating a higher mean response at endpoint 0.058L (driven by a sharper decline in the placebo group of -0.072L vs. -0.014L) compared with -0.033L mean change at endpoint for females (related to a smaller mean decline of -0.017L compared with a mean improvement at endpoint of 0.016L).

No significant difference was seen in any of the parameters used to measure exacerbations. The rates of 0.448 and 0.483 level II/III exacerbations per year where considerably lower than previous cilomilast studies (placebo group level II/III exacerbation rate 039 0.955, 042 0.964, 091 1.166 and 156 0.618) and lower than the estimate of 0.8 level II/III exacerbations per year for placebo group subjects used to power the study. Results were equivalent in both ITT and PP populations. The low level of exacerbations may result in part from the removal of the requirement for patients to be

symptomatic at entry, which was stipulated in previous pivotal cilomilast studies (039, 042 and 091) apart from study 156 which also showed a reduced exacerbation rate. This is supported by a sub analysis of subjects within this study who met the symptom requirement at entry. These subjects showed a higher exacerbation rate (level ii/iii exacerbation rates of 0.655 and 0.637 placebo and cilomilast groups respectively). Although this subset of patients show increased exacerbation rates this is still short of the expected rates seen in previous studies with matching inclusion criteria, which suggests that further elements have contributed to this phenomenon. The 52-week treatment duration and placebo controlled nature of the study may have influenced investigator decisions on patients selected for study inclusion. Uptake of influenza vaccination both prior and during the study interval is not likely to have contributed to reduced exacerbation rates as the overall rate of approximately 4% influenza vaccination seen in this study is in line with levels in previous Phase III cilomilast studies.

The secondary endpoints demonstrate a number of parameters which support a general improvement in lung function as demonstrated by the trough FEV_1 data. Post bronchodilator FEV_1 shows an improvement of 0.34L (p=0.004) over placebo in average change from baseline over 52 weeks. This is also maintained at endpoint (0.053L, p=0.001). Mean change in PEF as measured at clinic visits over 52 weeks shows a 5.5L/min improvement in favour of cilomilast (p=0.023) and FVC demonstrates a statistically significant 0.042L of mean improvement over placebo when averaged over 52 weeks (p=0.037) which is maintained at endpoint 0.050L although this endpoint data only shows a trend towards significance (p=0.076).

FEF_{25-75} and a small sub population of 44 patients where residual volume was measured do not show any significant difference between treatment groups.

Review of the diary data does not demonstrate any significant treatment effect. Parameters collected include: domiciliary PEF, use of reliever medication, number of days with no rescue medication, summary symptom scores and nighttime awakenings.

Secondary measures to review exacerbations equally did not reveal any treatment differences. Exacerbation free survival rates were comparable for both treatment arms with 69.9% and 68.4% of subjects free from a level II/III exacerbation and 50.7% and 51.2% of subjects free from any level of exacerbation (data presented for placebo and cilomilast groups respectively). Relative rates of exacerbations were broadly equal for all level exacerbations with an incidence density ratio of 0.9537 (p=0.654) and rates of 0.909 and 0.867 for placebo and cilomilast respectively. Frequency of all level exacerbations do show a slight reduction in frequency of level I and level II exacerbations for the cilomilast group, although this is not sufficient to alter the overall exacerbation rates per group. The mean duration of exacerbations was reduced from 44.25 days for placebo group subjects by 8.35 days to 35.9 days within the cilomilast group. However this was not significant (p=0.325).

There was no statistical difference between the groups for the change from baseline in either blood CD4+/CD8+ ratio or C-reactive protein. Minor reductions in both parameters was seen on cilomilast treatment (-0.037 and -0.018 respectively) although these changes were not statistically significant (p=0.45 and p=0.991 respectively).

There was no statistical difference between the cilomilast and placebo groups in relation to SGRQ response in total score or subscales. SGRQ total score decreased on average over the 52-week treatment period by 1.5 points in the placebo group and 1.3 points in the cilomilast group indicating an improvement relative to baseline in both groups. The mean difference between treatments was 0.202 points which was not significant (p=0.835). Analysis of change by week shows a different pattern of improvement between the two treatments. Placebo subjects reach maximum benefit at week 28 with a declining effect at week 52 and endpoint (-1.822, -1.235 and -0.637 respectively). Alternatively the cilomilast group demonstrate an increasing effect towards week 52 (-1.407 and -1.522) with maximum differentiation over placebo at endpoint -0.499 in favour of cilomilast, although this is neither clinically of statistically significant at this point (p=0.627).

Global subject and investigator assessments undertaken at weeks 28, 52 and endpoint both show the number of subjects who had at least improved was greater in the cilomilast group compared to placebo. For the patient assessment this approaches statistical significance at week 52 (p=0.0609) and for the investigator assessment, the number of subjects who had improved was significantly greater in the cilomilast group than the placebo group reached significance at both week 52 and endpoint (p=0.0077 and 0.0363 respectively.

Health status improvements were seen in favour of treatment in the visual analogue EQ-5D health status thermometer with changes over placebo approaching statistical significance (2.226, p=0.094) at week 52 and finally attaining statistically significance (2.488, p=0.044) at endpoint.. These were not however mirrored in the EQ-5D health state tariff where no discernible treatment difference was noted.

The safety of cilomilast was extensively assessed in this study with particular emphasis on gastrointestinal and cardiovascular monitoring. In addition to the normal reporting of AEs, GIAEs were proactively assessed by way of specific questioning at each visit and specific assessment visits for any GIAE that caused concern to either patients or investigators. Subjects were instructed to visit the investigator for a full assessment if they experienced bloody or black stools, abdominal discomfort such as pain or cramps, diarrhoea or vomiting which cause the patient concern or interfered with usual activity (including eating and sleeping) at any time during the study. The Investigator was instructed to assess these adverse events within 24 hours of occurrence. Additionally, subjects were provided with a diary card in order to record gastrointestinal related symptoms between visits. Faecal occult blood testing and orthostatic vital signs assessments were performed in subjects experiencing GIAEs of Concern (at the time of event) and in all subjects at their final study visit and at visit 11 where an optional protocol amendment was passed.

In order to facilitate review of gastrointestinal safety data, subjects with a positive faecal occult blood test during the run-in period or clinically relevant postural hypotension were excluded from the study. Subjects with GIAEs of concern who additionally developed a positive FOB test, or developed frank melaena were referred to a GI specialist for colonoscopy.

This combination of visits, specific questioning, diary record and procedures plus detailed patient information sheets at study start ensured that the GI safety data collected for this study was fully optimised.

Cardiovascular safety of cilomilast was monitored by recording sitting vital signs at all visits and orthostatic vital signs and 12-lead ECGs at trough plasma levels at visits 1, 3, 7, 9, and 12. Routine laboratory variables were measured at all study visits bar visit 2 and 4.

Overall percentages of subjects reporting on-therapy AEs were well matched with 77% and 76% in the placebo and cilomilast groups respectively. There was a higher incidence of COPD exacerbations reported as adverse experiences in the placebo group compared with cilomilast (46.2% and 42.0% respectively), and a higher incidence of adverse experiences relating to the gastrointestinal system in the cilomilast group compared with placebo (28% and 15% respectively). The adverse experience profile provided no evidence for an adverse effect of cilomilast on other body systems including the CNS/peripheral, cardiovascular system (including heart rate and rhythm), liver and biliary system, psychiatric body system, resistance mechanism (i.e., infections and infestations) or reproductive system.

There were twelve deaths during the study (8 placebo; 4 cilomilast) and most were due to cardiopulmonary disease or cancer. None of deaths were considered related to study medication. SAE levels were broadly comparable between treatment groups with 55 subjects (12.2%) of placebo group patients and 53 (11.6%) of cilomilast subjects developing a SAE. Five subjects experienced an SAE which was interpreted as possibly or probably drug related. These were all experience in the cilomilast arm and include pancreatitis and diabetes mellitus, diarrhoea, gastritis and reflux oesophagitis, ventricular tachycardia and a duodenal ulcer. Narratives of all SAEs are provided in Section 16.

SAEs post therapy are broadly equally divided between the treatment arms with 15 (3.3%) of placebo patients and 11 (2.4%) of cilomilast patients experiencing a SAE.

The gastrointestinal adverse event profile was similar to that experienced in other European pivotal studies [042, 091] with a 2-fold increase in GIAE events in general. Specific examples of increased cilomilast AEs include nausea (3.1 vs. 9.7%), diarrhoea (2.9% vs. 7.3%), vomiting (1.8% vs. 4.6%) and headache (4.9% vs. 7.7%). Within AE's of >4% frequency in any group only hypertension (4% vs. 2.9%), nasopharyngitis (11.9% vs. 9.5% and backache (4.4% vs. 1%) are more prevalent in the placebo group (in addition to the COPD exacerbation data already stated).

AEs interpreted by the investigator to be of suspected or probably relationship to study drug show a two fold increase in the cilomilast group relative to placebo. These are largely related to the GI body system and are dominated by Nausea (1.1 vs. 7.3%), diarrhoea (1.3 vs. 4.4%), vomiting (0.7 vs. 2.4%), dyspepsia (0.4 vs. 2.2% and combined abdominal and upper abdominal pain (0.6 vs. 3.8%).

The majority of on-therapy adverse experiences were mild or moderate in severity in both treatment groups with only 11.1% of placebo patients and 10.8% of cilomilast patients classified with a severe event.

Time to onset has a bias towards cilomilast treatment which is driven by increased GIAE events. Within the placebo group the highest percentage of new AEs occurred in week one (11.1%) with a total of 33.4% of subjects experiencing an AE in the first 28 days. This compares with 19.3 % of cilomilast subjects with an AE within the first week and 49.4% of patient experiencing an AE in the 28 days. However, post day 28 the AE rates start to show convergence between the two arms with 24.7% declining to 12.3% between day 29-56 and 141-168 in the placebo arm and 21.8% declining to 13.0% over the same period of time in the cilomilast arm. Post day 168 AEs were seen in 46.9% of placebo subjects and 43.9% of cilomilast subjects. GIAE's post day 168 had reduced to 1.8% in the placebo group and 2.7% in the cilomilast group. This suggests that there is a continued small increase in GIAE incidence on treatment although the majority of GIAEs are related to the onset of treatment.

There were a higher proportion of subjects with either dose interruption or withdrawal due to AEs in the cilomilast group compared to the placebo group (5.3% vs. 8.8% for dose interruption 8.8% vs. 16.5% for withdrawal respectively).

The higher incidence of GIAE events, their concentration at the onset of therapy and the increased withdrawal rate associated with this, affect the overall mean exposure to treatment (309.5 days for placebo and 275.4 days for cilomilast).

GIAEs of concern were reported by 11 (2.4%) and 30 (6.6%) of subjects in the placebo and cilomilast groups respectively during the 52-week double-blind period. GIAEs of concern led to the withdrawal of 0.2% of placebo and 3.7% of cilomilast subjects. The most common GIAEs of concern which led to withdrawal on cilomilast were diarrhoea (1.3%), abdominal pain (0.7%), nausea (0.9%) and vomiting (0.7%).

The number of subjects with GI events that were assessed by the Investigator to be of severe intensity was 2 (0.4%) in the placebo group and 6 (1.3%) in the cilomilast group. In the placebo group, one subject had upper abdominal pain and one had iron deficiency anaemia with suspected melaena. In the cilomilast group six subjects experienced severe cases including two cases of diarrhoea, blood in stool, upper abdominal pain and gastritis, ileus and reflux oesophagitis and nausea.

In Subjects who developed GIAEs of Concern during the 52-week double-blind phase and a positive faecal occult blood result or frank blood at the time of GIAE, 6 were in the placebo group and 9 were in the cilomilast group. Detailed review of these subjects reveals no sinister pathology and no indication of any vasculopathy of the colon.

There was no evidence for a treatment effect of cilomilast on routine faecal occult blood results or clinically important changes in orthostatic vital signs.

In summary, the results of the intensive gastrointestinal monitoring performed in this study suggests a general 2 fold increase in GI symptoms largely driven by mild to moderate AEs of nausea, diarrhoea, abdominal pain, vomiting and dyspepsia, although no suggestion for more sinister effects related to mesenteric vasculopathy.

In relation to cardiovascular safety, there were no marked differences in the mean changes from baseline for sitting vital signs between the cilomilast and placebo groups or

in the percentages of subjects with transitions in sitting vital signs from normal at baseline to values of potential clinical concern on-therapy or at endpoint.

Mean changes from baseline for 12-lead ECGs values performed at trough showed minimal changes in mean values over the period of the study and no significant difference between treatment groups. Equally transitions to levels of concern in ECG parameters were again low with no clinically-relevant differences between the placebo and cilomilast groups. There were very little difference in new onset ECG abnormalities observed on-therapy. Atrial Fibrillation was seen in higher rates for cilomilast subjects 0.9% vs. 0.4% although overall numbers were low in relation to baseline values (2.7 vs. 2.6%) and the potential for atrial fibrillation in such an elderly COPD population with high levels of co-morbidities.

Review of laboratory parameters revealed no differences in the mean changes from baseline between cilomilast and placebo groups. The percentages of subjects who reported laboratory abnormalities or other investigations based AEs were also comparable between the two treatment arms (36 (8 %) vs. 34 (7.5%) placebo and cilomilast respectively). Analysis of individual lab abnormalities also shows no specific signal for an increased effect in either placebo or cilomilast groups.

11. CONCLUSIONS

Treatment with cilomilast 15mg bd provided improvement in a range of spirometric parameters. Change from placebo in FEV1 both pre and post bronchodilator (at trough plasma levels) reached levels of statistical significance when averaged over 52 weeks. The difference over placebo reached statistical significance from week 4 and this was maintained for the duration of the treatment period.

FEV_1 was maintained in both current non-smokers and smokers although the largest mean difference was seen in current smokers (0.049L p=0.006).

FEV_1 at endpoint demonstrated an average decline within the cilomilast group of 0.015L relative to a predicted normal decline of broadly 0.030L for a healthy individual [ECCS, 1983] or 0.053L for a COPD patient (ISOLDE data). The placebo group demonstrated a decline of 0.061L.

Statistically significant improvements were also seen in clinic PEF (averaged over 52 weeks and at endpoint) and in FVC (averaged over 52 weeks).

No significant difference was seen in any of the parameters used to measure exacerbations. The rate of COPD exacerbations experienced was considerably lower than the *a priori* estimate (0.8 level II/III exacerbations a year) required for adequate power to demonstrate treatment effect. The rates of 0.448 and 0.483 level II/III exacerbations per year where considerably lower than previous Ariflo studies and the removal of the requirement to be symptomatic at entry appears to have contributed to this.

No significant effect was seen in FEF_{25-75} or residual volume.

There was no evidence to suggest that withdrawals led to a significant or systematic bias in the estimation of treatment effects.

No clinically significant improvements were seen in Health status as measured by SGRQ or EQ5D health state tariff. However, there was a small statistically significant improvement in favour of treatment in the visual analogue health scale thermometer at week 52 and endpoint. This improvement at endpoint supports the trend seen in SGRQ total score of increasing effect over placebo with time. The lack of a treatment effect potentially ties in to the lack of any differentiation in the exacerbation rates between the two arms. However, both Investigator and Patient-rated global assessments do show more subjects categorised as improved in the cilomilast group compared to placebo.

Cilomilast 15mg bd was generally well tolerated in this study. The incidence of on-therapy adverse experiences was comparable between the two treatment groups, with the majority of adverse experiences mild or moderate in intensity. COPD exacerbations were more frequent, and led an increased (41%) level of withdrawals in the placebo group over subjects taking cilomilast. The general increase in adverse event rate was most notable in the first 28 days on therapy, after this point rates were broadly comparable or only marginally higher in the cilomilast group. The bulk of this increased AE rate was attributable to a higher frequency of gastrointestinal adverse events with nausea,

diarrhoea, abdominal pain, vomiting and dyspepsia generally increased by 2 to 4 fold over placebo rates. GIAE events generally peak within the first week with rates comparable between the two groups after 28 days. Placebo group GIAE rates were higher than would normally be expected for a similar group of COPD subjects. This is attributed to the proactive nature of adverse event questioning and the intensive GIAE monitoring undertaken within the study.

Intensive monitoring of subjects with GIAEs of concern produced no evidence of treatment-related effects on faecal occult blood results or orthostatic vital signs, or evidence of more significant gastrointestinal pathology on endoscopic examination. No evidence was seen for any vasculopathy in the colon. Gastroscopic evaluation revealed episodes of gastritis, duodenitis and oesophagitis in small numbers of patients although overall numbers of patients suffering these events were only marginally more common in cilomilast patients. However, GI events rated as severe by investigators were twice as common in cilomilast patients as placebo.

Extensive cardiovascular monitoring, including assessments of on-therapy vital signs (including orthostatic vital signs) and 12-lead ECG recording at each visit did not suggest any concerns about the cardiovascular safety of cilomilast.

There was also no evidence for any increased risk of investigations or laboratory parameter based adverse events.

12. REFERENCES

ATS: American Thoracic Society. 1995. Standardisation of spirometry. Am J Crit Care Med, 152, 1107-1136.

Calverley P M A, Burge P S, Spencer S, Anderson J A and Jones P W. Bronchodilator reversibility testing in chronic obstructive pulmonary disease. Thorax 2003;58;659-664

Connors AF JR, Dawson NV, Thomas C, Harrell FEJR, Desbiens N, Fulkerson WJ. 1996. Outcomes following acute exacerbation of severe chronic obstructive lung disease. The SUPPORT Investigators (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments. Am J Resp Crit Care Med, 154, 959-67.

Doll R, Peto R, Wheatley K, Gray R, Sutherland I. 1994. Mortality in relation to smoking: 40 years observations on male British doctors. British Medical Journal, 309, 901-10.

ECCS: European Community For Coal And Steel. 1983. Standardisation of Lung Function Tests. Bull Europ Physiopath Resp, Suppl 5,

Fletcher CM, Peto R.. 1977. The natural history of chronic airflow obstruction.. British Medical Journal, 1, 1645-8.

Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop Report. WHO/NHLBI, 2001

Jones PW, Quirk FH, Baveystock CM.. 1991a. The St George's Respiratory Questionnaire. Respiratory Medicine, 85 (supp B), 25 - 31.

Jones PW. 1991b. Measurement of Quality of Life in Chronic Obstructive Lung Disease. Eur Resp Rev, 1(5), 445-453.

Jones PW, et al. 1992. A self-complete measure for chronic airflow limitation, the St. George's Respiratory Questionnaire. Am Rev Respir Dis, 145, 1321-1327.

Jones PW. 1995. Issues concerning health-related Quality of Life in COPD. Chest, 107, 187S-193S.

Jones PW. 1997. Changes in quality of life in COPD subjects treated with salmeterol. Am J Respir Crit Care Med, 155, 1283-1289.

Murray CJL, Lopez AD. 1997. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. Lancet, 349, 1498.

SB 207499 Investigator Brochure. Fifth Edition (September 2000).

Seemungal TA, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA.. 1998. Effect of exacerbation on quality of life in subjects with chronic obstructive pulmonary disease. Am J Resp Crit Care Med, 157, 1418-22.

The Euroqol Group. 1990. EuroQol - a new facility for the measurement of health-related quality of life. Health Policy, 16, 199-208.

The EuroQol Group: EuroQol EQ-5D user guide.

Thom TJ. 1989. International comparisons in COPD mortality. American Review Respiratory Diseases, 140, 27 - 34.

Torphy TJ, Undem BJ. 1991. Phospodiesterase inhibitors:new opportunities for the treatment of asthma.. Thorax, 46, 512-523.

Weinberger M, Oddone EZ, Henderson WG. 1996. Does primary care reduce hospital readmissions? Veterans Affairs Cooperative Study Group on Primary Care and Hospital Readmissions. N Engl J Med, 334, 1441-7

13. Safety Data Source Tables

Page

TABLE 13.1A SUMMARY OF PATIENT DISPOSITION BY TREATMENT GROUP . 142

TABLE 13.1B SUMMARY OF PATIENT DISPOSITION BY COUNTRY AND TREATMENT GROUP 143

TABLE 13.2 DISTRIBUTION OF RANDOMIZED PATIENTS IN STUDY BY VISIT/WEEK AND TREATMENT GROUP 146

TABLE 13.3 REASONS FOR CONCLUDING THE RUN-IN PERIOD 147

TABLE 13.4 REASONS FOR CONCLUDING THE DOUBLE BLIND PERIOD BY TREATMENT GROUP 148

TABLE 13.5 SUMMARY OF EARLY WITHDRAWALS DURING THE DOUBLE-BLIND TREATMENT PERIOD BY TIME OF WITHDRAWAL, REASON AND TREATMENT GROUP 149

TABLE 13.6A SUMMARY OF PROTOCOL VIOLATIONS RESULTING IN EXCLUSION FROM PER PROTOCOL ANALYSIS BY TREATMENT GROUP . 150

TABLE 13.6B SUMMARY OF PROTOCOL VIOLATIONS RESULTING IN EXCLUSION FROM PER PROTOCOL ANALYSIS BY TREATMENT GROUP AND VISIT/WEEK 152

TABLE 13.6C SUMMARY OF CONDUCT OF STUDY DEVIATIONS BY TREATMENT GROUP 158

TABLE 13.7A SUMMARY OF DEMOGRAPHIC CHARACTERISTICS AT SCREENING BY TREATMENT GROUP - ALL RANDOMIZED PATIENTS . . . 159

TABLE 13.7B SUMMARY OF DEMOGRAPHIC CHARACTERISTICS AT SCREENING BY TREATMENT GROUP - PP 160

TABLE 13.7C SUMMARY OF DEMOGRAPHIC CHARACTERISTICS AT SCREENING BY TREATMENT GROUP - CURRENT-SMOKERS 161

TABLE 13.7D SUMMARY OF DEMOGRAPHIC CHARACTERISTICS AT SCREENING BY TREATMENT GROUP-PREVIOUS SMOKERS 162

TABLE 13.7E SUMMARY OF PRIOR SYSTEMIC AND INHALED STEROID BY TREATMENT GROUP - ALL RANDOMIZED PATIENTS 163

TABLE 13.7F SUMMARY OF LABA (LONG-ACTING BETA 2-AGONISTS) BY TREATMENT GROUP - ALL RANDOMIZED PATIENTS 164

TABLE 13.8 DESCRIPTIVE STATISTICS FOR VITAL SIGNS AT SCREENING BY TREATMENT GROUP - ALL RANDOMIZED PATIENTS 165

TABLE 13.9A DESCRIPTIVE STATISTICS FOR PULMONARY FUNCTION PARAMETERS* AT SCREENING BY TREATMENT GROUP - ALL RANDOMIZED PATIENTS 166

TABLE 13.9B DESCRIPTIVE STATISTICS FOR PULMONARY FUNCTION PARAMETERS* AT SCREENING BY TREATMENT GROUP - PP 169

TABLE 13.9C DESCRIPTIVE STATISTICS FOR PULMONARY FUNCTION PARAMETERS* AT SCREENING BY TREATMENT GROUP - CURRENT SMOKERS 172

TABLE 13.9D DESCRIPTIVE STATISTICS FOR PULMONARY FUNCTION PARAMETERS* AT SCREENING BY TREATMENT GROUP - PREVIOUS SMOKERS 175

TABLE 13.11 SUMMARY OF PULMONARY HISTORY BY TREATMENT GROUP - ALL RANDOMIZED PATIENTS 178

TABLE 13.12A DESCRIPTIVE STATISTICS AT SCREENING FOR SMOKING HISTORY, ALCOHOL INTAKE AND DURATION OF COPD BY TREATMENT GROUP - ALL RANDOMIZED PATIENTS 179

TABLE 13.12B DESCRIPTIVE STATISTICS AT SCREENING FOR SMOKING HISTORY, ALCOHOL INTAKE AND DURATION OF COPD BY TREATMENT GROUP - PER PROTOCOL PATIENTS 180

TABLE 13.12C DESCRIPTIVE STATISTICS AT SCREENING FOR SMOKING HISTORY, ALCOHOL INTAKE AND DURATION OF COPD BY TREATMENT GROUP - RANDOMIZED CURRENT SMOKERS AT BASELINE 181

TABLE 13.12D DESCRIPTIVE STATISTICS AT SCREENING FOR SMOKING HISTORY, ALCOHOL INTAKE AND DURATION OF COPD BY TREATMENT GROUP - RANDOMIZED FORMER SMOKERS AT BASELINE 182

TABLE 13.13A SUMMARY OF PRIOR MEDICAL CONDITIONS AT SCREENING BY DISEASE CODE LEVEL, MEDDRA PREFERRED TERM, AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS 183

TABLE 13.13B SUMMARY OF CURRENT/ACTIVE MEDICAL CONDITIONS AT SCREENING BY DISEASE CODE LEVEL, MEDDRA PREFERRED TERM, AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS 197

TABLE 13.14 SUMMARY OF BASELINE SIGNS AND SYMPTOMS BY MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM 210

TABLE 13.15A SUMMARY OF PRIOR MEDICATIONS BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS 217

TABLE 13.15B SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS 248

TABLE 13.15C SUMMARY OF POST-THERAPY MEDICATIONS BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS 294

TABLE 13.15D SUMMARY OF MEDICATIONS GIVEN FOR COPD EXACERBATIONS BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS 305

TABLE 13.16A SUMMARY OF STUDY MEDICATION COMPLIANCE (%) BY TREATMENT GROUP AND VISIT/WEEK 315

TABLE 13.16B DESCRIPTIVE STATISTICS FOR STUDY MEDICATION COMPLIANCE (%) BY TREATMENT GROUP AND VISIT/WEEK 317

TABLE 13.17 SUMMARY OF PATIENT SMOKING STATUS BY BASELINE STATUS, TREATMENT GROUP AND VISIT/WEEK 320

SB 207499

TABLE 13.1A

SUMMARY OF PATIENT DISPOSITION BY TREATMENT GROUP

PROTOCOL 157

DISPOSITION	TREATMENT GROUP PLACEBO (N=452)		SB 207499 (N=455)		TOTAL (N=907)	
RANDOMIZED	452	(100.0%)	455	(100.0%)	907	(100.0%)
SAFETY ANALYSIS	452	(100.0%)	455	(100.0%)	907	(100.0%)
ITT EFFICACY ANALYSIS	433	(95.8%)	412	(90.5%)	845	(93.2%)
PP EFFICACY ANALYSIS	375	(83.0%)	345	(75.8%)	720	(79.4%)
COMPLETED DB	331	(73.2%)	288	(63.3%)	619	(68.2%)
ESSENTIAL ASSESSMENTS	18	(4.0%)	33	(7.3%)	51	(5.6%)

1. SAMPLE SIZE REFLECTS THE PERCENTAGE OF PATIENTS RANDOMIZED.
2. PP POPULATION REPRESENTS THOSE PATIENTS INCLUDED IN THE PER-PROTOCOL ANALYSIS OF FEV1.

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 13.1B

SUMMARY OF PATIENT DISPOSITION BY COUNTRY AND TREATMENT GROUP

PROTOCOL 157

COUNTRY	DISPOSITION	TREATMENT GROUP PLACEBO	SB 207499	NON. RAND	TOTAL
Australia	SINGLE-BLIND	32	26	54	112
	RANDOMIZED	32 (100.0%)	26 (100.0%)	0 .	58 (100.0%)
	ITT EFFICACY	32 (100.0%)	24 (92.3%)	0 .	56 (96.6%)
	PP EFFICACY	29 (90.6%)	22 (84.6%)	0 .	51 (87.9%)
	COMPLETED DB	21 (65.6%)	14 (53.8%)	0 .	35 (60.3%)
	ESSENTIAL ASSESSMENTS	1 (3.1%)	5 (19.2%)	0 .	6 (10.3%)
Belgium	SINGLE-BLIND	11	10	22	43
	RANDOMIZED	11 (100.0%)	10 (100.0%)	0 .	21 (100.0%)
	ITT EFFICACY	11 (100.0%)	9 (90.0%)	0 .	20 (95.2%)
	PP EFFICACY	8 (72.7%)	8 (80.0%)	0 .	16 (76.2%)
	COMPLETED DB	7 (63.6%)	5 (50.0%)	0 .	12 (57.1%)
Czech Republic	SINGLE-BLIND	16	19	9	44
	RANDOMIZED	16 (100.0%)	19 (100.0%)	0 .	35 (100.0%)
	ITT EFFICACY	16 (100.0%)	19 (100.0%)	0 .	35 (100.0%)
	PP EFFICACY	13 (81.3%)	17 (89.5%)	0 .	30 (85.7%)
	COMPLETED DB	14 (87.5%)	15 (78.9%)	0 .	29 (82.9%)
	ESSENTIAL ASSESSMENTS	1 (6.3%)	2 (10.5%)	0 .	3 (8.6%)
Denmark	SINGLE-BLIND	12	11	9	32
	RANDOMIZED	12 (100.0%)	11 (100.0%)	0 .	23 (100.0%)
	ITT EFFICACY	11 (91.7%)	7 (63.6%)	0 .	18 (78.3%)
	PP EFFICACY	8 (66.7%)	6 (54.5%)	0 .	14 (60.9%)
	COMPLETED DB	9 (75.0%)	4 (36.4%)	0 .	13 (56.5%)
Finland	SINGLE-BLIND	14	12	26	52
	RANDOMIZED	14 (100.0%)	12 (100.0%)	0 .	26 (100.0%)
	ITT EFFICACY	14 (100.0%)	10 (83.3%)	0 .	24 (92.3%)
	PP EFFICACY	13 (92.9%)	8 (66.7%)	0 .	21 (80.8%)
	COMPLETED DB	11 (78.6%)	8 (66.7%)	0 .	19 (73.1%)
	ESSENTIAL ASSESSMENTS	3 (21.4%)	3 (25.0%)	0 .	6 (23.1%)
France	SINGLE-BLIND	19	12	37	68
	RANDOMIZED	19 (100.0%)	12 (100.0%)	0 .	31 (100.0%)
	ITT EFFICACY	17 (89.5%)	11 (91.7%)	0 .	28 (90.3%)
	PP EFFICACY	16 (84.2%)	10 (83.3%)	0 .	26 (83.9%)
	COMPLETED DB	9 (47.4%)	7 (58.3%)	0 .	16 (51.6%)
Germany	SINGLE-BLIND	76	75	65	216
	RANDOMIZED	76 (100.0%)	75 (100.0%)	0 .	151 (100.0%)
	ITT EFFICACY	72 (94.7%)	68 (90.7%)	0 .	140 (92.7%)
	PP EFFICACY	63 (82.9%)	59 (78.7%)	0 .	122 (80.8%)
	COMPLETED DB	61 (80.3%)	60 (80.0%)	0 .	121 (80.1%)

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED WITHIN EACH COUNTRY.
2. TOTAL ROWS REPRESENT THE TOTAL ACROSS ALL COUNTRIES.

CONFIDENTIAL

SB 207499

TABLE 13.1B

SUMMARY OF PATIENT DISPOSITION BY COUNTRY AND TREATMENT GROUP

PROTOCOL 157

COUNTRY	DISPOSITION	TREATMENT GROUP PLACEBO	SB 207499	NON. RAND	TOTAL
Italy	SINGLE-BLIND	40	53	24	117
	RANDOMIZED	40 (100.0%)	53 (100.0%)	0 .	93 (100.0%)
	ITT EFFICACY	39 (97.5%)	51 (96.2%)	0 .	90 (96.8%)
	PP EFFICACY	20 (50.0%)	21 (39.6%)	0 .	41 (44.1%)
	COMPLETED DB	28 (70.0%)	29 (54.7%)	0 .	57 (61.3%)
Netherlands	SINGLE-BLIND	15	22	28	65
	RANDOMIZED	15 (100.0%)	22 (100.0%)	0 .	37 (100.0%)
	ITT EFFICACY	14 (93.3%)	20 (90.9%)	0 .	34 (91.9%)
	PP EFFICACY	14 (93.3%)	17 (77.3%)	0 .	31 (83.8%)
	COMPLETED DB	12 (80.0%)	11 (50.0%)	0 .	23 (62.2%)
	ESSENTIAL ASSESSMENTS	3 (20.0%)	6 (27.3%)	0 .	9 (24.3%)
New Zealand	SINGLE-BLIND	13	12	20	45
	RANDOMIZED	13 (100.0%)	12 (100.0%)	0 .	25 (100.0%)
	ITT EFFICACY	12 (92.3%)	11 (91.7%)	0 .	23 (92.0%)
	PP EFFICACY	12 (92.3%)	11 (91.7%)	0 .	23 (92.0%)
	COMPLETED DB	10 (76.9%)	9 (75.0%)	0 .	19 (76.0%)
	ESSENTIAL ASSESSMENTS	0 .	2 (16.7%)	0 .	2 (8.0%)
Poland	SINGLE-BLIND	3	9	4	16
	RANDOMIZED	3 (100.0%)	9 (100.0%)	0 .	12 (100.0%)
	ITT EFFICACY	3 (100.0%)	8 (88.9%)	0 .	11 (91.7%)
	PP EFFICACY	3 (100.0%)	7 (77.8%)	0 .	10 (83.3%)
	COMPLETED DB	2 (66.7%)	5 (55.6%)	0 .	7 (58.3%)
Russia	SINGLE-BLIND	34	31	11	76
	RANDOMIZED	34 (100.0%)	31 (100.0%)	0 .	65 (100.0%)
	ITT EFFICACY	34 (100.0%)	30 (96.8%)	0 .	64 (98.5%)
	PP EFFICACY	33 (97.1%)	29 (93.5%)	0 .	62 (95.4%)
	COMPLETED DB	29 (85.3%)	23 (74.2%)	0 .	52 (80.0%)
Slovakia	SINGLE-BLIND	13	12	9	34
	RANDOMIZED	13 (100.0%)	12 (100.0%)	0 .	25 (100.0%)
	ITT EFFICACY	13 (100.0%)	12 (100.0%)	0 .	25 (100.0%)
	PP EFFICACY	12 (92.3%)	11 (91.7%)	0 .	23 (92.0%)
	COMPLETED DB	10 (76.9%)	11 (91.7%)	0 .	21 (84.0%)
	ESSENTIAL ASSESSMENTS	3 (23.1%)	1 (8.3%)	0 .	4 (16.0%)
South Africa	SINGLE-BLIND	25	25	32	82
	RANDOMIZED	25 (100.0%)	25 (100.0%)	0 .	50 (100.0%)
	ITT EFFICACY	24 (96.0%)	24 (96.0%)	0 .	48 (96.0%)
	PP EFFICACY	21 (84.0%)	21 (84.0%)	0 .	42 (84.0%)
	COMPLETED DB	17 (68.0%)	16 (64.0%)	0 .	33 (66.0%)

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED WITHIN EACH COUNTRY.
2. TOTAL ROWS REPRESENT THE TOTAL ACROSS ALL COUNTRIES.

CONFIDENTIAL

SB 207499

TABLE 13.1B

SUMMARY OF PATIENT DISPOSITION BY COUNTRY AND TREATMENT GROUP

PROTOCOL 157

COUNTRY	DISPOSITION	TREATMENT GROUP PLACEBO	SB 207499	NON. RAND	TOTAL
South Africa	ESSENTIAL ASSESSMENTS	1 (4.0%)	3 (12.0%)	0 .	4 (8.0%)
Spain	SINGLE-BLIND	51	51	55	157
	RANDOMIZED	51 (100.0%)	51 (100.0%)	0 .	102 (100.0%)
	ITT EFFICACY	47 (92.2%)	48 (94.1%)	0 .	95 (93.1%)
	PP EFFICACY	41 (80.4%)	43 (84.3%)	0 .	84 (82.4%)
	COMPLETED DB	37 (72.5%)	35 (68.6%)	0 .	72 (70.6%)
Sweden	SINGLE-BLIND	20	19	20	59
	RANDOMIZED	20 (100.0%)	19 (100.0%)	0 .	39 (100.0%)
	ITT EFFICACY	20 (100.0%)	13 (68.4%)	0 .	33 (84.6%)
	PP EFFICACY	20 (100.0%)	13 (68.4%)	0 .	33 (84.6%)
	COMPLETED DB	19 (95.0%)	11 (57.9%)	0 .	30 (76.9%)
	ESSENTIAL ASSESSMENTS	1 (5.0%)	8 (42.1%)	0 .	9 (23.1%)
Taiwan	SINGLE-BLIND	13	14	17	44
	RANDOMIZED	13 (100.0%)	14 (100.0%)	0 .	27 (100.0%)
	ITT EFFICACY	12 (92.3%)	11 (78.6%)	0 .	23 (85.2%)
	PP EFFICACY	12 (92.3%)	10 (71.4%)	0 .	22 (81.5%)
	COMPLETED DB	4 (30.8%)	5 (35.7%)	0 .	9 (33.3%)
United Kingdom	SINGLE-BLIND	45	42	41	128
	RANDOMIZED	45 (100.0%)	42 (100.0%)	0 .	87 (100.0%)
	ITT EFFICACY	42 (93.3%)	36 (85.7%)	0 .	78 (89.7%)
	PP EFFICACY	37 (82.2%)	32 (76.2%)	0 .	69 (79.3%)
	COMPLETED DB	31 (68.9%)	20 (47.6%)	0 .	51 (58.6%)
	ESSENTIAL ASSESSMENTS	5 (11.1%)	3 (7.1%)	0 .	8 (9.2%)
TOTAL	SINGLE-BLIND	452	455	483	1390
	RANDOMIZED	452 (100.0%)	455 (100.0%)	0 .	907 (100.0%)
	ITT EFFICACY	433 (95.8%)	412 (90.5%)	0 .	845 (93.2%)
	PP EFFICACY	375 (83.0%)	345 (75.8%)	0 .	720 (79.4%)
	COMPLETED DB	331 (73.2%)	288 (63.3%)	0 .	619 (68.2%)
	ESSENTIAL ASSESSMENTS	18 (4.0%)	33 (7.3%)	0 .	51 (5.6%)

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED WITHIN EACH COUNTRY.
2. TOTAL ROWS REPRESENT THE TOTAL ACROSS ALL COUNTRIES.

CONFIDENTIAL

SB 207499

TABLE 13.2

DISTRIBUTION OF RANDOMIZED PATIENTS IN STUDY BY VISIT/WEEK AND TREATMENT GROUP

PROTOCOL 157

	TREATMENT GROUP			ESSENTIAL ASSESSMENT		
VISIT/WEEK	PLACEBO (N=452)	SB 207499 (N=455)	TOTAL (N=907)	PLACEBO (N=452)	SB 207499 (N=455)	TOTAL (N=907)
VISIT 3/BASELINE	452 (100.0%)	455 (100.0%)	907 (100.0%)	0 .	0 .	0 .
VISIT 4/WEEK 2	446 (98.7%)	443 (97.4%)	889 (98.0%)	0 .	1 (0.2%)	1 (0.1%)
VISIT 5/WEEK 4	435 (96.2%)	418 (91.9%)	853 (94.0%)	2 (0.4%)	7 (1.5%)	9 (1.0%)
VISIT 6/WEEK 8	422 (93.4%)	404 (88.8%)	826 (91.1%)	3 (0.7%)	13 (2.9%)	16 (1.8%)
VISIT 7/WEEK 12	410 (90.7%)	382 (84.0%)	792 (87.3%)	4 (0.9%)	15 (3.3%)	19 (2.1%)
VISIT 8/WEEK 20	396 (87.6%)	354 (77.8%)	750 (82.7%)	8 (1.8%)	18 (4.0%)	26 (2.9%)
VISIT 9/WEEK 28	385 (85.2%)	333 (73.2%)	718 (79.2%)	9 (2.0%)	21 (4.6%)	30 (3.3%)
VISIT 10/WEEK 36	365 (80.8%)	317 (69.7%)	682 (75.2%)	13 (2.9%)	27 (5.9%)	40 (4.4%)
VISIT 11/WEEK 44	348 (77.0%)	302 (66.4%)	650 (71.7%)	16 (3.5%)	27 (5.9%)	43 (4.7%)
VISIT 12/WEEK 52	338 (74.8%)	295 (64.8%)	633 (69.8%)	16 (3.5%)	26 (5.7%)	42 (4.6%)
FOLLOW-UP	333 (73.7%)	311 (68.4%)	644 (71.0%)	0 .	0 .	0 .

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED.

CONFIDENTIAL

SB 207499

TABLE 13.3

REASONS FOR CONCLUDING THE RUN-IN PERIOD

PROTOCOL 157

REASON	TOTAL (N=1390)
BASELINE SIGNS AND SYMPTOMS	57 (4.1%)
COPD EXACERBATION	30 (2.2%)
PROTOCOL DEVIATION (INCLUDING NON-COMPLIANCE)	42 (3.0%)
LOST TO FOLLOW-UP	25 (1.8%)
OTHER	84 (6.0%)
DOES NOT MEET INCLUSION/EXCLUSION CRITERIA	271 (19.5%)
TOTAL WITHDRAWN	479 (34.5%)
COMPLETED SINGLE BLIND RUN-IN	911 (65.5%)

1. PERCENTAGES ARE BASED ON TOTAL NUMBER OF PATIENTS ENTERING SINGLE-BLIND RUN-IN.
2. BASELINE SIGNS AND SYMPTOMS ROW INCLUDES COPD EXACERBATIONS.

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 13.4

REASONS FOR CONCLUDING THE DOUBLE BLIND PERIOD BY TREATMENT GROUP

PROTOCOL 157

REASON	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	TOTAL (N=907)
ADVERSE EXPERIENCE	46 (10.2%)	80 (17.6%)	126 (13.9%)
COPD EXACERBATION	17 (3.8%)	12 (2.6%)	29 (3.2%)
INSUFFICIENT THERAPEUTIC EFFECT	18 (4.0%)	8 (1.8%)	26 (2.9%)
PROTOCOL DEVIATION	8 (1.8%)	16 (3.5%)	24 (2.6%)
LOST TO FOLLOW-UP	10 (2.2%)	32 (7.0%)	42 (4.6%)
OTHER	39 (8.6%)	31 (6.8%)	70 (7.7%)
TOTAL WITHDRAWN	121 (26.8%)	167 (36.7%)	288 (31.8%)
COMPLETED DOUBLE-BLIND	331 (73.2%)	288 (63.3%)	619 (68.2%)

1. PERCENTAGES ARE BASED ON NUMBER OF RANDOMIZED PATIENTS .
2. ADVERSE EXPERIENCE ROW INCLUDES COPD EXACERBATIONS.

CONFIDENTIAL

SB 207499

TABLE 13.5

SUMMARY OF EARLY WITHDRAWALS DURING THE DOUBLE-BLIND TREATMENT PERIOD
BY TIME OF WITHDRAWAL, REASON AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP

	PLACEBO (N=452)					SB 207499 (N=455)				
TIME (DAYS)	AE (%)	PD (%)	LTFU (%)	ITE (%)	OTHER (%)	AE (%)	PD (%)	LTFU (%)	ITE (%)	OTHER (%)
<= 14	0.9	0.7	0.2	0.5	0.9	3.3	0.7	0.4	0.0	0.4
<= 28	1.3	0.9	0.2	1.4	1.1	6.3	0.9	1.1	0.5	0.9
<= 56	3.0	1.4	0.2	1.4	2.3	8.8	1.6	1.4	0.7	1.9
<= 84	4.4	1.4	0.2	1.6	3.5	12.1	1.6	2.4	1.0	3.2
<= 140	5.8	1.4	0.5	2.1	4.4	14.8	2.5	3.8	1.0	4.0
<= 196	6.8	1.4	1.0	2.9	5.7	17.5	3.0	4.6	1.6	5.2
<= 252	8.5	1.6	1.5	3.9	6.4	17.8	3.3	6.1	1.6	5.5
<= 308	10.6	1.9	1.8	4.5	6.9	18.8	4.3	7.3	1.9	7.0
<= 364	11.1	1.9	2.2	4.5	8.3	18.8	4.3	7.9	2.2	7.9

1. PERCENTAGES ARE CUMULATIVE ESTIMATES BASED ON THE TOTAL NUMBER OF RANDOMIZED PATIENTS 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.

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 13.6A

SUMMARY OF PROTOCOL VIOLATIONS RESULTING IN EXCLUSION FROM PER PROTOCOL ANALYSIS
BY TREATMENT GROUP
PROTOCOL 157

TYPE OF VIOLATION	VIOLATION	TREATMENT GROUP PLACEBO (N=433)	TREATMENT GROUP SB 207499 (N=412)
VIOLATION OF ELIGIBILITY CRITERIA	Pre-salbutamol FEV1/FVC ratio > 0.71 at Visit 1	2 (0.5%)	3 (0.7%)
	Increase in FEV1 of > 17 percent absolute (pre Protocol amendment 2) and > 10 percent of predicted normal (post Protocol amendment 2) and > 200ml following salbutamol at Visit 1	1 (0.2%)	
	Post-salbutamol FEV1 < 27 percent or > 72 percent of predicted value at Visit 1	3 (0.7%)	2 (0.5%)
	Greater than a 22 percent change in pre-salbutamol clinic FEV1 between Visits 1 and 3	20 (4.6%)	16 (3.9%)
	TOTAL	24 (5.5%)	20 (4.9%)
EXCLUSIONARY MEDICATIONS	Concomitant oral or IV xanthine use within 2 weeks prior to Visit 3	1 (0.2%)	2 (0.5%)
	Concomitant oral or inhaled long-acting beta-2 agonist use within 2 weeks prior to Visit 3	1 (0.2%)	3 (0.7%)
	Concomitant inhaled short acting beta-2 agonist use other than salbutamol within 2 weeks prior to Visit 3		1 (0.2%)
	Concomitant oral and/or inhaled corticosteroid (ICS/OCS) within 2 weeks prior to Visit 3	2 (0.5%)	2 (0.5%)
	Anticholinergics initiated after Visit 1	2 (0.5%)	1 (0.2%)
	Exclusionary medication use for COPD exacerbation for > 6 weeks total exposure during the double-blind period	15 (3.5%)	10 (2.4%)
	Concomitant mucolytic use within 2 weeks of visit 3	1 (0.2%)	4 (1.0%)
	Concomitant tiotropium use within 2 weeks of visit 3	1 (0.2%)	
	Concomitant oxitropium use within 2 weeks of visit 3	23 (5.3%)	30 (7.3%)
	>42 Days Steroid Use	4 (0.9%)	5 (1.2%)
	TOTAL	48 (11.1%)	52 (12.6%)
VISIT SPECIFIC VIOLATIONS	Study medication compliance < 80 percent or > 120 percent during active, on-therapy dosing	93 (21.5%)	106 (25.7%)
	Salbutamol and/or anti-cholinergic medication within 2 hours of pulmonary function testing	3 (0.7%)	11 (2.7%)
	Entered a Pulmonary Rehabilitation Program (PRP) during the study	16 (3.7%)	17 (4.1%)
	Use of study medication within 7 hours of trough PFT	31 (7.2%)	20 (4.9%)
	TOTAL	129 (29.8%)	138 (33.5%)
ALL VIOLATIONS	Partial Exclusions	119 (27.5%)	114 (27.7%)
	Complete Exclusions	58 (13.4%)	67 (16.3%)

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS WITH EFFICACY DATA WITHIN EACH TREATMENT GROUP.
2. PARTIAL EXCLUSIONS RESULT FROM INDIVIDUAL VISIT EXCLUSIONS OR MULTIPLE VISIT EXCLUSIONS STARTING AT THE VIOLATED VISIT THROUGH ALL SUBSEQUENT DATA.
3. COMPLETE EXCLUSIONS ARE THOSE PATIENTS EXCLUDED ENTIRELY FROM PP ANALYSIS.

CONFIDENTIAL

SB 207499

TABLE 13.6A

SUMMARY OF PROTOCOL VIOLATIONS RESULTING IN EXCLUSION FROM PER PROTOCOL ANALYSIS
BY TREATMENT GROUP
PROTOCOL 157

TYPE OF VIOLATION	VIOLATION	TREATMENT GROUP PLACEBO (N=433)	TREATMENT GROUP SB 207499 (N=412)
ALL VIOLATIONS	At Least One Protocol Violation	177 (40.9%)	181 (43.9%)

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS WITH EFFICACY DATA WITHIN EACH TREATMENT GROUP.
2. PARTIAL EXCLUSIONS RESULT FROM INDIVIDUAL VISIT EXCLUSIONS OR MULTIPLE VISIT EXCLUSIONS STARTING AT THE VIOLATED VISIT THROUGH ALL SUBSEQUENT DATA.
3. COMPLETE EXCLUSIONS ARE THOSE PATIENTS EXCLUDED ENTIRELY FROM PP ANALYSIS.

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 13.6B

SUMMARY OF PROTOCOL VIOLATIONS RESULTING IN EXCLUSION FROM PER PROTOCOL ANALYSIS BY TREATMENT GROUP AND VISIT/WEEK

PROTOCOL 157

VISIT/WEEK	VIOLATION	TREATMENT GROUP PLACEBO (N=433)	SB 207499 (N=412)
VISIT 3/BASELINE	Pre-salbutamol FEV1/FVC ratio > 0.71 at Visit 1	2/433 (0.5%)	3/412 (0.7%)
	Increase in FEV1 of > 17 percent absolute (pre Protocol amendment 2) and > 10 percent of predicted normal (post Protocol amendment 2) and > 200ml following salbutamol at Visit 1	1/433 (0.2%)	0/412 (0.0%)
	Post-salbutamol FEV1 < 27 percent or > 72 percent of predicted value at Visit 1	3/433 (0.7%)	2/412 (0.5%)
	Greater than a 22 percent change in pre-salbutamol clinic FEV1 between Visits 1 and 3	20/433 (4.6%)	16/412 (3.9%)
	Concomitant oral or IV xanthine use within 2 weeks prior to Visit 3	1/433 (0.2%)	2/412 (0.5%)
	Concomitant oral or inhaled long-acting beta-2 agonist use within 2 weeks prior to Visit 3	1/433 (0.2%)	3/412 (0.7%)
	Concomitant inhaled short acting beta-2 agonist use other than salbutamol within 2 weeks prior to Visit 3	0/433 (0.0%)	1/412 (0.2%)
	Concomitant oral and/or inhaled corticosteroid (ICS/OCS) within 2 weeks prior to Visit 3	2/433 (0.5%)	1/412 (0.2%)
	Exclusionary medication use for COPD exacerbation for > 6 weeks total exposure during the double-blind period	0/433 (0.0%)	1/412 (0.2%)
	Concomitant mucolytic use within 2 weeks of visit 3	1/433 (0.2%)	4/412 (1.0%)
	Concomitant oxitropium use within 2 weeks of visit 3	23/433 (5.3%)	30/412 (7.3%)
	Entered a Pulmonary Rehabilitation Program (PRP) during the study	5/433 (1.2%)	7/412 (1.7%)
	TOTAL	54/433 (12.5%)	61/412 (14.8%)
VISIT 5/WEEK 4	Pre-salbutamol FEV1/FVC ratio > 0.71 at Visit 1	2/430 (0.5%)	3/404 (0.7%)
	Increase in FEV1 of > 17 percent absolute (pre Protocol amendment 2) and > 10 percent of predicted normal (post Protocol amendment 2) and > 200ml following salbutamol at Visit 1	1/430 (0.2%)	0/404 (0.0%)
	Post-salbutamol FEV1 < 27 percent or > 72 percent of predicted value at Visit 1	3/430 (0.7%)	2/404 (0.5%)
	Greater than a 22 percent change in pre-salbutamol clinic FEV1 between Visits 1 and 3	18/430 (4.2%)	15/404 (3.7%)
	Concomitant oral or IV xanthine use within 2 weeks prior to Visit 3	1/430 (0.2%)	2/404 (0.5%)
	Concomitant oral or inhaled long-acting beta-2 agonist use within 2 weeks prior to Visit 3	1/430 (0.2%)	3/404 (0.7%)
	Concomitant inhaled short acting beta-2 agonist use other than salbutamol within 2 weeks prior to Visit 3	0/430 (0.0%)	1/404 (0.2%)
	Concomitant oral and/or inhaled corticosteroid (ICS/OCS) within 2 weeks prior to Visit 3	2/430 (0.5%)	2/404 (0.5%)
	Anticholinergics initiated after Visit 1	1/430 (0.2%)	1/404 (0.2%)

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS WITH EFFICACY DATA WITHIN EACH GROUP AT EACH VISIT.
2. TOTAL ROW REPRESENTS THE TOTAL NUMBER OF PATIENTS EXCLUDED FOR A PROTOCOL VIOLATION AT A GIVEN VISIT.

CONFIDENTIAL

SB 207499

TABLE 13.6B

SUMMARY OF PROTOCOL VIOLATIONS RESULTING IN EXCLUSION FROM PER PROTOCOL ANALYSIS BY TREATMENT GROUP AND VISIT/WEEK

PROTOCOL 157

VISIT/WEEK	VIOLATION	TREATMENT GROUP PLACEBO (N=433)		SB 207499 (N=412)	
VISIT 5/WEEK 4	Exclusionary medication use for COPD exacerbation for > 6 weeks total exposure during the double-blind period	2/430	(0.5%)	2/404	(0.5%)
	Concomitant mucolytic use within 2 weeks of visit 3	1/430	(0.2%)	4/404	(1.0%)
	Concomitant oxitropium use within 2 weeks of visit 3	23/430	(5.3%)	30/404	(7.4%)
	Study medication compliance < 80 percent or > 120 percent during active, on-therapy dosing	21/430	(4.9%)	25/404	(6.2%)
	Entered a Pulmonary Rehabilitation Program (PRP) during the study	8/430	(1.9%)	11/404	(2.7%)
	Use of study medication within 7 hours of trough PFT	7/430	(1.6%)	1/404	(0.2%)
	TOTAL	82/430	(19.1%)	85/404	(21.0%)
VISIT 6/WEEK 8	Pre-salbutamol FEV1/FVC ratio > 0.71 at Visit 1	2/419	(0.5%)	3/398	(0.8%)
	Increase in FEV1 of > 17 percent absolute (pre Protocol amendment 2) and > 10 percent of predicted normal (post Protocol amendment 2) and > 200ml following salbutamol at Visit 1	1/419	(0.2%)	0/398	(0.0%)
	Post-salbutamol FEV1 < 27 percent or > 72 percent of predicted value at Visit 1	2/419	(0.5%)	2/398	(0.5%)
	Greater than a 22 percent change in pre-salbutamol clinic FEV1 between Visits 1 and 3	17/419	(4.1%)	15/398	(3.8%)
	Concomitant oral or IV xanthine use within 2 weeks prior to Visit 3	1/419	(0.2%)	2/398	(0.5%)
	Concomitant oral or inhaled long-acting beta-2 agonist use within 2 weeks prior to Visit 3	1/419	(0.2%)	3/398	(0.8%)
	Concomitant inhaled short acting beta-2 agonist use other than salbutamol within 2 weeks prior to Visit 3	0/419	(0.0%)	1/398	(0.3%)
	Concomitant oral and/or inhaled corticosteroid (ICS/OCS) within 2 weeks prior to Visit 3	2/419	(0.5%)	2/398	(0.5%)
	Anticholinergics initiated after Visit 1	2/419	(0.5%)	1/398	(0.3%)
	Exclusionary medication use for COPD exacerbation for > 6 weeks total exposure during the double-blind period	8/419	(1.9%)	2/398	(0.5%)
	Concomitant mucolytic use within 2 weeks of visit 3	1/419	(0.2%)	4/398	(1.0%)
	Concomitant oxitropium use within 2 weeks of visit 3	23/419	(5.5%)	30/398	(7.5%)
	Study medication compliance < 80 percent or > 120 percent during active, on-therapy dosing	12/419	(2.9%)	21/398	(5.3%)
	Salbutamol and/or anti-cholinergic medication within 2 hours of pulmonary function testing	1/419	(0.2%)	4/398	(1.0%)
	Entered a Pulmonary Rehabilitation Program (PRP) during the study	9/419	(2.1%)	12/398	(3.0%)
	Use of study medication within 7 hours of trough PFT	9/419	(2.1%)	1/398	(0.3%)
	TOTAL	83/419	(19.8%)	90/398	(22.6%)
VISIT 7/WEEK 12	Pre-salbutamol FEV1/FVC ratio > 0.71 at Visit 1	2/406	(0.5%)	2/376	(0.5%)

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS WITH EFFICACY DATA WITHIN EACH GROUP AT EACH VISIT.
2. TOTAL ROW REPRESENTS THE TOTAL NUMBER OF PATIENTS EXCLUDED FOR A PROTOCOL VIOLATION AT A GIVEN VISIT.

CONFIDENTIAL

SB 207499

TABLE 13.6B

SUMMARY OF PROTOCOL VIOLATIONS RESULTING IN EXCLUSION FROM PER PROTOCOL ANALYSIS BY TREATMENT GROUP AND VISIT/WEEK

PROTOCOL 157

VISIT/WEEK	VIOLATION	TREATMENT GROUP PLACEBO (N=433)	SB 207499 (N=412)
VISIT 7/WEEK 12	Increase in FEV1 of > 17 percent absolute (pre Protocol amendment 2) and > 10 percent of predicted normal (post Protocol amendment 2) and > 200ml following salbutamol at Visit 1	1/406 (0.2%)	0/376 (0.0%)
	Post-salbutamol FEV1 < 27 percent or > 72 percent of predicted value at Visit 1	2/406 (0.5%)	2/376 (0.5%)
	Greater than a 22 percent change in pre-salbutamol clinic FEV1 between Visits 1 and 3	17/406 (4.2%)	13/376 (3.5%)
	Concomitant oral or IV xanthine use within 2 weeks prior to Visit 3	1/406 (0.2%)	2/376 (0.5%)
	Concomitant oral or inhaled long-acting beta-2 agonist use within 2 weeks prior to Visit 3	1/406 (0.2%)	3/376 (0.8%)
	Concomitant inhaled short acting beta-2 agonist use other than salbutamol within 2 weeks prior to Visit 3	0/406 (0.0%)	1/376 (0.3%)
	Concomitant oral and/or inhaled corticosteroid (ICS/OCS) within 2 weeks prior to Visit 3	2/406 (0.5%)	2/376 (0.5%)
	Anticholinergics initiated after Visit 1	2/406 (0.5%)	0/376 (0.0%)
	Exclusionary medication use for COPD exacerbation for > 6 weeks total exposure during the double-blind period	8/406 (2.0%)	3/376 (0.8%)
	Concomitant mucolytic use within 2 weeks of visit 3	1/406 (0.2%)	3/376 (0.8%)
	Concomitant oxitropium use within 2 weeks of visit 3	22/406 (5.4%)	26/376 (6.9%)
	Study medication compliance < 80 percent or > 120 percent during active, on-therapy dosing	12/406 (3.0%)	23/376 (6.1%)
	Entered a Pulmonary Rehabilitation Program (PRP) during the study	8/406 (2.0%)	12/376 (3.2%)
	Use of study medication within 7 hours of trough PFT	6/406 (1.5%)	8/376 (2.1%)
	TOTAL	81/406 (20.0%)	85/376 (22.6%)
VISIT 8/WEEK 20	Pre-salbutamol FEV1/FVC ratio > 0.71 at Visit 1	1/393 (0.3%)	1/349 (0.3%)
	Increase in FEV1 of > 17 percent absolute (pre Protocol amendment 2) and > 10 percent of predicted normal (post Protocol amendment 2) and > 200ml following salbutamol at Visit 1	1/393 (0.3%)	0/349 (0.0%)
	Post-salbutamol FEV1 < 27 percent or > 72 percent of predicted value at Visit 1	2/393 (0.5%)	2/349 (0.6%)
	Greater than a 22 percent change in pre-salbutamol clinic FEV1 between Visits 1 and 3	17/393 (4.3%)	11/349 (3.2%)
	Concomitant oral or IV xanthine use within 2 weeks prior to Visit 3	1/393 (0.3%)	2/349 (0.6%)
	Concomitant oral or inhaled long-acting beta-2 agonist use within 2 weeks prior to Visit 3	1/393 (0.3%)	2/349 (0.6%)
	Concomitant oral and/or inhaled corticosteroid (ICS/OCS) within 2 weeks prior to Visit 3	2/393 (0.5%)	1/349 (0.3%)

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS WITH EFFICACY DATA WITHIN EACH GROUP AT EACH VISIT.
2. TOTAL ROW REPRESENTS THE TOTAL NUMBER OF PATIENTS EXCLUDED FOR A PROTOCOL VIOLATION AT A GIVEN VISIT.

CONFIDENTIAL

SB 207499

TABLE 13.6B

SUMMARY OF PROTOCOL VIOLATIONS RESULTING IN EXCLUSION FROM PER PROTOCOL ANALYSIS BY TREATMENT GROUP AND VISIT/WEEK

PROTOCOL 157

VISIT/WEEK	VIOLATION	TREATMENT GROUP PLACEBO (N=433)		SB 207499 (N=412)	
VISIT 8/WEEK 20	Anticholinergics initiated after Visit 1	2/393	(0.5%)	0/349	(0.0%)
	Exclusionary medication use for COPD exacerbation for > 6 weeks total exposure during the double-blind period	9/393	(2.3%)	4/349	(1.1%)
	Concomitant mucolytic use within 2 weeks of visit 3	1/393	(0.3%)	3/349	(0.9%)
	Concomitant oxitropium use within 2 weeks of visit 3	23/393	(5.9%)	23/349	(6.6%)
	>42 Days Steroid Use	1/393	(0.3%)	3/349	(0.9%)
	Study medication compliance < 80 percent or > 120 percent during active, on-therapy dosing	12/393	(3.1%)	17/349	(4.9%)
	Entered a Pulmonary Rehabilitation Program (PRP) during the study	11/393	(2.8%)	11/349	(3.2%)
	Use of study medication within 7 hours of trough PFT	7/393	(1.8%)	3/349	(0.9%)
	TOTAL	82/393	(20.9%)	73/349	(20.9%)
VISIT 9/WEEK 28	Pre-salbutamol FEV1/FVC ratio > 0.71 at Visit 1	1/382	(0.3%)	1/328	(0.3%)
	Increase in FEV1 of > 17 percent absolute (pre Protocol amendment 2) and > 10 percent of predicted normal (post Protocol amendment 2) and > 200ml following salbutamol at Visit 1	1/382	(0.3%)	0/328	(0.0%)
	Post-salbutamol FEV1 < 27 percent or > 72 percent of predicted value at Visit 1	2/382	(0.5%)	2/328	(0.6%)
	Greater than a 22 percent change in pre-salbutamol clinic FEV1 between Visits 1 and 3	16/382	(4.2%)	9/328	(2.7%)
	Concomitant oral or IV xanthine use within 2 weeks prior to Visit 3	1/382	(0.3%)	2/328	(0.6%)
	Concomitant oral or inhaled long-acting beta-2 agonist use within 2 weeks prior to Visit 3	1/382	(0.3%)	2/328	(0.6%)
	Concomitant oral and/or inhaled corticosteroid (ICS/OCS) within 2 weeks prior to Visit 3	2/382	(0.5%)	1/328	(0.3%)
	Anticholinergics initiated after Visit 1	2/382	(0.5%)	0/328	(0.0%)
	Exclusionary medication use for COPD exacerbation for > 6 weeks total exposure during the double-blind period	10/382	(2.6%)	6/328	(1.8%)
	Concomitant mucolytic use within 2 weeks of visit 3	1/382	(0.3%)	3/328	(0.9%)
	Concomitant oxitropium use within 2 weeks of visit 3	23/382	(6.0%)	21/328	(6.4%)
	>42 Days Steroid Use	2/382	(0.5%)	3/328	(0.9%)
	Study medication compliance < 80 percent or > 120 percent during active, on-therapy dosing	13/382	(3.4%)	17/328	(5.2%)
	Entered a Pulmonary Rehabilitation Program (PRP) during the study	11/382	(2.9%)	9/328	(2.7%)
	Use of study medication within 7 hours of trough PFT	14/382	(3.7%)	5/328	(1.5%)
	TOTAL	91/382	(23.8%)	72/328	(22.0%)
VISIT 10/WEEK 36	Pre-salbutamol FEV1/FVC ratio > 0.71 at Visit 1	1/361	(0.3%)	1/312	(0.3%)

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS WITH EFFICACY DATA WITHIN EACH GROUP AT EACH VISIT.
2. TOTAL ROW REPRESENTS THE TOTAL NUMBER OF PATIENTS EXCLUDED FOR A PROTOCOL VIOLATION AT A GIVEN VISIT.

CONFIDENTIAL

SB 207499

TABLE 13.6B

SUMMARY OF PROTOCOL VIOLATIONS RESULTING IN EXCLUSION FROM PER PROTOCOL ANALYSIS BY TREATMENT GROUP AND VISIT/WEEK

PROTOCOL 157

VISIT/WEEK	VIOLATION	TREATMENT GROUP PLACEBO (N=433)	SB 207499 (N=412)
VISIT 10/WEEK 36	Increase in FEV1 of > 17 percent absolute (pre Protocol amendment 2) and > 10 percent of predicted normal (post Protocol amendment 2) and > 200ml following salbutamol at Visit 1	1/361 (0.3%)	0/312 (0.0%)
	Post-salbutamol FEV1 < 27 percent or > 72 percent of predicted value at Visit 1	2/361 (0.6%)	2/312 (0.6%)
	Greater than a 22 percent change in pre-salbutamol clinic FEV1 between Visits 1 and 3	15/361 (4.2%)	8/312 (2.6%)
	Concomitant oral or IV xanthine use within 2 weeks prior to Visit 3	1/361 (0.3%)	0/312 (0.0%)
	Concomitant oral or inhaled long-acting beta-2 agonist use within 2 weeks prior to Visit 3	1/361 (0.3%)	2/312 (0.6%)
	Concomitant oral and/or inhaled corticosteroid (ICS/OCS) within 2 weeks prior to Visit 3	2/361 (0.6%)	1/312 (0.3%)
	Anticholinergics initiated after Visit 1	2/361 (0.6%)	0/312 (0.0%)
	Exclusionary medication use for COPD exacerbation for > 6 weeks total exposure during the double-blind period	13/361 (3.6%)	6/312 (1.9%)
	Concomitant mucolytic use within 2 weeks of visit 3	1/361 (0.3%)	2/312 (0.6%)
	Concomitant oxitropium use within 2 weeks of visit 3	22/361 (6.1%)	20/312 (6.4%)
	>42 Days Steroid Use	2/361 (0.6%)	3/312 (1.0%)
	Study medication compliance < 80 percent or > 120 percent during active, on-therapy dosing	14/361 (3.9%)	9/312 (2.9%)
	Salbutamol and/or anti-cholinergic medication within 2 hours of pulmonary function testing	2/361 (0.6%)	2/312 (0.6%)
	Entered a Pulmonary Rehabilitation Program (PRP) during the study	10/361 (2.8%)	7/312 (2.2%)
	Use of study medication within 7 hours of trough PFT	12/361 (3.3%)	7/312 (2.2%)
	TOTAL	86/361 (23.8%)	60/312 (19.2%)
VISIT 11/WEEK 44	Pre-salbutamol FEV1/FVC ratio > 0.71 at Visit 1	1/346 (0.3%)	1/299 (0.3%)
	Increase in FEV1 of > 17 percent absolute (pre Protocol amendment 2) and > 10 percent of predicted normal (post Protocol amendment 2) and > 200ml following salbutamol at Visit 1	1/346 (0.3%)	0/299 (0.0%)
	Post-salbutamol FEV1 < 27 percent or > 72 percent of predicted value at Visit 1	1/346 (0.3%)	1/299 (0.3%)
	Greater than a 22 percent change in pre-salbutamol clinic FEV1 between Visits 1 and 3	15/346 (4.3%)	6/299 (2.0%)
	Concomitant oral or inhaled long-acting beta-2 agonist use within 2 weeks prior to Visit 3	1/346 (0.3%)	2/299 (0.7%)
	Concomitant oral and/or inhaled corticosteroid (ICS/OCS) within 2 weeks prior to Visit 3	2/346 (0.6%)	1/299 (0.3%)
	Anticholinergics initiated after Visit 1	2/346 (0.6%)	0/299 (0.0%)

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS WITH EFFICACY DATA WITHIN EACH GROUP AT EACH VISIT.
2. TOTAL ROW REPRESENTS THE TOTAL NUMBER OF PATIENTS EXCLUDED FOR A PROTOCOL VIOLATION AT A GIVEN VISIT.

CONFIDENTIAL

SB 207499

TABLE 13.6B

SUMMARY OF PROTOCOL VIOLATIONS RESULTING IN EXCLUSION FROM PER PROTOCOL ANALYSIS BY TREATMENT GROUP AND VISIT/WEEK

PROTOCOL 157

VISIT/WEEK	VIOLATION	TREATMENT GROUP PLACEBO (N=433)	SB 207499 (N=412)
VISIT 11/WEEK 44	Exclusionary medication use for COPD exacerbation for > 6 weeks total exposure during the double-blind period	12/346 (3.5%)	7/299 (2.3%)
	Concomitant mucolytic use within 2 weeks of visit 3	0/346 (0.0%)	2/299 (0.7%)
	Concomitant oxitropium use within 2 weeks of visit 3	20/346 (5.8%)	20/299 (6.7%)
	>42 Days Steroid Use	3/346 (0.9%)	5/299 (1.7%)
	Study medication compliance < 80 percent or > 120 percent during active, on-therapy dosing	14/346 (4.0%)	12/299 (4.0%)
	Salbutamol and/or anti-cholinergic medication within 2 hours of pulmonary function testing	0/346 (0.0%)	1/299 (0.3%)
	Entered a Pulmonary Rehabilitation Program (PRP) during the study	9/346 (2.6%)	7/299 (2.3%)
	Use of study medication within 7 hours of trough PFT	9/346 (2.6%)	5/299 (1.7%)
	TOTAL	79/346 (22.8%)	60/299 (20.1%)
VISIT 12/WEEK 52	Pre-salbutamol FEV1/FVC ratio > 0.71 at Visit 1	1/336 (0.3%)	1/290 (0.3%)
	Increase in FEV1 of > 17 percent absolute (pre Protocol amendment 2) and > 10 percent of predicted normal (post Protocol amendment 2) and > 200ml following salbutamol at Visit 1	1/336 (0.3%)	0/290 (0.0%)
	Post-salbutamol FEV1 < 27 percent or > 72 percent of predicted value at Visit 1	2/336 (0.6%)	1/290 (0.3%)
	Greater than a 22 percent change in pre-salbutamol clinic FEV1 between Visits 1 and 3	14/336 (4.2%)	6/290 (2.1%)
	Concomitant oral or inhaled long-acting beta-2 agonist use within 2 weeks prior to Visit 3	1/336 (0.3%)	2/290 (0.7%)
	Concomitant oral and/or inhaled corticosteroid (ICS/OCS) within 2 weeks prior to Visit 3	2/336 (0.6%)	1/290 (0.3%)
	Anticholinergics initiated after Visit 1	2/336 (0.6%)	0/290 (0.0%)
	Exclusionary medication use for COPD exacerbation for > 6 weeks total exposure during the double-blind period	10/336 (3.0%)	7/290 (2.4%)
	Concomitant mucolytic use within 2 weeks of visit 3	0/336 (0.0%)	2/290 (0.7%)
	Concomitant tiotropium use within 2 weeks of visit 3	1/336 (0.3%)	0/290 (0.0%)
	Concomitant oxitropium use within 2 weeks of visit 3	18/336 (5.4%)	17/290 (5.9%)
	>42 Days Steroid Use	3/336 (0.9%)	3/290 (1.0%)
	Study medication compliance < 80 percent or > 120 percent during active, on-therapy dosing	16/336 (4.8%)	12/290 (4.1%)
	Entered a Pulmonary Rehabilitation Program (PRP) during the study	10/336 (3.0%)	10/290 (3.4%)
	Use of study medication within 7 hours of trough PFT	13/336 (3.9%)	3/290 (1.0%)
	TOTAL	80/336 (23.8%)	56/290 (19.3%)

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS WITH EFFICACY DATA WITHIN EACH GROUP AT EACH VISIT.
2. TOTAL ROW REPRESENTS THE TOTAL NUMBER OF PATIENTS EXCLUDED FOR A PROTOCOL VIOLATION AT A GIVEN VISIT.

CONFIDENTIAL

SB 207499

TABLE 13.6C

SUMMARY OF CONDUCT OF STUDY DEVIATIONS BY TREATMENT GROUP

PROTOCOL 157

CONDUCT OF STUDY DEVIATION	TREATMENT GROUP PLACEBO (N=433)	SB 207499 (N=412)
Study medication compliance <80 percent or >120 percent during placebo run-in period	19 (4.4%)	21 (5.1%)
Level 2 or level 3 exacerbation of COPD within 6 weeks prior to visit 3	4 (0.9%)	2 (0.5%)
Exclusionary medication used more than 2 weeks for COPD exacerbation (does not include patients exceeding 6 weeks total exposure)	17 (3.9%)	15 (3.6%)
Exclusionary medication used less than 2 weeks for indication other than COPD exacerbation	11 (2.5%)	9 (2.2%)
Exclusionary medication used more than 2 weeks for indication other than COPD exacerbation	2 (0.5%)	3 (0.7%)
Oxygen Therapy		1 (0.2%)
Smoking within 2 hours of pulmonary function testing (at visit 3 or later)	63 (14.5%)	48 (11.7%)
TOTAL	105 (24.2%)	87 (21.1%)

1. PERCENTAGES ARE BASED ON TOTAL NUMBER OF PATIENTS WITH EFFICACY DATA WITHIN EACH TREATMENT GROUP.

CONFIDENTIAL

SB 207499

TABLE 13.7A

SUMMARY OF DEMOGRAPHIC CHARACTERISTICS AT SCREENING BY TREATMENT GROUP - ALL RANDOMIZED PATIENTS

PROTOCOL 157

CHARACTERISTIC		TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	TOTAL (N=907)
SEX	Female	122 (27.0%)	98 (21.5%)	220 (24.3%)
	Male	330 (73.0%)	357 (78.5%)	687 (75.7%)
RACE	Black	2 (0.4%)	0 .	2 (0.2%)
	Caucasian	433 (95.8%)	436 (95.8%)	869 (95.8%)
	Oriental	13 (2.9%)	16 (3.5%)	29 (3.2%)
	Other	4 (0.9%)	3 (0.7%)	7 (0.8%)
AGE (YRS)	< 50	34 (7.5%)	20 (4.4%)	54 (6.0%)
	50-65	215 (47.6%)	213 (46.8%)	428 (47.2%)
	> 65	203 (44.9%)	222 (48.8%)	425 (46.9%)
	N	452	455	907
	MEAN	63.3	64.6	63.9
	MEDIAN	64.0	65.0	64.0
	STD	8.9	8.7	8.8
	MIN	40	42	40
	MAX	79	80	80
WEIGHT (KG)	N	450	454	904
	MEAN	74.3	74.3	74.3
	MEDIAN	74.0	73.0	73.0
	STD	15.2	14.7	14.9
	MIN	38	34	34
	MAX	125	125	125
HEIGHT (CM)	N	452	455	907
	MEAN	168.9	169.3	169.1
	MEDIAN	169.0	170.0	169.0
	STD	8.4	8.3	8.4
	MIN	146	142	142
	MAX	195	190	195

1. PERCENTAGES ARE BASED ON THE TOTAL NUMBER OF PATIENTS RANDOMIZED WITHIN EACH TREATMENT GROUP.

CONFIDENTIAL

SB 207499

TABLE 13.7B

SUMMARY OF DEMOGRAPHIC CHARACTERISTICS AT SCREENING BY TREATMENT GROUP - PP

PROTOCOL 157

CHARACTERISTIC		TREATMENT GROUP PLACEBO (N=375)	SB 207499 (N=345)	TOTAL (N=720)
SEX	Female	102 (27.2%)	71 (20.6%)	173 (24.0%)
	Male	273 (72.8%)	274 (79.4%)	547 (76.0%)
RACE	Black	2 (0.5%)	0 .	2 (0.3%)
	Caucasian	358 (95.5%)	330 (95.7%)	688 (95.6%)
	Oriental	12 (3.2%)	12 (3.5%)	24 (3.3%)
	Other	3 (0.8%)	3 (0.9%)	6 (0.8%)
AGE (YRS)	< 50	29 (7.7%)	18 (5.2%)	47 (6.5%)
	50-65	177 (47.2%)	166 (48.1%)	343 (47.6%)
	> 65	169 (45.1%)	161 (46.7%)	330 (45.8%)
	N	375	345	720
	MEAN	63.1	64.0	63.5
	MEDIAN	64.0	64.0	64.0
	STD	9.0	8.8	8.9
	MIN	40	42	40
	MAX	79	80	80
WEIGHT (KG)	N	373	344	717
	MEAN	73.9	74.5	74.2
	MEDIAN	73.0	74.0	74.0
	STD	15.2	14.8	15.0
	MIN	38	34	34
	MAX	125	125	125
HEIGHT (CM)	N	375	345	720
	MEAN	169.1	169.6	169.3
	MEDIAN	169.0	170.0	170.0
	STD	8.6	8.4	8.5
	MIN	146	142	142
	MAX	195	190	195

1. PERCENTAGES ARE BASED ON THE TOTAL NUMBER OF PATIENTS IN THE PP POPULATION WITHIN EACH TREATMENT GROUP.

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 13.7C

SUMMARY OF DEMOGRAPHIC CHARACTERISTICS AT SCREENING
BY TREATMENT GROUP - CURRENT-SMOKERS
PROTOCOL 157

CHARACTERISTIC		TREATMENT GROUP PLACEBO (N=188)	SB 207499 (N=196)	TOTAL (N=384)
SEX	Female	56 (29.8%)	57 (29.1%)	113 (29.4%)
	Male	132 (70.2%)	139 (70.9%)	271 (70.6%)
RACE	Black	1 (0.5%)	0 .	1 (0.3%)
	Caucasian	183 (97.3%)	186 (94.9%)	369 (96.1%)
	Oriental	2 (1.1%)	8 (4.1%)	10 (2.6%)
	Other	2 (1.1%)	2 (1.0%)	4 (1.0%)
AGE (YRS)	< 50	23 (12.2%)	13 (6.6%)	36 (9.4%)
	50-65	108 (57.4%)	120 (61.2%)	228 (59.4%)
	> 65	57 (30.3%)	63 (32.1%)	120 (31.3%)
	N	188	196	384
	MEAN	60.0	61.2	60.6
	MEDIAN	60.0	61.0	61.0
	STD	8.7	8.2	8.5
	MIN	40	42	40
	MAX	77	79	79
WEIGHT (KG)	N	188	196	384
	MEAN	71.8	71.5	71.6
	MEDIAN	70.0	70.5	70.0
	STD	15.2	15.2	15.2
	MIN	40	34	34
	MAX	125	124	125
HEIGHT (CM)	N	188	196	384
	MEAN	169.9	169.2	169.6
	MEDIAN	170.0	170.0	170.0
	STD	8.2	8.5	8.4
	MIN	152	147	147
	MAX	195	190	195

1. PERCENTAGES ARE BASED ON THE TOTAL NUMBER OF PATIENTS RANDOMIZED WITHIN EACH TREATMENT GROUP.

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 13.7D

SUMMARY OF DEMOGRAPHIC CHARACTERISTICS AT SCREENING BY TREATMENT GROUP-PREVIOUS SMOKERS

PROTOCOL 157

CHARACTERISTIC		TREATMENT GROUP PLACEBO (N=264)	SB 207499 (N=259)	TOTAL (N=523)
SEX	Female	66 (25.0%)	41 (15.8%)	107 (20.5%)
	Male	198 (75.0%)	218 (84.2%)	416 (79.5%)
RACE	Black	1 (0.4%)	0 .	1 (0.2%)
	Caucasian	250 (94.7%)	250 (96.5%)	500 (95.6%)
	Oriental	11 (4.2%)	8 (3.1%)	19 (3.6%)
	Other	2 (0.8%)	1 (0.4%)	3 (0.6%)
AGE (YRS)	< 50	11 (4.2%)	7 (2.7%)	18 (3.4%)
	50-65	107 (40.5%)	93 (35.9%)	200 (38.2%)
	> 65	146 (55.3%)	159 (61.4%)	305 (58.3%)
	N	264	259	523
	MEAN	65.6	67.1	66.3
	MEDIAN	67.0	68.0	68.0
	STD	8.3	8.3	8.3
	MIN	41	42	41
	MAX	79	80	80
WEIGHT (KG)	N	262	258	520
	MEAN	76.0	76.4	76.2
	MEDIAN	76.9	75.0	75.7
	STD	15.0	13.9	14.5
	MIN	38	42	38
	MAX	112	125	125
HEIGHT (CM)	N	264	259	523
	MEAN	168.2	169.3	168.7
	MEDIAN	168.0	170.0	169.0
	STD	8.4	8.2	8.3
	MIN	146	142	142
	MAX	189	189	189

1. PERCENTAGES ARE BASED ON THE TOTAL NUMBER OF PATIENTS RANDOMIZED WITHIN EACH TREATMENT GROUP.

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 13.7E

SUMMARY OF PRIOR SYSTEMIC AND INHALED STEROID BY TREATMENT GROUP - ALL RANDOMIZED PATIENTS

PROTOCOL 157

	TREATMENT GROUP		
	PLACEBO (N=452)	SB 207499 (N=455)	TOTAL (N=907)
INHALATION	190 (42.0%)	200 (44.0%)	390 (43.0%)
SYSTEMIC	17 (3.8%)	12 (2.6%)	29 (3.2%)

1. SYSTEMIC INCLUDES ORAL AND INTRAMUSCULAR

CONFIDENTIAL

SB 207499

TABLE 13.7F

SUMMARY OF LABA (LONG-ACTING BETA 2-AGONISTS) BY TREATMENT GROUP - ALL RANDOMIZED PATIENTS

PROTOCOL 157

	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	TOTAL (N=907)
INHALATION	83 (18.4%)	94 (20.7%)	177 (19.5%)
SYSTEMIC	2 (0.4%)	3 (0.7%)	5 (0.6%)

1. SYSTEMIC INCLUDES ORAL AND INTRAMUSCULAR

CONFIDENTIAL

SB 207499

TABLE 13.8

DESCRIPTIVE STATISTICS FOR VITAL SIGNS AT SCREENING BY TREATMENT GROUP - ALL RANDOMIZED PATIENTS

PROTOCOL 157

PARAMETER		TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	TOTAL (N=907)
SYSTOLIC BP (MM HG)	N	452	455	907
	MEAN	136.4	136.0	136.2
	STD	16.9	16.2	16.5
	MEDIAN	136.0	135.0	135.0
	MIN	80	95	80
	MAX	220	225	225
DIASTOLIC BP (MM HG)	N	452	455	907
	MEAN	80.5	80.5	80.5
	STD	9.1	9.4	9.2
	MEDIAN	80.0	80.0	80.0
	MIN	50	60	50
	MAX	110	125	125
HEART RATE (BPM)	N	452	455	907
	MEAN	75.9	76.1	76.0
	STD	10.6	10.3	10.4
	MEDIAN	76.0	76.0	76.0
	MIN	50	50	50
	MAX	120	110	120

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 13.9A

DESCRIPTIVE STATISTICS FOR PULMONARY FUNCTION PARAMETERS* AT SCREENING
BY TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

PARAMETER		TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	TOTAL (N=907)
FEV1 (L)	N	452	455	907
	MEAN	1.42	1.36	1.39
	STD	0.45	0.45	0.45
	MEDIAN	1.40	1.30	1.35
	MIN	0.54	0.48	0.48
	MAX	3.06	2.91	3.06
%PREDICTED FEV1	< 35%	25 (5.5%)	52 (11.4%)	77 (8.5%)
	35 - 50%	152 (33.6%)	163 (35.8%)	315 (34.7%)
	>= 50%	273 (60.4%)	238 (52.3%)	511 (56.3%)
	N	450	453	903
	MEAN	52.66	50.41	51.53
	STD	11.12	12.20	11.72
	MEDIAN	52.98	50.88	52.16
	MIN	26.64	21.92	21.92
	MAX	79.56	76.94	79.56
FEV1/FVC	N	452	455	907
	MEAN	0.50	0.49	0.50
	STD	0.10	0.11	0.10
	MEDIAN	0.50	0.49	0.50
	MIN	0.27	0.22	0.22
	MAX	0.72	0.75	0.75
VOLUME REVERSIBILITY (ML)	N	450	453	903
	MEAN	67.69	65.04	66.36
	STD	106.37	106.91	106.59
	MEDIAN	70.00	70.00	70.00
	MIN	-670.00	-1140.00	-1140.00
	MAX	340.00	310.00	340.00
SALBUTAMOL REVERSIBILITY (%)	N	450	453	903
	MEAN	5.59	5.60	5.60
	STD	7.98	8.20	8.08
	MEDIAN	5.62	5.41	5.43
	MIN	-29.65	-54.29	-54.29

* PULMONARY FUNCTION PARAMETERS INCLUDE FEV1, FVC, PEF, FEF25-75, VOLUME REVERSIBILITY, SALBUTAMOL REVERSIBILITY, IPRATROPIUM REVERSIBILITY, PERCENT PREDICTED FEV1, FEV1/FVC RATIO, PREDICTED SALBUTAMOL REVERSIBILITY, AND PREDICTED IPRATROPIUM REVERSIBILITY

1. FEV1, FVC, PEF, AND FEF25-75 ARE REPORTED PRE-ALBUTEROL INHALATION.
2. PERCENT PREDICTED FEV1 IS REPORTED POST-ALBUTEROL INHALATION.
3. SUMMARY IS FOR RANDOMIZED PATIENTS.
4. PREDICTED SALBUTAMOL REVERSIBILITY (%) AND PREDICTED IPRATROPIUM REVERSIBILITY (%) ARE CALCULATED USING THE FOLLOWING FORMULA: 100x(POST BRONCHODILATOR FEV1 - PRE BRONCHODILATOR FEV1) / PREDICTED FEV1
5. IPRATROPIUM REVERSIBILITY AND PREDICTED IPRATROPIUM REVERSIBILITY ARE CALCULATED AT VISIT 2.

CONFIDENTIAL

SB 207499

TABLE 13.9A

DESCRIPTIVE STATISTICS FOR PULMONARY FUNCTION PARAMETERS* AT SCREENING
BY TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

PARAMETER		TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	TOTAL (N=907)
SALBUTAMOL REVERSIBILITY (%)	MAX	45.95	37.84	45.95
PREDICTED SALBUTAMOL REVERSIBILITY (%)	N	450	453	903
	MEAN	2.51	2.37	2.44
	STD	3.75	3.78	3.77
	MEDIAN	2.66	2.44	2.57
	MIN	-19.98	-37.16	-37.16
	MAX	12.48	11.10	12.48
IPRATROPIUM REVERSIBILITY (%)	N	449	452	901
	MEAN	9.93	9.64	9.79
	STD	11.03	11.75	11.39
	MEDIAN	9.04	8.14	8.56
	MIN	-29.66	-26.74	-29.66
	MAX	56.96	91.82	91.82
PREDICTED IPRATROPIUM REVERSIBILITY (%)	N	449	452	901
	MEAN	4.43	4.09	4.26
	STD	4.93	5.17	5.05
	MEDIAN	4.18	3.48	3.80
	MIN	-16.19	-14.65	-16.19
	MAX	28.69	47.84	47.84
FVC (L)	N	452	455	907
	MEAN	2.86	2.78	2.82
	STD	0.83	0.76	0.80
	MEDIAN	2.81	2.75	2.77
	MIN	1.22	1.09	1.09
	MAX	5.66	5.29	5.66
PEF (L/MIN)	N	452	453	905
	MEAN	194.79	191.61	193.20
	STD	73.52	77.43	75.48
	MEDIAN	185.00	179.00	181.00

* PULMONARY FUNCTION PARAMETERS INCLUDE FEV1, FVC, PEF, FEF25-75, VOLUME REVERSIBILITY, SALBUTAMOL REVERSIBILITY, IPRATROPIUM REVERSIBILITY, PERCENT PREDICTED FEV1, FEV1/FVC RATIO, PREDICTED SALBUTAMOL REVERSIBILITY, AND PREDICTED IPRATROPIUM REVERSIBILITY

1. FEV1, FVC, PEF, AND FEF25-75 ARE REPORTED PRE-ALBUTEROL INHALATION.
2. PERCENT PREDICTED FEV1 IS REPORTED POST-ALBUTEROL INHALATION.
3. SUMMARY IS FOR RANDOMIZED PATIENTS.
4. PREDICTED SALBUTAMOL REVERSIBILITY (%) AND PREDICTED IPRATROPIUM REVERSIBILITY (%) ARE CALCULATED USING THE FOLLOWING FORMULA: 100x(POST BRONCHODILATOR FEV1 - PRE BRONCHODILATOR FEV1) / PREDICTED FEV1
5. IPRATROPIUM REVERSIBILITY AND PREDICTED IPRATROPIUM REVERSIBILITY ARE CALCULATED AT VISIT 2.

CONFIDENTIAL

SB 207499

TABLE 13.9A

DESCRIPTIVE STATISTICS FOR PULMONARY FUNCTION PARAMETERS* AT SCREENING
BY TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

PARAMETER		TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	TOTAL (N=907)
PEF (L/MIN)	MIN	68.00	35.00	35.00
	MAX	474.00	690.00	690.00
FEF25-75 (L/SEC)	N	452	455	907
	MEAN	0.61	0.58	0.59
	STD	0.33	0.32	0.33
	MEDIAN	0.54	0.51	0.52
	MIN	0.02	0.12	0.02
	MAX	3.91	2.75	3.91

* PULMONARY FUNCTION PARAMETERS INCLUDE FEV1, FVC, PEF, FEF25-75, VOLUME REVERSIBILITY, SALBUTAMOL REVERSIBILITY, IPRATROPIUM REVERSIBILITY, PERCENT PREDICTED FEV1, FEV1/FVC RATIO, PREDICTED SALBUTAMOL REVERSIBILITY, AND PREDICTED IPRATROPIUM REVERSIBILITY

1. FEV1, FVC, PEF, AND FEF25-75 ARE REPORTED PRE-ALBUTEROL INHALATION.
2. PERCENT PREDICTED FEV1 IS REPORTED POST-ALBUTEROL INHALATION.
3. SUMMARY IS FOR RANDOMIZED PATIENTS.
4. PREDICTED SALBUTAMOL REVERSIBILITY (%) AND PREDICTED IPRATROPIUM REVERSIBILITY (%) ARE CALCULATED USING THE FOLLOWING FORMULA: 100x(POST BRONCHODILATOR FEV1 - PRE BRONCHODILATOR FEV1) / PREDICTED FEV1
5. IPRATROPIUM REVERSIBILITY AND PREDICTED IPRATROPIUM REVERSIBILITY ARE CALCULATED AT VISIT 2.

CONFIDENTIAL

SB 207499

TABLE 13.9B

DESCRIPTIVE STATISTICS FOR PULMONARY FUNCTION PARAMETERS* AT SCREENING
BY TREATMENT GROUP - PP
PROTOCOL 157

PARAMETER		TREATMENT GROUP PLACEBO (N=375)	SB 207499 (N=345)	TOTAL (N=720)
FEV1 (L)	N	375	345	720
	MEAN	1.43	1.37	1.40
	STD	0.45	0.46	0.46
	MEDIAN	1.40	1.31	1.36
	MIN	0.54	0.48	0.48
	MAX	3.06	2.91	3.06
%PREDICTED FEV1	< 35%	18 (4.8%)	40 (11.6%)	58 (8.1%)
	35 - 50%	127 (33.9%)	127 (36.8%)	254 (35.3%)
	>= 50%	228 (60.8%)	176 (51.0%)	404 (56.1%)
	N	373	343	716
	MEAN	52.79	50.05	51.47
	STD	10.99	11.93	11.52
	MEDIAN	52.89	50.13	52.11
	MIN	29.83	29.72	29.72
	MAX	71.79	70.27	71.79
FEV1/FVC	N	375	345	720
	MEAN	0.50	0.49	0.50
	STD	0.10	0.11	0.10
	MEDIAN	0.50	0.49	0.50
	MIN	0.27	0.22	0.22
	MAX	0.70	0.70	0.70
VOLUME REVERSIBILITY (ML)	N	373	343	716
	MEAN	66.54	65.34	65.97
	STD	105.90	89.71	98.41
	MEDIAN	70.00	70.00	70.00
	MIN	-670.00	-250.00	-670.00
	MAX	340.00	310.00	340.00
SALBUTAMOL REVERSIBILITY (%)	N	373	343	716
	MEAN	5.51	5.61	5.56
	STD	8.14	7.69	7.92
	MEDIAN	5.26	5.22	5.22
	MIN	-29.65	-15.82	-29.65

* PULMONARY FUNCTION PARAMETERS INCLUDE FEV1, FVC, PEF, FEF25-75, VOLUME REVERSIBILITY, SALBUTAMOL REVERSIBILITY, IPRATROPIUM REVERSIBILITY, PERCENT PREDICTED FEV1, FEV1/FVC RATIO, PREDICTED SALBUTAMOL REVERSIBILITY, AND PREDICTED IPRATROPIUM REVERSIBILITY

1. FEV1, FVC, PEF AND FEF25-75 ARE REPORTED PRE-ALBUTEROL INHALATION.
2. PERCENT PREDICTED FEV1 IS REPORTED POST-ALBUTEROL INHALATION.
3. SUMMARY IS FOR PER PROTOCOL PATIENTS.
4. PREDICTED SALBUTAMOL REVERSIBILITY (%) AND PREDICTED IPRATROPIUM REVERSIBILITY (%) ARE CALCULATED USING THE FOLLOWING FORMULA: 100x(POST BRONCHODILATOR FEV1 - PRE BRONCHODILATOR FEV1) / PREDICTED FEV1
5. IPRATROPIUM REVERSIBILITY AND PREDICTED IPRATROPIUM REVERSIBILITY ARE CALCULATED AT VISIT 2.

CONFIDENTIAL

SB 207499

TABLE 13.9B

DESCRIPTIVE STATISTICS FOR PULMONARY FUNCTION PARAMETERS* AT SCREENING
BY TREATMENT GROUP - PP
PROTOCOL 157

PARAMETER		TREATMENT GROUP PLACEBO (N=375)	SB 207499 (N=345)	TOTAL (N=720)
SALBUTAMOL REVERSIBILITY (%)	MAX	45.95	37.84	45.95
PREDICTED SALBUTAMOL REVERSIBILITY (%)	N	373	343	716
	MEAN	2.46	2.34	2.40
	STD	3.76	3.21	3.51
	MEDIAN	2.62	2.38	2.46
	MIN	-19.98	-9.94	-19.98
	MAX	11.97	11.10	11.97
IPRATROPIUM REVERSIBILITY (%)	N	372	343	715
	MEAN	9.73	9.20	9.48
	STD	10.56	12.18	11.36
	MEDIAN	8.66	7.28	7.98
	MIN	-28.05	-26.74	-28.05
	MAX	56.96	91.82	91.82
PREDICTED IPRATROPIUM REVERSIBILITY (%)	N	372	343	715
	MEAN	4.40	3.86	4.14
	STD	4.78	5.34	5.06
	MEDIAN	4.10	3.24	3.60
	MIN	-16.19	-14.65	-16.19
	MAX	28.69	47.84	47.84
FVC (L)	N	375	345	720
	MEAN	2.88	2.81	2.85
	STD	0.86	0.77	0.81
	MEDIAN	2.81	2.78	2.81
	MIN	1.22	1.09	1.09
	MAX	5.66	5.29	5.66
PEF (L/MIN)	N	375	343	718
	MEAN	195.29	192.45	193.93
	STD	75.40	79.63	77.41
	MEDIAN	184.00	179.00	180.00

* PULMONARY FUNCTION PARAMETERS INCLUDE FEV1, FVC, PEF, FEF25-75, VOLUME REVERSIBILITY, SALBUTAMOL REVERSIBILITY, IPRATROPIUM REVERSIBILITY, PERCENT PREDICTED FEV1, FEV1/FVC RATIO, PREDICTED SALBUTAMOL REVERSIBILITY, AND PREDICTED IPRATROPIUM REVERSIBILITY

1. FEV1, FVC, PEF AND FEF25-75 ARE REPORTED PRE-ALBUTEROL INHALATION.
2. PERCENT PREDICTED FEV1 IS REPORTED POST-ALBUTEROL INHALATION.
3. SUMMARY IS FOR PER PROTOCOL PATIENTS.
4. PREDICTED SALBUTAMOL REVERSIBILITY (%) AND PREDICTED IPRATROPIUM REVERSIBILITY (%) ARE CALCULATED USING THE FOLLOWING FORMULA: 100x(POST BRONCHODILATOR FEV1 - PRE BRONCHODILATOR FEV1) / PREDICTED FEV1
5. IPRATROPIUM REVERSIBILITY AND PREDICTED IPRATROPIUM REVERSIBILITY ARE CALCULATED AT VISIT 2.

CONFIDENTIAL

SB 207499

TABLE 13.9B

DESCRIPTIVE STATISTICS FOR PULMONARY FUNCTION PARAMETERS* AT SCREENING
BY TREATMENT GROUP - PP
PROTOCOL 157

PARAMETER		TREATMENT GROUP PLACEBO (N=375)	SB 207499 (N=345)	TOTAL (N=720)
PEF (L/MIN)	MIN	70.00	35.00	35.00
	MAX	474.00	690.00	690.00
FEF25-75 (L/SEC)	N	375	345	720
	MEAN	0.60	0.58	0.59
	STD	0.29	0.33	0.31
	MEDIAN	0.53	0.52	0.52
	MIN	0.02	0.12	0.02
	MAX	1.90	2.75	2.75

* PULMONARY FUNCTION PARAMETERS INCLUDE FEV1, FVC, PEF, FEF25-75, VOLUME REVERSIBILITY, SALBUTAMOL REVERSIBILITY, IPRATROPIUM REVERSIBILITY, PERCENT PREDICTED FEV1, FEV1/FVC RATIO, PREDICTED SALBUTAMOL REVERSIBILITY, AND PREDICTED IPRATROPIUM REVERSIBILITY

1. FEV1, FVC, PEF AND FEF25-75 ARE REPORTED PRE-ALBUTEROL INHALATION.
2. PERCENT PREDICTED FEV1 IS REPORTED POST-ALBUTEROL INHALATION.
3. SUMMARY IS FOR PER PROTOCOL PATIENTS.
4. PREDICTED SALBUTAMOL REVERSIBILITY (%) AND PREDICTED IPRATROPIUM REVERSIBILITY (%) ARE CALCULATED USING THE FOLLOWING FORMULA: 100x(POST BRONCHODILATOR FEV1 - PRE BRONCHODILATOR FEV1) / PREDICTED FEV1
5. IPRATROPIUM REVERSIBILITY AND PREDICTED IPRATROPIUM REVERSIBILITY ARE CALCULATED AT VISIT 2.

CONFIDENTIAL

SB 207499

TABLE 13.9C

DESCRIPTIVE STATISTICS FOR PULMONARY FUNCTION PARAMETERS* AT SCREENING
BY TREATMENT GROUP - CURRENT SMOKERS
PROTOCOL 157

PARAMETER		TREATMENT GROUP PLACEBO (N=149)	SB 207499 (N=158)	TOTAL (N=307)
FEV1 (L)	N	149	158	307
	MEAN	1.56	1.43	1.49
	STD	0.45	0.47	0.47
	MEDIAN	1.54	1.35	1.45
	MIN	0.54	0.48	0.48
	MAX	2.82	2.91	2.91
%PREDICTED FEV1	< 35%	4 (2.7%)	15 (9.5%)	19 (6.2%)
	35 - 50%	48 (32.2%)	57 (36.1%)	105 (34.2%)
	>= 50%	96 (64.4%)	86 (54.4%)	182 (59.3%)
	N	148	158	306
	MEAN	54.17	50.95	52.51
	STD	10.64	11.77	11.33
	MEDIAN	53.52	51.89	52.69
	MIN	31.18	27.58	27.58
	MAX	70.38	69.97	70.38
FEV1/FVC	N	149	158	307
	MEAN	0.51	0.50	0.51
	STD	0.10	0.11	0.10
	MEDIAN	0.51	0.51	0.51
	MIN	0.27	0.22	0.22
	MAX	0.70	0.75	0.75
VOLUME REVERSIBILITY (ML)	N	148	158	306
	MEAN	56.82	63.12	60.08
	STD	126.05	134.10	130.09
	MEDIAN	70.00	65.00	70.00
	MIN	-670.00	-1140.00	-1140.00
	MAX	310.00	310.00	310.00
SALBUTAMOL REVERSIBILITY (%)	N	148	158	306
	MEAN	4.55	5.45	5.01
	STD	8.20	9.07	8.66
	MEDIAN	4.84	4.89	4.87
	MIN	-29.65	-54.29	-54.29

* PULMONARY FUNCTION PARAMETERS INCLUDE FEV1, FVC, PEF, FEF25-75, VOLUME REVERSIBILITY, SALBUTAMOL REVERSIBILITY, IPRATROPIUM REVERSIBILITY, PERCENT PREDICTED FEV1, FEV1/FVC RATIO, PREDICTED SALBUTAMOL REVERSIBILITY, AND PREDICTED IPRATROPIUM REVERSIBILITY

1. FEV1, FVC, PEF AND FEF25-75 ARE REPORTED PRE-ALBUTEROL INHALATION.
2. PERCENT PREDICTED FEV1 IS REPORTED POST-ALBUTEROL INHALATION.
3. SUMMARY IS FOR RANDOMIZED PATIENTS.
4. PREDICTED SALBUTAMOL REVERSIBILITY (%) AND PREDICTED IPRATROPIUM REVERSIBILITY (%) ARE CALCULATED USING THE FOLLOWING FORMULA: 100x(POST BRONCHODILATOR FEV1 - PRE BRONCHODILATOR FEV1) / PREDICTED FEV1
5. IPRATROPIUM REVERSIBILITY AND PREDICTED IPRATROPIUM REVERSIBILITY ARE CALCULATED AT VISIT 2.

CONFIDENTIAL

SB 207499

TABLE 13.9C

DESCRIPTIVE STATISTICS FOR PULMONARY FUNCTION PARAMETERS* AT SCREENING
BY TREATMENT GROUP - CURRENT SMOKERS
PROTOCOL 157

PARAMETER		TREATMENT GROUP PLACEBO (N=149)	SB 207499 (N=158)	TOTAL (N=307)
SALBUTAMOL REVERSIBILITY (%)	MAX	31.48	35.63	35.63
PREDICTED SALBUTAMOL REVERSIBILITY (%)	N	148	158	306
	MEAN	2.02	2.25	2.14
	STD	4.14	4.59	4.37
	MEDIAN	2.57	2.24	2.32
	MIN	-19.98	-37.16	-37.16
	MAX	11.03	10.07	11.03
IPRATROPIUM REVERSIBILITY (%)	N	148	158	306
	MEAN	8.44	10.73	9.62
	STD	11.31	12.11	11.77
	MEDIAN	7.88	9.13	8.72
	MIN	-29.66	-25.25	-29.66
	MAX	50.79	58.54	58.54
PREDICTED IPRATROPIUM REVERSIBILITY (%)	N	148	158	306
	MEAN	3.94	4.64	4.30
	STD	5.28	5.31	5.30
	MEDIAN	3.35	4.08	3.82
	MIN	-15.82	-14.65	-15.82
	MAX	18.30	27.07	27.07
FVC (L)	N	149	158	307
	MEAN	3.07	2.88	2.97
	STD	0.84	0.77	0.81
	MEDIAN	3.01	2.81	2.90
	MIN	1.22	1.13	1.13
	MAX	5.66	5.08	5.66
PEF (L/MIN)	N	149	157	306
	MEAN	200.40	191.68	195.93
	STD	70.10	77.90	74.21
	MEDIAN	190.00	175.00	187.50

* PULMONARY FUNCTION PARAMETERS INCLUDE FEV1, FVC, PEF, FEF25-75, VOLUME REVERSIBILITY, SALBUTAMOL REVERSIBILITY, IPRATROPIUM REVERSIBILITY, PERCENT PREDICTED FEV1, FEV1/FVC RATIO, PREDICTED SALBUTAMOL REVERSIBILITY, AND PREDICTED IPRATROPIUM REVERSIBILITY

1. FEV1, FVC, PEF AND FEF25-75 ARE REPORTED PRE-ALBUTEROL INHALATION.
2. PERCENT PREDICTED FEV1 IS REPORTED POST-ALBUTEROL INHALATION.
3. SUMMARY IS FOR RANDOMIZED PATIENTS.
4. PREDICTED SALBUTAMOL REVERSIBILITY (%) AND PREDICTED IPRATROPIUM REVERSIBILITY (%) ARE CALCULATED USING THE FOLLOWING FORMULA: 100x(POST BRONCHODILATOR FEV1 - PRE BRONCHODILATOR FEV1) / PREDICTED FEV1
5. IPRATROPIUM REVERSIBILITY AND PREDICTED IPRATROPIUM REVERSIBILITY ARE CALCULATED AT VISIT 2.

CONFIDENTIAL

SB 207499

TABLE 13.9C

DESCRIPTIVE STATISTICS FOR PULMONARY FUNCTION PARAMETERS* AT SCREENING
BY TREATMENT GROUP - CURRENT SMOKERS
PROTOCOL 157

PARAMETER		TREATMENT GROUP PLACEBO (N=149)	SB 207499 (N=158)	TOTAL (N=307)
PEF (L/MIN)	MIN	72.00	60.00	60.00
	MAX	434.00	468.00	468.00
FEF25-75 (L/SEC)	N	149	158	307
	MEAN	0.68	0.61	0.64
	STD	0.32	0.30	0.31
	MEDIAN	0.63	0.54	0.59
	MIN	0.19	0.12	0.12
	MAX	1.75	1.69	1.75

* PULMONARY FUNCTION PARAMETERS INCLUDE FEV1, FVC, PEF, FEF25-75, VOLUME REVERSIBILITY, SALBUTAMOL REVERSIBILITY, IPRATROPIUM REVERSIBILITY, PERCENT PREDICTED FEV1, FEV1/FVC RATIO, PREDICTED SALBUTAMOL REVERSIBILITY, AND PREDICTED IPRATROPIUM REVERSIBILITY

1. FEV1, FVC, PEF AND FEF25-75 ARE REPORTED PRE-ALBUTEROL INHALATION.
2. PERCENT PREDICTED FEV1 IS REPORTED POST-ALBUTEROL INHALATION.
3. SUMMARY IS FOR RANDOMIZED PATIENTS.
4. PREDICTED SALBUTAMOL REVERSIBILITY (%) AND PREDICTED IPRATROPIUM REVERSIBILITY (%) ARE CALCULATED USING THE FOLLOWING FORMULA: 100x(POST BRONCHODILATOR FEV1 - PRE BRONCHODILATOR FEV1) / PREDICTED FEV1
5. IPRATROPIUM REVERSIBILITY AND PREDICTED IPRATROPIUM REVERSIBILITY ARE CALCULATED AT VISIT 2.

CONFIDENTIAL

SB 207499

TABLE 13.9D

DESCRIPTIVE STATISTICS FOR PULMONARY FUNCTION PARAMETERS* AT SCREENING
BY TREATMENT GROUP - PREVIOUS SMOKERS
PROTOCOL 157

PARAMETER		TREATMENT GROUP PLACEBO (N=238)	SB 207499 (N=236)	TOTAL (N=474)
FEV1 (L)	N	238	236	474
	MEAN	1.33	1.31	1.32
	STD	0.42	0.42	0.42
	MEDIAN	1.31	1.29	1.30
	MIN	0.57	0.48	0.48
	MAX	2.56	2.87	2.87
%PREDICTED FEV1	< 35%	18 (7.6%)	31 (13.1%)	49 (10.3%)
	35 - 50%	86 (36.1%)	83 (35.2%)	169 (35.7%)
	>= 50%	134 (56.3%)	120 (50.8%)	254 (53.6%)
	N	238	234	472
	MEAN	51.53	49.66	50.61
	STD	11.42	12.34	11.91
	MEDIAN	51.78	50.01	50.97
	MIN	26.64	21.92	21.92
	MAX	79.56	76.94	79.56
FEV1/FVC	N	238	236	474
	MEAN	0.49	0.49	0.49
	STD	0.10	0.11	0.10
	MEDIAN	0.50	0.49	0.49
	MIN	0.27	0.24	0.24
	MAX	0.70	0.74	0.74
VOLUME REVERSIBILITY (ML)	N	238	234	472
	MEAN	73.66	65.85	69.79
	STD	95.35	85.72	90.69
	MEDIAN	80.00	70.00	70.00
	MIN	-320.00	-160.00	-320.00
	MAX	340.00	280.00	340.00
SALBUTAMOL REVERSIBILITY (%)	N	238	234	472
	MEAN	6.27	5.71	5.99
	STD	8.09	7.45	7.77
	MEDIAN	5.94	5.59	5.78
	MIN	-18.08	-12.68	-18.08

* PULMONARY FUNCTION PARAMETERS INCLUDE FEV1, FVC, PEF, FEF25-75, VOLUME REVERSIBILITY, SALBUTAMOL REVERSIBILITY, IPRATROPIUM REVERSIBILITY, PERCENT PREDICTED FEV1, FEV1/FVC RATIO, PREDICTED SALBUTAMOL REVERSIBILITY, AND PREDICTED IPRATROPIUM REVERSIBILITY

1. FEV1, FVC, PEF AND FEF25-75 ARE REPORTED PRE-ALBUTEROL INHALATION.
2. PERCENT PREDICTED FEV1 IS REPORTED POST-ALBUTEROL INHALATION.
3. SUMMARY IS FOR RANDOMIZED PATIENTS.
4. PREDICTED SALBUTAMOL REVERSIBILITY (%) AND PREDICTED IPRATROPIUM REVERSIBILITY (%) ARE CALCULATED USING THE FOLLOWING FORMULA: 100x(POST BRONCHODILATOR FEV1 - PRE BRONCHODILATOR FEV1) / PREDICTED FEV1
5. IPRATROPIUM REVERSIBILITY AND PREDICTED IPRATROPIUM REVERSIBILITY ARE CALCULATED AT VISIT 2.

CONFIDENTIAL

SB 207499

TABLE 13.9D

DESCRIPTIVE STATISTICS FOR PULMONARY FUNCTION PARAMETERS* AT SCREENING
BY TREATMENT GROUP - PREVIOUS SMOKERS
PROTOCOL 157

PARAMETER		TREATMENT GROUP PLACEBO (N=238)	SB 207499 (N=236)	TOTAL (N=474)
SALBUTAMOL REVERSIBILITY (%)	MAX	45.95	37.84	45.95
PREDICTED SALBUTAMOL REVERSIBILITY (%)	N	238	234	472
	MEAN	2.80	2.43	2.62
	STD	3.57	3.16	3.37
	MEDIAN	2.81	2.67	2.75
	MIN	-9.18	-5.28	-9.18
	MAX	12.48	11.10	12.48
IPRATROPIUM REVERSIBILITY (%)	N	236	234	470
	MEAN	10.70	8.47	9.59
	STD	11.20	10.32	10.82
	MEDIAN	9.20	6.94	8.14
	MIN	-15.11	-20.41	-20.41
	MAX	56.96	56.12	56.96
PREDICTED IPRATROPIUM REVERSIBILITY (%)	N	236	234	470
	MEAN	4.64	3.47	4.06
	STD	4.73	4.39	4.60
	MEDIAN	4.48	3.02	3.60
	MIN	-6.69	-10.27	-10.27
	MAX	28.69	20.54	28.69
FVC (L)	N	238	236	474
	MEAN	2.73	2.70	2.72
	STD	0.80	0.73	0.76
	MEDIAN	2.61	2.68	2.65
	MIN	1.25	1.09	1.09
	MAX	5.12	5.29	5.29
PEF (L/MIN)	N	238	236	474
	MEAN	187.27	190.76	189.01
	STD	74.23	77.20	75.66
	MEDIAN	176.00	179.50	179.00

* PULMONARY FUNCTION PARAMETERS INCLUDE FEV1, FVC, PEF, FEF25-75, VOLUME REVERSIBILITY, SALBUTAMOL REVERSIBILITY, IPRATROPIUM REVERSIBILITY, PERCENT PREDICTED FEV1, FEV1/FVC RATIO, PREDICTED SALBUTAMOL REVERSIBILITY, AND PREDICTED IPRATROPIUM REVERSIBILITY

1. FEV1, FVC, PEF AND FEF25-75 ARE REPORTED PRE-ALBUTEROL INHALATION.
2. PERCENT PREDICTED FEV1 IS REPORTED POST-ALBUTEROL INHALATION.
3. SUMMARY IS FOR RANDOMIZED PATIENTS.
4. PREDICTED SALBUTAMOL REVERSIBILITY (%) AND PREDICTED IPRATROPIUM REVERSIBILITY (%) ARE CALCULATED USING THE FOLLOWING FORMULA: 100x(POST BRONCHODILATOR FEV1 - PRE BRONCHODILATOR FEV1) / PREDICTED FEV1
5. IPRATROPIUM REVERSIBILITY AND PREDICTED IPRATROPIUM REVERSIBILITY ARE CALCULATED AT VISIT 2.

CONFIDENTIAL

SB 207499

TABLE 13.9D

DESCRIPTIVE STATISTICS FOR PULMONARY FUNCTION PARAMETERS* AT SCREENING
BY TREATMENT GROUP - PREVIOUS SMOKERS
PROTOCOL 157

PARAMETER		TREATMENT GROUP PLACEBO (N=238)	SB 207499 (N=236)	TOTAL (N=474)
PEF (L/MIN)	MIN	68.00	35.00	35.00
	MAX	474.00	690.00	690.00
FEF25-75 (L/SEC)	N	238	236	474
	MEAN	0.55	0.56	0.55
	STD	0.34	0.34	0.34
	MEDIAN	0.48	0.48	0.48
	MIN	0.02	0.14	0.02
	MAX	3.91	2.75	3.91

* PULMONARY FUNCTION PARAMETERS INCLUDE FEV1, FVC, PEF, FEF25-75, VOLUME REVERSIBILITY, SALBUTAMOL REVERSIBILITY, IPRATROPIUM REVERSIBILITY, PERCENT PREDICTED FEV1, FEV1/FVC RATIO, PREDICTED SALBUTAMOL REVERSIBILITY, AND PREDICTED IPRATROPIUM REVERSIBILITY

1. FEV1, FVC, PEF AND FEF25-75 ARE REPORTED PRE-ALBUTEROL INHALATION.
2. PERCENT PREDICTED FEV1 IS REPORTED POST-ALBUTEROL INHALATION.
3. SUMMARY IS FOR RANDOMIZED PATIENTS.
4. PREDICTED SALBUTAMOL REVERSIBILITY (%) AND PREDICTED IPRATROPIUM REVERSIBILITY (%) ARE CALCULATED USING THE FOLLOWING FORMULA: 100x(POST BRONCHODILATOR FEV1 - PRE BRONCHODILATOR FEV1) / PREDICTED FEV1
5. IPRATROPIUM REVERSIBILITY AND PREDICTED IPRATROPIUM REVERSIBILITY ARE CALCULATED AT VISIT 2.

CONFIDENTIAL

SB 207499

TABLE 13.11

SUMMARY OF PULMONARY HISTORY
BY TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

HISTORY	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
CHRONIC BRONCHITITS	286 (63.3%)	260 (57.1%)	546 (60.2%)
LUNG REDUCTION SURGERY	1 (0.2%)	2 (0.4%)	3 (0.3%)

1. PERCENTAGES ARE BASED ON NUMBER OF RANDOMIZED PATIENTS.
2. PULMONARY REHABILITATION PROGRAMS WITHIN FOUR WEEKS PRIOR TO SCREENING VISIT ARE REPORTED
3. COPD EXACERBATIONS OCCURING WITHIN TWO WEEKS PRIOR TO SCREENING VISIT ARE REPORTED

CONFIDENTIAL

SB 207499

TABLE 13.12A

DESCRIPTIVE STATISTICS AT SCREENING FOR SMOKING HISTORY, ALCOHOL INTAKE AND DURATION OF COPD
BY TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

Parameter		TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
SMOKING STATUS AT BASELINE	FORMER SMOKER	264 (58.4%)	259 (56.9%)	523 (57.7%)
	CURRENT SMOKER	188 (41.6%)	196 (43.1%)	384 (42.3%)
PACK YEARS	N	452	455	907
	MEAN	43.8	44.8	44.3
	STD	27.3	26.0	26.6
	MEDIAN	40.0	40.0	40.0
	MIN	10.0	10.0	10.0
	MAX	275.0	200.0	275.0
CIGARETTES/DAY	N	206	206	412
	MEAN	16.9	17.0	17.0
	STD	10.1	8.9	9.5
	MEDIAN	20.0	20.0	20.0
	MIN	0.0	0.0	0.0
	MAX	58.0	50.0	58.0
ALCOHOL INTAKE(UNITS/WEEK)	N	450	455	905
	MEAN	5.6	6.1	5.8
	STD	8.2	9.0	8.7
	MEDIAN	1.0	2.0	2.0
	MIN	0.0	0.0	0.0
	MAX	56.0	56.0	56.0
DURATION COPD(YEARS)	N	452	455	907
	MEAN	7.8	7.9	7.8
	STD	7.4	7.4	7.4
	MEDIAN	5.0	5.0	5.0
	MIN	0.0	0.0	0.0
	MAX	55.0	45.0	55.0

1. ALL PARAMETERS EXCEPT SMOKING STATUS ARE EVALUATED AT SCREENING.

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 13.12B

DESCRIPTIVE STATISTICS AT SCREENING FOR SMOKING HISTORY, ALCOHOL INTAKE AND DURATION OF COPD
BY TREATMENT GROUP - PER PROTOCOL PATIENTS
PROTOCOL 157

Parameter		TREATMENT GROUP PLACEBO (N=375)	SB 207499 (N=345)	Total (N=720)
PACK YEARS	N	375	345	720
	MEAN	43.6	45.0	44.3
	STD	27.3	26.0	26.7
	MEDIAN	40.0	40.0	40.0
	MIN	10.0	10.0	10.0
	MAX	275.0	200.0	275.0
CIGARETTES/DAY	N	183	166	349
	MEAN	16.9	16.6	16.8
	STD	9.8	9.0	9.4
	MEDIAN	20.0	20.0	20.0
	MIN	0.0	0.0	0.0
	MAX	50.0	50.0	50.0
ALCOHOL INTAKE(UNITS/WEEK)	N	375	345	720
	MEAN	5.4	6.0	5.7
	STD	7.9	9.1	8.5
	MEDIAN	2.0	2.0	2.0
	MIN	0.0	0.0	0.0
	MAX	56.0	56.0	56.0
DURATION COPD(YEARS)	N	375	345	720
	MEAN	7.6	7.8	7.7
	STD	7.4	7.4	7.4
	MEDIAN	5.0	6.0	6.0
	MIN	0.0	0.0	0.0
	MAX	55.0	45.0	55.0

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 13.12C

DESCRIPTIVE STATISTICS AT SCREENING FOR SMOKING HISTORY, ALCOHOL INTAKE AND DURATION OF COPD
BY TREATMENT GROUP - RANDOMIZED CURRENT SMOKERS AT BASELINE
PROTOCOL 157

Parameter		TREATMENT GROUP PLACEBO (N=188)	SB 207499 (N=196)	Total (N=384)
PACK YEARS	N	188	196	384
	MEAN	44.3	45.2	44.8
	STD	23.2	21.1	22.2
	MEDIAN	39.0	41.2	40.0
	MIN	11.3	15.0	11.3
	MAX	146.0	165.0	165.0
CIGARETTES/DAY	N	184	193	377
	MEAN	17.7	17.0	17.3
	STD	10.2	8.8	9.5
	MEDIAN	20.0	20.0	20.0
	MIN	0.0	1.0	0.0
	MAX	58.0	50.0	58.0
ALCOHOL INTAKE(UNITS/WEEK)	N	187	196	383
	MEAN	6.0	6.1	6.1
	STD	8.3	9.4	8.9
	MEDIAN	3.0	2.0	3.0
	MIN	0.0	0.0	0.0
	MAX	56.0	50.0	56.0
DURATION COPD(YEARS)	N	188	196	384
	MEAN	7.4	6.9	7.1
	STD	6.8	6.3	6.5
	MEDIAN	5.0	5.0	5.0
	MIN	0.0	0.0	0.0
	MAX	32.0	34.0	34.0

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 13.12D

DESCRIPTIVE STATISTICS AT SCREENING FOR SMOKING HISTORY, ALCOHOL INTAKE AND DURATION OF COPD
BY TREATMENT GROUP - RANDOMIZED FORMER SMOKERS AT BASELINE
PROTOCOL 157

Parameter		TREATMENT GROUP PLACEBO (N=264)	SB 207499 (N=259)	Total (N=523)
PACK YEARS	N	264	259	523
	MEAN	43.4	44.5	43.9
	STD	30.0	29.1	29.5
	MEDIAN	40.0	40.0	40.0
	MIN	10.0	10.0	10.0
	MAX	275.0	200.0	275.0
CIGARETTES/DAY	N	22	13	35
	MEAN	11.0	17.7	13.5
	STD	7.3	11.2	9.4
	MEDIAN	10.0	20.0	10.0
	MIN	0.0	0.0	0.0
	MAX	20.0	40.0	40.0
ALCOHOL INTAKE(UNITS/WEEK)	N	263	259	522
	MEAN	5.3	6.0	5.7
	STD	8.2	8.8	8.5
	MEDIAN	1.0	2.0	1.0
	MIN	0.0	0.0	0.0
	MAX	50.0	56.0	56.0
DURATION COPD(YEARS)	N	264	259	523
	MEAN	8.1	8.6	8.3
	STD	7.8	8.1	7.9
	MEDIAN	6.0	6.0	6.0
	MIN	0.0	0.0	0.0
	MAX	55.0	45.0	55.0

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 13.13A

SUMMARY OF PRIOR MEDICAL CONDITIONS AT SCREENING
BY DISEASE CODE LEVEL, MEDDRA PREFERRED TERM, AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

DISEASE CODE	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	TOTAL (N=907)
TOTAL	TOTAL	267 (59.1%)	262 (57.6%)	529 (58.3%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	TOTAL		3 (0.7%)	3 (0.3%)
	ANAEMIA		1 (0.2%)	1 (0.1%)
	ANAEMIA MACROCYTIC		1 (0.2%)	1 (0.1%)
	PURPURA NON-THROMBOCYTOPENIC		1 (0.2%)	1 (0.1%)
CARDIAC DISORDERS	TOTAL	30 (6.6%)	46 (10.1%)	76 (8.4%)
	ACUTE MYOCARDIAL INFARCTION	2 (0.4%)	4 (0.9%)	6 (0.7%)
	AGE INDETERMINATE MYOCARDIAL INFARCTION	2 (0.4%)	3 (0.7%)	5 (0.6%)
	ANGINA PECTORIS	4 (0.9%)	1 (0.2%)	5 (0.6%)
	AORTIC VALVE INCOMPETENCE	1 (0.2%)		1 (0.1%)
	ARRHYTHMIA	1 (0.2%)	5 (1.1%)	6 (0.7%)
	ATRIAL FIBRILLATION	4 (0.9%)	3 (0.7%)	7 (0.8%)
	ATRIAL TACHYCARDIA	1 (0.2%)		1 (0.1%)
	CARDIAC FAILURE		1 (0.2%)	1 (0.1%)
	CARDIAC FAILURE CONGESTIVE		3 (0.7%)	3 (0.3%)
	CORONARY ARTERY DISEASE		4 (0.9%)	4 (0.4%)
	LEFT VENTRICULAR FAILURE		1 (0.2%)	1 (0.1%)
	MITRAL VALVE DISEASE		1 (0.2%)	1 (0.1%)
	MYOCARDIAL INFARCTION	13 (2.9%)	17 (3.7%)	30 (3.3%)
	MYOCARDIAL ISCHAEMIA	1 (0.2%)	4 (0.9%)	5 (0.6%)
	PERICARDITIS		1 (0.2%)	1 (0.1%)
	RHEUMATIC FEVER		1 (0.2%)	1 (0.1%)
	SINUS TACHYCARDIA	1 (0.2%)		1 (0.1%)
	SUPRAVENTRICULAR EXTRASYSTOLES	1 (0.2%)		1 (0.1%)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	TOTAL	2 (0.4%)	1 (0.2%)	3 (0.3%)
	CONGENITAL ATRIAL SEPTAL DEFECT		1 (0.2%)	1 (0.1%)
	DERMOID CYST	2 (0.4%)		2 (0.2%)
EAR AND LABYRINTH DISORDERS	TOTAL	5 (1.1%)	4 (0.9%)	9 (1.0%)
	AURAL POLYP	1 (0.2%)		1 (0.1%)
	DEAFNESS	1 (0.2%)		1 (0.1%)
	DEAFNESS NEUROSENSORY		1 (0.2%)	1 (0.1%)
	TINNITUS		2 (0.4%)	2 (0.2%)
	TYMPANIC MEMBRANE PERFORATION	2 (0.4%)	1 (0.2%)	3 (0.3%)
	VERTIGO	1 (0.2%)		1 (0.1%)
ENDOCRINE DISORDERS	TOTAL	4 (0.9%)	3 (0.7%)	7 (0.8%)

1. PERCENTAGES ARE BASED ON NUMBER OF RANDOMIZED PATIENTS.
2. EXCLUSIVELY PRIOR CONDITIONS-ONGOING CONDITIONS SUMMARIZED IN TABLE 13.13B

CONFIDENTIAL

SB 207499

TABLE 13.13A

SUMMARY OF PRIOR MEDICAL CONDITIONS AT SCREENING
BY DISEASE CODE LEVEL, MEDDRA PREFERRED TERM, AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

DISEASE CODE	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	TOTAL (N=907)
ENDOCRINE DISORDERS	GOITRE	2 (0.4%)	1 (0.2%)	3 (0.3%)
	HYPERTHYROIDISM	1 (0.2%)		1 (0.1%)
	THYROID NODULE		1 (0.2%)	1 (0.1%)
	THYROTOXICOSIS	1 (0.2%)	1 (0.2%)	2 (0.2%)
EYE DISORDERS	TOTAL	13 (2.9%)	7 (1.5%)	20 (2.2%)
	AMAUROSIS FUGAX	1 (0.2%)	1 (0.2%)	2 (0.2%)
	AMBLYOPIA TOBACCO		1 (0.2%)	1 (0.1%)
	BLEPHARITIS	1 (0.2%)	1 (0.2%)	2 (0.2%)
	CATARACT	3 (0.7%)	3 (0.7%)	6 (0.7%)
	CONJUNCTIVAL HAEMORRHAGE	1 (0.2%)		1 (0.1%)
	CONJUNCTIVITIS		1 (0.2%)	1 (0.1%)
	DIPLOPIA	1 (0.2%)		1 (0.1%)
	GLAUCOMA	1 (0.2%)		1 (0.1%)
	PTERYGIUM	1 (0.2%)		1 (0.1%)
	RETINAL DETACHMENT	4 (0.9%)		4 (0.4%)
	RETINAL HAEMORRHAGE	1 (0.2%)		1 (0.1%)
	RETINAL TEAR		1 (0.2%)	1 (0.1%)
	VISION BLURRED		1 (0.2%)	1 (0.1%)
GASTROINTESTINAL DISORDERS	TOTAL	66 (14.6%)	63 (13.8%)	129 (14.2%)
	ABDOMINAL HERNIA		1 (0.2%)	1 (0.1%)
	ACQUIRED PYLORIC STENOSIS		1 (0.2%)	1 (0.1%)
	ANAL FISSURE	2 (0.4%)		2 (0.2%)
	ANAL FISTULA	3 (0.7%)	1 (0.2%)	4 (0.4%)
	BENIGN COLONIC POLYP	1 (0.2%)		1 (0.1%)
	BENIGN GASTRIC POLYP	1 (0.2%)		1 (0.1%)
	COLITIS	2 (0.4%)		2 (0.2%)
	COLONIC POLYP		3 (0.7%)	3 (0.3%)
	CONSTIPATION	1 (0.2%)	1 (0.2%)	2 (0.2%)
	DIARRHOEA	1 (0.2%)		1 (0.1%)
	DIVERTICULUM	1 (0.2%)	1 (0.2%)	2 (0.2%)
	DIVERTICULUM INTESTINAL	1 (0.2%)	1 (0.2%)	2 (0.2%)
	DUODENAL ULCER	10 (2.2%)	12 (2.6%)	22 (2.4%)
	DUODENAL ULCER HAEMORRHAGE	2 (0.4%)		2 (0.2%)
	DUODENITIS		2 (0.4%)	2 (0.2%)
	DYSPEPSIA		2 (0.4%)	2 (0.2%)
	FAECAL INCONTINENCE	1 (0.2%)		1 (0.1%)
	GASTRIC POLYPS	1 (0.2%)		1 (0.1%)
	GASTRIC ULCER	13 (2.9%)	10 (2.2%)	23 (2.5%)
	GASTRIC ULCER HAEMORRHAGE		1 (0.2%)	1 (0.1%)
	GASTRIC ULCER PERFORATION	1 (0.2%)		1 (0.1%)

1. PERCENTAGES ARE BASED ON NUMBER OF RANDOMIZED PATIENTS.
2. EXCLUSIVELY PRIOR CONDITIONS-ONGOING CONDITIONS SUMMARIZED IN TABLE 13.13B

CONFIDENTIAL

SB 207499

TABLE 13.13A

SUMMARY OF PRIOR MEDICAL CONDITIONS AT SCREENING
BY DISEASE CODE LEVEL, MEDDRA PREFERRED TERM, AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

DISEASE CODE	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	TOTAL (N=907)
GASTROINTESTINAL DISORDERS	GASTRITIS	3 (0.7%)	3 (0.7%)	6 (0.7%)
	GASTRODUODENAL ULCER		2 (0.4%)	2 (0.2%)
	GASTROINTESTINAL DISORDER		1 (0.2%)	1 (0.1%)
	GASTROOESOPHAGEAL REFLUX DISEASE	2 (0.4%)		2 (0.2%)
	HAEMORRHOIDAL HAEMORRHAGE	1 (0.2%)		1 (0.1%)
	HAEMORRHOIDS	2 (0.4%)	4 (0.9%)	6 (0.7%)
	HIATUS HERNIA	4 (0.9%)	4 (0.9%)	8 (0.9%)
	INGUINAL HERNIA	9 (2.0%)	10 (2.2%)	19 (2.1%)
	INTESTINAL HAEMORRHAGE	2 (0.4%)		2 (0.2%)
	INTESTINAL OBSTRUCTION	1 (0.2%)		1 (0.1%)
	INTESTINAL POLYP	1 (0.2%)	1 (0.2%)	2 (0.2%)
	IRRITABLE BOWEL SYNDROME		2 (0.4%)	2 (0.2%)
	LUMBAR HERNIA	1 (0.2%)		1 (0.1%)
	OESOPHAGITIS		3 (0.7%)	3 (0.3%)
	PANCREATIC DISORDER	1 (0.2%)		1 (0.1%)
	PANCREATITIS	5 (1.1%)		5 (0.6%)
	PANCREATITIS ACUTE	1 (0.2%)		1 (0.1%)
	PEPTIC ULCER	2 (0.4%)	6 (1.3%)	8 (0.9%)
	PERIODONTITIS		1 (0.2%)	1 (0.1%)
	PERITONITIS	2 (0.4%)	1 (0.2%)	3 (0.3%)
	RECTAL HAEMORRHAGE	2 (0.4%)	2 (0.4%)	4 (0.4%)
	RECTAL POLYP	1 (0.2%)	1 (0.2%)	2 (0.2%)
	SALIVARY GLAND CALCULUS	1 (0.2%)		1 (0.1%)
	STRESS ULCER	1 (0.2%)		1 (0.1%)
	UMBILICAL HERNIA		1 (0.2%)	1 (0.1%)
	UPPER GASTROINTESTINAL HAEMORRHAGE	1 (0.2%)	1 (0.2%)	2 (0.2%)
	VOMITING	1 (0.2%)		1 (0.1%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	TOTAL	4 (0.9%)	5 (1.1%)	9 (1.0%)
	CHEST DISCOMFORT	1 (0.2%)		1 (0.1%)
	CHEST PAIN	3 (0.7%)	2 (0.4%)	5 (0.6%)
	HERNIA		2 (0.4%)	2 (0.2%)
	OEDEMA PERIPHERAL		1 (0.2%)	1 (0.1%)
	SUDDEN DEATH		1 (0.2%)	1 (0.1%)
HEPATOBILIARY DISORDERS	TOTAL	6 (1.3%)	13 (2.9%)	19 (2.1%)
	BILIARY COLIC		2 (0.4%)	2 (0.2%)
	CHOLECYSTITIS		3 (0.7%)	3 (0.3%)
	CHOLELITHIASIS	4 (0.9%)	3 (0.7%)	7 (0.8%)
	HEPATIC FUNCTION ABNORMAL	1 (0.2%)		1 (0.1%)
	HEPATITIS	1 (0.2%)	2 (0.4%)	3 (0.3%)

1. PERCENTAGES ARE BASED ON NUMBER OF RANDOMIZED PATIENTS.
2. EXCLUSIVELY PRIOR CONDITIONS-ONGOING CONDITIONS SUMMARIZED IN TABLE 13.13B

CONFIDENTIAL

SB 207499

TABLE 13.13A

SUMMARY OF PRIOR MEDICAL CONDITIONS AT SCREENING
BY DISEASE CODE LEVEL, MEDDRA PREFERRED TERM, AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

DISEASE CODE	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	TOTAL (N=907)
HEPATOBILIARY DISORDERS	JAUNDICE		1 (0.2%)	1 (0.1%)
	LIVER DISORDER		1 (0.2%)	1 (0.1%)
	POST CHOLECYSTECTOMY SYNDROME		1 (0.2%)	1 (0.1%)
IMMUNE SYSTEM DISORDERS	TOTAL	2 (0.4%)	1 (0.2%)	3 (0.3%)
	HYPERSENSITIVITY		1 (0.2%)	1 (0.1%)
	SARCOIDOSIS	1 (0.2%)		1 (0.1%)
	SEASONAL ALLERGY	1 (0.2%)		1 (0.1%)
INFECTIONS AND INFESTATIONS	TOTAL	74 (16.4%)	73 (16.0%)	147 (16.2%)
	APPENDICITIS	1 (0.2%)	1 (0.2%)	2 (0.2%)
	BREAST ABSCESS		1 (0.2%)	1 (0.1%)
	BRONCHIAL INFECTION	1 (0.2%)		1 (0.1%)
	BRONCHIECTASIS		1 (0.2%)	1 (0.1%)
	BRONCHIOLITIS	1 (0.2%)		1 (0.1%)
	BRONCHITIS	1 (0.2%)		1 (0.1%)
	BRONCHITIS ACUTE	1 (0.2%)	2 (0.4%)	3 (0.3%)
	BRONCHITIS CHRONIC	2 (0.4%)	1 (0.2%)	3 (0.3%)
	BRONCHOPNEUMONIA	4 (0.9%)	3 (0.7%)	7 (0.8%)
	BRUCELLOSIS	1 (0.2%)		1 (0.1%)
	CHRONIC SINUSITIS		1 (0.2%)	1 (0.1%)
	DIPHTHERIA	1 (0.2%)		1 (0.1%)
	ECHINOCOCCIASIS	1 (0.2%)	1 (0.2%)	2 (0.2%)
	EMPYEMA	1 (0.2%)		1 (0.1%)
	EYE INFECTION	1 (0.2%)		1 (0.1%)
	FUNGAL INFECTION		1 (0.2%)	1 (0.1%)
	FURUNCLE	1 (0.2%)		1 (0.1%)
	GASTROENTERITIS HELICOBACTER	1 (0.2%)		1 (0.1%)
	HELICOBACTER GASTRITIS		1 (0.2%)	1 (0.1%)
	HELICOBACTER INFECTION		1 (0.2%)	1 (0.1%)
	HEPATITIS A	2 (0.4%)		2 (0.2%)
	HEPATITIS B	1 (0.2%)	2 (0.4%)	3 (0.3%)
	HEPATITIS INFECTIOUS	1 (0.2%)		1 (0.1%)
	HEPATITIS VIRAL		1 (0.2%)	1 (0.1%)
	HERPES ZOSTER	3 (0.7%)	4 (0.9%)	7 (0.8%)
	LARYNGITIS	1 (0.2%)		1 (0.1%)
	LIVER ABSCESS	1 (0.2%)		1 (0.1%)
	LOBAR PNEUMONIA	1 (0.2%)	1 (0.2%)	2 (0.2%)
	LOWER RESPIRATORY TRACT INFECTION	1 (0.2%)		1 (0.1%)
	LUNG ABSCESS	3 (0.7%)	3 (0.7%)	6 (0.7%)
	LYMPH NODE TUBERCULOSIS	1 (0.2%)		1 (0.1%)
	MALARIA		3 (0.7%)	3 (0.3%)

1. PERCENTAGES ARE BASED ON NUMBER OF RANDOMIZED PATIENTS.
2. EXCLUSIVELY PRIOR CONDITIONS-ONGOING CONDITIONS SUMMARIZED IN TABLE 13.13B

CONFIDENTIAL

SB 207499

TABLE 13.13A

SUMMARY OF PRIOR MEDICAL CONDITIONS AT SCREENING
BY DISEASE CODE LEVEL, MEDDRA PREFERRED TERM, AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

DISEASE CODE	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	TOTAL (N=907)
INFECTIONS AND INFESTATIONS	MENINGITIS	2 (0.4%)	1 (0.2%)	3 (0.3%)
	NASOPHARYNGITIS	1 (0.2%)	2 (0.4%)	3 (0.3%)
	OESOPHAGEAL CANDIDIASIS	1 (0.2%)		1 (0.1%)
	ONYCHOMYCOSIS		1 (0.2%)	1 (0.1%)
	ORCHITIS	1 (0.2%)	1 (0.2%)	2 (0.2%)
	OSTEOMYELITIS	1 (0.2%)	2 (0.4%)	3 (0.3%)
	OTITIS EXTERNA	1 (0.2%)	1 (0.2%)	2 (0.2%)
	OTITIS MEDIA CHRONIC		1 (0.2%)	1 (0.1%)
	PERIANAL ABSCESS	1 (0.2%)	2 (0.4%)	3 (0.3%)
	PHARYNGITIS	1 (0.2%)	2 (0.4%)	3 (0.3%)
	PNEUMONIA	22 (4.9%)	20 (4.4%)	42 (4.6%)
	PNEUMONIA LEGIONELLA		1 (0.2%)	1 (0.1%)
	PNEUMONIA NECROTISING		1 (0.2%)	1 (0.1%)
	POLIOMYELITIS		2 (0.4%)	2 (0.2%)
	PULMONARY TUBERCULOSIS	10 (2.2%)	13 (2.9%)	23 (2.5%)
	PYELONEPHRITIS CHRONIC	1 (0.2%)		1 (0.1%)
	RECTAL ABSCESS	1 (0.2%)		1 (0.1%)
	REITER'S SYNDROME		1 (0.2%)	1 (0.1%)
	SEPSIS	2 (0.4%)		2 (0.2%)
	SINUSITIS	5 (1.1%)	4 (0.9%)	9 (1.0%)
	SMALLPOX	1 (0.2%)		1 (0.1%)
	SYPHILIS		1 (0.2%)	1 (0.1%)
	TONSILLITIS		1 (0.2%)	1 (0.1%)
	TOXOPLASMOSIS	1 (0.2%)		1 (0.1%)
	TUBERCULOSIS	5 (1.1%)	10 (2.2%)	15 (1.7%)
	TUBERCULOUS PLEURISY		2 (0.4%)	2 (0.2%)
	TYPHOID FEVER	1 (0.2%)		1 (0.1%)
	TYPHUS	2 (0.4%)		2 (0.2%)
	UPPER RESPIRATORY TRACT INFECTION		1 (0.2%)	1 (0.1%)
	UROSEPSIS	1 (0.2%)		1 (0.1%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	TOTAL	25 (5.5%)	15 (3.3%)	40 (4.4%)
	ANKLE FRACTURE	3 (0.7%)		3 (0.3%)
	BRAIN CONTUSION	1 (0.2%)		1 (0.1%)
	CHEMICAL POISONING	1 (0.2%)		1 (0.1%)
	CHEST INJURY		1 (0.2%)	1 (0.1%)
	CLAVICLE FRACTURE		1 (0.2%)	1 (0.1%)
	CONCUSSION		1 (0.2%)	1 (0.1%)
	EPICONDYLITIS	1 (0.2%)		1 (0.1%)
	EXTRADURAL HAEMATOMA	1 (0.2%)		1 (0.1%)
	EYE INJURY	2 (0.4%)		2 (0.2%)

1. PERCENTAGES ARE BASED ON NUMBER OF RANDOMIZED PATIENTS.
2. EXCLUSIVELY PRIOR CONDITIONS-ONGOING CONDITIONS SUMMARIZED IN TABLE 13.13B

CONFIDENTIAL

SB 207499

TABLE 13.13A

SUMMARY OF PRIOR MEDICAL CONDITIONS AT SCREENING
BY DISEASE CODE LEVEL, MEDDRA PREFERRED TERM, AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

DISEASE CODE	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	TOTAL (N=907)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	FEMUR FRACTURE	1 (0.2%)	1 (0.2%)	2 (0.2%)
	FIBULA FRACTURE	1 (0.2%)	1 (0.2%)	2 (0.2%)
	FOOT FRACTURE	2 (0.4%)	1 (0.2%)	3 (0.3%)
	FOREIGN BODY TRAUMA	1 (0.2%)		1 (0.1%)
	HAND FRACTURE	1 (0.2%)	2 (0.4%)	3 (0.3%)
	HEAD INJURY	1 (0.2%)		1 (0.1%)
	INJURY		1 (0.2%)	1 (0.1%)
	LIMB INJURY		1 (0.2%)	1 (0.1%)
	LOWER LIMB FRACTURE	1 (0.2%)	1 (0.2%)	2 (0.2%)
	MENISCUS LESION		1 (0.2%)	1 (0.1%)
	POISONING	1 (0.2%)		1 (0.1%)
	RIB FRACTURE	4 (0.9%)	2 (0.4%)	6 (0.7%)
	ROAD TRAFFIC ACCIDENT	1 (0.2%)	2 (0.4%)	3 (0.3%)
	SILICOSIS	1 (0.2%)		1 (0.1%)
	TENDON RUPTURE	1 (0.2%)		1 (0.1%)
	THERMAL BURN	1 (0.2%)	1 (0.2%)	2 (0.2%)
	TIBIA FRACTURE	1 (0.2%)		1 (0.1%)
	UPPER LIMB FRACTURE	2 (0.4%)	1 (0.2%)	3 (0.3%)
	WRIST FRACTURE	2 (0.4%)	1 (0.2%)	3 (0.3%)
INVESTIGATIONS	TOTAL	9 (2.0%)	12 (2.6%)	21 (2.3%)
	ANGIOGRAM		1 (0.2%)	1 (0.1%)
	ARTERIOGRAM CORONARY	1 (0.2%)	2 (0.4%)	3 (0.3%)
	ARTHROSCOPY		2 (0.4%)	2 (0.2%)
	BIOPSY CERVIX		1 (0.2%)	1 (0.1%)
	BLOOD ALBUMIN DECREASED	1 (0.2%)		1 (0.1%)
	BLOOD GLUCOSE INCREASED	1 (0.2%)		1 (0.1%)
	CARDIAC MURMUR		2 (0.4%)	2 (0.2%)
	CARDIAC MURMUR FUNCTIONAL		1 (0.2%)	1 (0.1%)
	CHEST X-RAY ABNORMAL	1 (0.2%)		1 (0.1%)
	COLONOSCOPY	1 (0.2%)	3 (0.7%)	4 (0.4%)
	GAMMA-GLUTAMYLTRANSFERASE INCREASED	1 (0.2%)		1 (0.1%)
	HELICOBACTER PYLORI ANTIBODY POSITIVE		1 (0.2%)	1 (0.1%)
	HEPATITIS B SURFACE ANTIGEN POSITIVE	1 (0.2%)		1 (0.1%)
	SIGMOIDOSCOPY	1 (0.2%)	1 (0.2%)	2 (0.2%)
	SPUTUM ABNORMAL	1 (0.2%)		1 (0.1%)
	WEIGHT DECREASED	2 (0.4%)	1 (0.2%)	3 (0.3%)
METABOLISM AND NUTRITION DISORDERS	TOTAL	7 (1.5%)	3 (0.7%)	10 (1.1%)
	DEHYDRATION	1 (0.2%)		1 (0.1%)

1. PERCENTAGES ARE BASED ON NUMBER OF RANDOMIZED PATIENTS.
2. EXCLUSIVELY PRIOR CONDITIONS-ONGOING CONDITIONS SUMMARIZED IN TABLE 13.13B

CONFIDENTIAL

SB 207499

TABLE 13.13A

SUMMARY OF PRIOR MEDICAL CONDITIONS AT SCREENING
BY DISEASE CODE LEVEL, MEDDRA PREFERRED TERM, AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

DISEASE CODE	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	TOTAL (N=907)
METABOLISM AND NUTRITION DISORDERS	DIABETES MELLITUS		1 (0.2%)	1 (0.1%)
	GOUT	3 (0.7%)	1 (0.2%)	4 (0.4%)
	HYPERTRIGLYCERIDAEMIA	1 (0.2%)		1 (0.1%)
	HYPERURICAEMIA	1 (0.2%)	1 (0.2%)	2 (0.2%)
	TETANY	1 (0.2%)		1 (0.1%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	TOTAL	21 (4.6%)	26 (5.7%)	47 (5.2%)
	ANKYLOSING SPONDYLITIS		1 (0.2%)	1 (0.1%)
	ARTHRITIS	2 (0.4%)	1 (0.2%)	3 (0.3%)
	BACK PAIN	2 (0.4%)	2 (0.4%)	4 (0.4%)
	BONE SPUR		1 (0.2%)	1 (0.1%)
	BURSITIS		1 (0.2%)	1 (0.1%)
	DUPUYTREN'S CONTRACTURE	1 (0.2%)		1 (0.1%)
	EXOSTOSIS		1 (0.2%)	1 (0.1%)
	FISTULA	1 (0.2%)		1 (0.1%)
	GOUTY ARTHRITIS	1 (0.2%)		1 (0.1%)
	INTERVERTEBRAL DISC DISORDER	1 (0.2%)		1 (0.1%)
	INTERVERTEBRAL DISC PROTRUSION	6 (1.3%)	9 (2.0%)	15 (1.7%)
	MUSCULOSKELETAL CHEST PAIN	1 (0.2%)		1 (0.1%)
	MYOFASCIAL PAIN SYNDROME		1 (0.2%)	1 (0.1%)
	NECK PAIN	1 (0.2%)		1 (0.1%)
	NECK, SHOULDER AND ARM SYNDROME		1 (0.2%)	1 (0.1%)
	OSTEOARTHRITIS	1 (0.2%)	2 (0.4%)	3 (0.3%)
	OSTEOCHONDROSIS		1 (0.2%)	1 (0.1%)
	PERIARTHRITIS	2 (0.4%)		2 (0.2%)
	RHABDOMYOLYSIS		1 (0.2%)	1 (0.1%)
	ROTATOR CUFF SYNDROME		1 (0.2%)	1 (0.1%)
	SPINAL COMPRESSION FRACTURE		2 (0.4%)	2 (0.2%)
	SPINAL FUSION ACQUIRED		1 (0.2%)	1 (0.1%)
	SPONDYLOSIS	1 (0.2%)		1 (0.1%)
	SYSTEMIC LUPUS ERYTHEMATOSUS		1 (0.2%)	1 (0.1%)
	TENDONITIS	1 (0.2%)		1 (0.1%)
	TOE DEFORMITY	1 (0.2%)		1 (0.1%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	TOTAL	32 (7.1%)	23 (5.1%)	55 (6.1%)
	BASAL CELL CARCINOMA	4 (0.9%)	3 (0.7%)	7 (0.8%)
	BENIGN NEOPLASM		1 (0.2%)	1 (0.1%)
	BENIGN NEOPLASM OF SKIN		1 (0.2%)	1 (0.1%)

1. PERCENTAGES ARE BASED ON NUMBER OF RANDOMIZED PATIENTS.
2. EXCLUSIVELY PRIOR CONDITIONS-ONGOING CONDITIONS SUMMARIZED IN TABLE 13.13B

CONFIDENTIAL

SB 207499

TABLE 13.13A

SUMMARY OF PRIOR MEDICAL CONDITIONS AT SCREENING
BY DISEASE CODE LEVEL, MEDDRA PREFERRED TERM, AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

DISEASE CODE	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	TOTAL (N=907)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	BENIGN SALIVARY GLAND NEOPLASM	2 (0.4%)		2 (0.2%)
	BLADDER CANCER	1 (0.2%)	2 (0.4%)	3 (0.3%)
	BOWEN'S DISEASE	1 (0.2%)	1 (0.2%)	2 (0.2%)
	CARCINOMA	1 (0.2%)		1 (0.1%)
	CERVIX CARCINOMA STAGE 0		1 (0.2%)	1 (0.1%)
	CHOLESTEATOMA		1 (0.2%)	1 (0.1%)
	COLON ADENOMA	1 (0.2%)		1 (0.1%)
	COLON CANCER	1 (0.2%)	1 (0.2%)	2 (0.2%)
	COLON CANCER STAGE II	1 (0.2%)		1 (0.1%)
	CYST	1 (0.2%)		1 (0.1%)
	EPITHELIOMA	1 (0.2%)	1 (0.2%)	2 (0.2%)
	FIBROUS HISTIOCYTOMA	1 (0.2%)		1 (0.1%)
	FOLLICULAR THYROID CANCER	1 (0.2%)		1 (0.1%)
	GASTROINTESTINAL CARCINOMA		1 (0.2%)	1 (0.1%)
	GASTROINTESTINAL TRACT ADENOMA	1 (0.2%)		1 (0.1%)
	KERATOACANTHOMA	1 (0.2%)		1 (0.1%)
	LARYNGEAL CANCER	1 (0.2%)	2 (0.4%)	3 (0.3%)
	LIP NEOPLASM MALIGNANT STAGE UNSPECIFIED		1 (0.2%)	1 (0.1%)
	LUNG NEOPLASM MALIGNANT	1 (0.2%)		1 (0.1%)
	LYMPHOMA		1 (0.2%)	1 (0.1%)
	NEOPLASM		1 (0.2%)	1 (0.1%)
	OVARIAN CANCER	1 (0.2%)		1 (0.1%)
	PARATHYROID TUMOUR	1 (0.2%)		1 (0.1%)
	PENIS CARCINOMA		1 (0.2%)	1 (0.1%)
	PROSTATE CANCER	3 (0.7%)	1 (0.2%)	4 (0.4%)
	PROSTATIC ADENOMA	2 (0.4%)	1 (0.2%)	3 (0.3%)
	RECTAL CANCER	1 (0.2%)		1 (0.1%)
	RENAL CELL CARCINOMA STAGE UNSPECIFIED	1 (0.2%)		1 (0.1%)
	SKIN CARCINOMA	1 (0.2%)	1 (0.2%)	2 (0.2%)
	SQUAMOUS CELL CARCINOMA OF SKIN		1 (0.2%)	1 (0.1%)
	TONGUE NEOPLASM	1 (0.2%)		1 (0.1%)
	UTERINE CANCER		1 (0.2%)	1 (0.1%)
	UTERINE LEIOMYOMA	1 (0.2%)		1 (0.1%)
NERVOUS SYSTEM DISORDERS	TOTAL	14 (3.1%)	22 (4.8%)	36 (4.0%)
	CAROTID ARTERY STENOSIS	2 (0.4%)		2 (0.2%)
	CARPAL TUNNEL SYNDROME	1 (0.2%)	3 (0.7%)	4 (0.4%)
	CEREBRAL ARTERY EMBOLISM	1 (0.2%)		1 (0.1%)
	CEREBRAL INFARCTION	1 (0.2%)		1 (0.1%)
	CEREBRAL ISCHAEMIA		1 (0.2%)	1 (0.1%)

1. PERCENTAGES ARE BASED ON NUMBER OF RANDOMIZED PATIENTS.
2. EXCLUSIVELY PRIOR CONDITIONS-ONGOING CONDITIONS SUMMARIZED IN TABLE 13.13B

CONFIDENTIAL

SB 207499

TABLE 13.13A

SUMMARY OF PRIOR MEDICAL CONDITIONS AT SCREENING
BY DISEASE CODE LEVEL, MEDDRA PREFERRED TERM, AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

DISEASE CODE	MEDDRA PREFERRED TERM	PLACEBO (N=452)	TREATMENT GROUP SB 207499 (N=455)	TOTAL (N=907)
NERVOUS SYSTEM DISORDERS	CEREBRAL THROMBOSIS	1 (0.2%)		1 (0.1%)
	CEREBROVASCULAR ACCIDENT	2 (0.4%)	2 (0.4%)	4 (0.4%)
	CEREBROVASCULAR DISORDER		1 (0.2%)	1 (0.1%)
	CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY		1 (0.2%)	1 (0.1%)
	CONVULSION		1 (0.2%)	1 (0.1%)
	DIZZINESS	1 (0.2%)	1 (0.2%)	2 (0.2%)
	FACIAL PALSY		1 (0.2%)	1 (0.1%)
	FACIAL PARESIS		1 (0.2%)	1 (0.1%)
	HEADACHE		1 (0.2%)	1 (0.1%)
	ISCHAEMIC STROKE		1 (0.2%)	1 (0.1%)
	LOSS OF CONSCIOUSNESS	1 (0.2%)		1 (0.1%)
	MIGRAINE	1 (0.2%)	1 (0.2%)	2 (0.2%)
	NEURALGIA	1 (0.2%)		1 (0.1%)
	NEUROPATHY	1 (0.2%)		1 (0.1%)
	POLYNEUROPATHY		1 (0.2%)	1 (0.1%)
	SCIATICA		2 (0.4%)	2 (0.2%)
	SLEEP APNOEA SYNDROME		2 (0.4%)	2 (0.2%)
	TRANSIENT ISCHAEMIC ATTACK	3 (0.7%)	4 (0.9%)	7 (0.8%)
PSYCHIATRIC DISORDERS	TOTAL	10 (2.2%)	19 (4.2%)	29 (3.2%)
	ALCOHOLISM	4 (0.9%)	3 (0.7%)	7 (0.8%)
	ANXIETY		5 (1.1%)	5 (0.6%)
	CLAUSTROPHOBIA		1 (0.2%)	1 (0.1%)
	DEPRESSION	5 (1.1%)	11 (2.4%)	16 (1.8%)
	INSOMNIA		1 (0.2%)	1 (0.1%)
	NERVOUSNESS	1 (0.2%)		1 (0.1%)
RENAL AND URINARY DISORDERS	TOTAL	18 (4.0%)	8 (1.8%)	26 (2.9%)
	CALCULUS URINARY	2 (0.4%)	1 (0.2%)	3 (0.3%)
	CYSTITIS CHRONIC	1 (0.2%)		1 (0.1%)
	GLOMERULONEPHRITIS CHRONIC		1 (0.2%)	1 (0.1%)
	HAEMATURIA	2 (0.4%)		2 (0.2%)
	HYDRONEPHROSIS		1 (0.2%)	1 (0.1%)
	NEPHRITIS	1 (0.2%)		1 (0.1%)
	NEPHROLITHIASIS	4 (0.9%)	3 (0.7%)	7 (0.8%)
	OBSTRUCTIVE UROPATHY		1 (0.2%)	1 (0.1%)
	RENAL ARTERY STENOSIS	1 (0.2%)		1 (0.1%)
	RENAL COLIC	2 (0.4%)		2 (0.2%)
	RENAL DISORDER IN PREGNANCY	1 (0.2%)		1 (0.1%)
	RENAL IMPAIRMENT		1 (0.2%)	1 (0.1%)
	STRESS INCONTINENCE	2 (0.4%)		2 (0.2%)

1. PERCENTAGES ARE BASED ON NUMBER OF RANDOMIZED PATIENTS.
2. EXCLUSIVELY PRIOR CONDITIONS-ONGOING CONDITIONS SUMMARIZED IN TABLE 13.13B

CONFIDENTIAL

SB 207499

TABLE 13.13A

SUMMARY OF PRIOR MEDICAL CONDITIONS AT SCREENING
BY DISEASE CODE LEVEL, MEDDRA PREFERRED TERM, AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

DISEASE CODE	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	TOTAL (N=907)
RENAL AND URINARY DISORDERS	URETHRAL STRICTURE	2 (0.4%)		2 (0.2%)
	URINARY RETENTION	1 (0.2%)		1 (0.1%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	TOTAL	13 (2.9%)	17 (3.7%)	30 (3.3%)
	BENIGN PROSTATIC HYPERPLASIA	1 (0.2%)	6 (1.3%)	7 (0.8%)
	ENDOMETRIOSIS	1 (0.2%)		1 (0.1%)
	EPIDIDYMAL CYST		1 (0.2%)	1 (0.1%)
	FIBROCYSTIC BREAST DISEASE	1 (0.2%)		1 (0.1%)
	HYDROCELE	1 (0.2%)	3 (0.7%)	4 (0.4%)
	MENOMETRORRHAGIA		1 (0.2%)	1 (0.1%)
	MENORRHAGIA		1 (0.2%)	1 (0.1%)
	OVARIAN CYST	2 (0.4%)	2 (0.4%)	4 (0.4%)
	POSTMENOPAUSAL HAEMORRHAGE	2 (0.4%)		2 (0.2%)
	PROSTATIC HYPERTROPHY	2 (0.4%)	1 (0.2%)	3 (0.3%)
	PROSTATISM		1 (0.2%)	1 (0.1%)
	PROSTATITIS	1 (0.2%)		1 (0.1%)
	TESTICULAR CYST	1 (0.2%)		1 (0.1%)
	TESTICULAR PAIN		2 (0.4%)	2 (0.2%)
	TESTICULAR TORSION	1 (0.2%)		1 (0.1%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	TOTAL	31 (6.9%)	43 (9.5%)	74 (8.2%)
	ASTHMA	6 (1.3%)	7 (1.5%)	13 (1.4%)
	ATELECTASIS	1 (0.2%)		1 (0.1%)
	DYSPNOEA	1 (0.2%)		1 (0.1%)
	EMPHYSEMA	1 (0.2%)		1 (0.1%)
	EPISTAXIS	1 (0.2%)	1 (0.2%)	2 (0.2%)
	HAEMOPTYSIS		4 (0.9%)	4 (0.4%)
	HOARSENESS		1 (0.2%)	1 (0.1%)
	LUNG DISORDER	1 (0.2%)	2 (0.4%)	3 (0.3%)
	LUNG INFILTRATION		1 (0.2%)	1 (0.1%)
	NASAL CONGESTION		3 (0.7%)	3 (0.3%)
	NASAL POLYPS		1 (0.2%)	1 (0.1%)
	NASAL SEPTUM DEVIATION		1 (0.2%)	1 (0.1%)
	PLEURAL ADHESION		1 (0.2%)	1 (0.1%)
	PLEURAL EFFUSION	1 (0.2%)	2 (0.4%)	3 (0.3%)
	PLEURISY	4 (0.9%)	6 (1.3%)	10 (1.1%)
	PLEURITIC PAIN		1 (0.2%)	1 (0.1%)
	PNEUMOTHORAX	6 (1.3%)	8 (1.8%)	14 (1.5%)
	PULMONARY EMBOLISM	4 (0.9%)	3 (0.7%)	7 (0.8%)
	PULMONARY FIBROSIS	1 (0.2%)		1 (0.1%)

1. PERCENTAGES ARE BASED ON NUMBER OF RANDOMIZED PATIENTS.
2. EXCLUSIVELY PRIOR CONDITIONS-ONGOING CONDITIONS SUMMARIZED IN TABLE 13.13B

CONFIDENTIAL

SB 207499

TABLE 13.13A

SUMMARY OF PRIOR MEDICAL CONDITIONS AT SCREENING
BY DISEASE CODE LEVEL, MEDDRA PREFERRED TERM, AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

DISEASE CODE	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	TOTAL (N=907)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	PULMONARY GRANULOMA	1 (0.2%)		1 (0.1%)
	RESPIRATORY FAILURE	2 (0.4%)	1 (0.2%)	3 (0.3%)
	RHINITIS ALLERGIC		2 (0.4%)	2 (0.2%)
	RHINORRHOEA	1 (0.2%)		1 (0.1%)
	SNORING	1 (0.2%)		1 (0.1%)
	STATUS ASTHMATICUS	1 (0.2%)		1 (0.1%)
	TONSILLAR HYPERTROPHY		1 (0.2%)	1 (0.1%)
	VOCAL CORD POLYP	1 (0.2%)		1 (0.1%)
	VOCAL CORD THICKENING		1 (0.2%)	1 (0.1%)
	WHEEZING	1 (0.2%)		1 (0.1%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	TOTAL	6 (1.3%)	8 (1.8%)	14 (1.5%)
	ACANTHOSIS	1 (0.2%)		1 (0.1%)
	ACTINIC KERATOSIS		1 (0.2%)	1 (0.1%)
	DERMAL CYST	1 (0.2%)		1 (0.1%)
	DERMATITIS	1 (0.2%)		1 (0.1%)
	DERMATITIS ALLERGIC	1 (0.2%)		1 (0.1%)
	ECZEMA		2 (0.4%)	2 (0.2%)
	ERYTHEMA NODOSUM		1 (0.2%)	1 (0.1%)
	HIDRADENITIS	1 (0.2%)		1 (0.1%)
	HYPERKERATOSIS		1 (0.2%)	1 (0.1%)
	PSORIASIS	1 (0.2%)	1 (0.2%)	2 (0.2%)
	SKIN LESION		1 (0.2%)	1 (0.1%)
	STASIS DERMATITIS		1 (0.2%)	1 (0.1%)
	URTICARIA		2 (0.4%)	2 (0.2%)
SOCIAL CIRCUMSTANCES	TOTAL	4 (0.9%)	2 (0.4%)	6 (0.7%)
	ALCOHOL USE	3 (0.7%)		3 (0.3%)
	TOBACCO ABUSE	1 (0.2%)	2 (0.4%)	3 (0.3%)
SURGICAL AND MEDICAL PROCEDURES	TOTAL	120 (26.5%)	95 (20.9%)	215 (23.7%)
	ABDOMINAL HYSTERECTOMY	1 (0.2%)		1 (0.1%)
	ADENOIDECTOMY	1 (0.2%)		1 (0.1%)
	ANAL FISTULA EXCISION		1 (0.2%)	1 (0.1%)
	ANGIOPLASTY	2 (0.4%)	4 (0.9%)	6 (0.7%)
	AORTIC ANEURYSM REPAIR	1 (0.2%)	1 (0.2%)	2 (0.2%)
	AORTIC BYPASS	1 (0.2%)		1 (0.1%)
	AORTIC SURGERY	1 (0.2%)		1 (0.1%)
	AORTIC VALVE REPLACEMENT	1 (0.2%)		1 (0.1%)

1. PERCENTAGES ARE BASED ON NUMBER OF RANDOMIZED PATIENTS.
2. EXCLUSIVELY PRIOR CONDITIONS-ONGOING CONDITIONS SUMMARIZED IN TABLE 13.13B

CONFIDENTIAL

SB 207499

TABLE 13.13A

SUMMARY OF PRIOR MEDICAL CONDITIONS AT SCREENING
BY DISEASE CODE LEVEL, MEDDRA PREFERRED TERM, AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

DISEASE CODE	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	TOTAL (N=907)
SURGICAL AND MEDICAL PROCEDURES	APICECTOMY		1 (0.2%)	1 (0.1%)
	APPENDICECTOMY	19 (4.2%)	13 (2.9%)	32 (3.5%)
	ARTERIAL BYPASS OPERATION	1 (0.2%)	1 (0.2%)	2 (0.2%)
	ATRIAL SEPTAL DEFECT REPAIR	1 (0.2%)	1 (0.2%)	2 (0.2%)
	BILATERAL ORCHIDECTOMY	1 (0.2%)		1 (0.1%)
	BLADDER OPERATION		1 (0.2%)	1 (0.1%)
	BLADDER TUMOUR RESECTION	1 (0.2%)		1 (0.1%)
	BREAST OPERATION		1 (0.2%)	1 (0.1%)
	CAECAL LESION EXCISION	1 (0.2%)		1 (0.1%)
	CAROTID ENDARTERECTOMY	1 (0.2%)		1 (0.1%)
	CATARACT EXTRACTION	10 (2.2%)	8 (1.8%)	18 (2.0%)
	CERVICAL DIATHERMY		1 (0.2%)	1 (0.1%)
	CHOLECYSTECTOMY	16 (3.5%)	5 (1.1%)	21 (2.3%)
	COLECTOMY PARTIAL	1 (0.2%)		1 (0.1%)
	COLON POLYPECTOMY	1 (0.2%)	1 (0.2%)	2 (0.2%)
	COLOSTOMY	1 (0.2%)		1 (0.1%)
	COLPOSUSPENSION		2 (0.4%)	2 (0.2%)
	CORONARY ANGIOPLASTY	2 (0.4%)	2 (0.4%)	4 (0.4%)
	CORONARY ARTERIAL STENT INSERTION	1 (0.2%)	2 (0.4%)	3 (0.3%)
	CORONARY ARTERY SURGERY	4 (0.9%)	4 (0.9%)	8 (0.9%)
	CRANIOTOMY	1 (0.2%)		1 (0.1%)
	DOUBLE VESSEL BYPASS GRAFT	1 (0.2%)		1 (0.1%)
	DUODENECTOMY		1 (0.2%)	1 (0.1%)
	EMBOLECTOMY	1 (0.2%)		1 (0.1%)
	ENDARTERECTOMY	1 (0.2%)		1 (0.1%)
	EPIDIDYMECTOMY	1 (0.2%)		1 (0.1%)
	FINGER AMPUTATION	1 (0.2%)		1 (0.1%)
	FOOT OPERATION	1 (0.2%)		1 (0.1%)
	GALLBLADDER OPERATION	1 (0.2%)	2 (0.4%)	3 (0.3%)
	GASTRECTOMY	1 (0.2%)		1 (0.1%)
	GASTRECTOMY PARTIAL	5 (1.1%)	2 (0.4%)	7 (0.8%)
	GASTRIC BANDING	1 (0.2%)		1 (0.1%)
	GASTRIC OPERATION	1 (0.2%)		1 (0.1%)
	HAEMORRHOID OPERATION	5 (1.1%)	2 (0.4%)	7 (0.8%)
	HERNIA HIATUS REPAIR	2 (0.4%)		2 (0.2%)
	HERNIA REPAIR	2 (0.4%)	2 (0.4%)	4 (0.4%)
	HIP ARTHROPLASTY	6 (1.3%)	5 (1.1%)	11 (1.2%)
	HIP SURGERY		2 (0.4%)	2 (0.2%)
	HYSTERECTOMY	12 (2.7%)	10 (2.2%)	22 (2.4%)
	INGUINAL HERNIA REPAIR	7 (1.5%)	5 (1.1%)	12 (1.3%)
	INTERNAL FIXATION OF FRACTURE		1 (0.2%)	1 (0.1%)

1. PERCENTAGES ARE BASED ON NUMBER OF RANDOMIZED PATIENTS.
2. EXCLUSIVELY PRIOR CONDITIONS-ONGOING CONDITIONS SUMMARIZED IN TABLE 13.13B

CONFIDENTIAL

SB 207499

TABLE 13.13A

SUMMARY OF PRIOR MEDICAL CONDITIONS AT SCREENING
BY DISEASE CODE LEVEL, MEDDRA PREFERRED TERM, AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

DISEASE CODE	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	TOTAL (N=907)
SURGICAL AND MEDICAL PROCEDURES	INTERVERTEBRAL DISC OPERATION	1 (0.2%)	3 (0.7%)	4 (0.4%)
	INTRA-NASAL ANTROSTOMY	1 (0.2%)		1 (0.1%)
	KNEE ARTHROPLASTY		4 (0.9%)	4 (0.4%)
	KNEE OPERATION	2 (0.4%)	2 (0.4%)	4 (0.4%)
	LAPAROTOMY		1 (0.2%)	1 (0.1%)
	LIFE SUPPORT		1 (0.2%)	1 (0.1%)
	LIMB OPERATION		2 (0.4%)	2 (0.2%)
	LUNG LOBECTOMY	2 (0.4%)		2 (0.2%)
	LUNG OPERATION	1 (0.2%)	1 (0.2%)	2 (0.2%)
	MASTECTOMY	2 (0.4%)	1 (0.2%)	3 (0.3%)
	MASTOIDECTOMY		1 (0.2%)	1 (0.1%)
	MEDICAL DEVICE IMPLANTATION	1 (0.2%)		1 (0.1%)
	MENISCUS OPERATION		1 (0.2%)	1 (0.1%)
	MYRINGOPLASTY		1 (0.2%)	1 (0.1%)
	NASAL POLYPECTOMY	2 (0.4%)		2 (0.2%)
	NASAL SEPTAL OPERATION	2 (0.4%)	1 (0.2%)	3 (0.3%)
	NEPHRECTOMY	4 (0.9%)	2 (0.4%)	6 (0.7%)
	OOPHORECTOMY	3 (0.7%)		3 (0.3%)
	ORCHIDECTOMY	2 (0.4%)	1 (0.2%)	3 (0.3%)
	ORCHIDOPEXY	1 (0.2%)		1 (0.1%)
	PELVIC FLOOR REPAIR	2 (0.4%)		2 (0.2%)
	PLEURODESIS		1 (0.2%)	1 (0.1%)
	POLYPECTOMY	1 (0.2%)	1 (0.2%)	2 (0.2%)
	PROSTATECTOMY	5 (1.1%)	4 (0.9%)	9 (1.0%)
	PTERYGIUM OPERATION	1 (0.2%)		1 (0.1%)
	PYLOROPLASTY	1 (0.2%)	1 (0.2%)	2 (0.2%)
	RENAL STONE REMOVAL	1 (0.2%)		1 (0.1%)
	RENAL SURGERY		1 (0.2%)	1 (0.1%)
	ROTATOR CUFF REPAIR	1 (0.2%)		1 (0.1%)
	SALPINGECTOMY	1 (0.2%)		1 (0.1%)
	SEPTOPLASTY		1 (0.2%)	1 (0.1%)
	SHOULDER ARTHROPLASTY		1 (0.2%)	1 (0.1%)
	SHOULDER OPERATION		1 (0.2%)	1 (0.1%)
	SPINAL DECOMPRESSION		1 (0.2%)	1 (0.1%)
	SPINAL LAMINECTOMY	1 (0.2%)		1 (0.1%)
	SPINAL OPERATION		1 (0.2%)	1 (0.1%)
	STENT PLACEMENT		2 (0.4%)	2 (0.2%)
	STERILISATION	2 (0.4%)	1 (0.2%)	3 (0.3%)
	STEROID THERAPY		1 (0.2%)	1 (0.1%)
	SURGERY	1 (0.2%)	1 (0.2%)	2 (0.2%)
	SYMPATHECTOMY		1 (0.2%)	1 (0.1%)

1. PERCENTAGES ARE BASED ON NUMBER OF RANDOMIZED PATIENTS.
2. EXCLUSIVELY PRIOR CONDITIONS-ONGOING CONDITIONS SUMMARIZED IN TABLE 13.13B

CONFIDENTIAL

SB 207499

TABLE 13.13A

SUMMARY OF PRIOR MEDICAL CONDITIONS AT SCREENING
BY DISEASE CODE LEVEL, MEDDRA PREFERRED TERM, AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

DISEASE CODE	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	TOTAL (N=907)
SURGICAL AND MEDICAL PROCEDURES	TENDON REPAIR		1 (0.2%)	1 (0.1%)
	TENDON SHEATH LESION EXCISION	2 (0.4%)	1 (0.2%)	3 (0.3%)
	THALAMOTOMY	1 (0.2%)		1 (0.1%)
	THORACOTOMY	1 (0.2%)		1 (0.1%)
	THYROIDECTOMY	3 (0.7%)	4 (0.9%)	7 (0.8%)
	THYROIDECTOMY PARTIAL	2 (0.4%)	2 (0.4%)	4 (0.4%)
	TOE AMPUTATION		1 (0.2%)	1 (0.1%)
	TONSILLECTOMY	5 (1.1%)	2 (0.4%)	7 (0.8%)
	TOOTH EXTRACTION	1 (0.2%)	1 (0.2%)	2 (0.2%)
	TRACHEOSTOMY		1 (0.2%)	1 (0.1%)
	TRANSURETHRAL BLADDER RESECTION		1 (0.2%)	1 (0.1%)
	TRANSURETHRAL PROSTATECTOMY	5 (1.1%)	2 (0.4%)	7 (0.8%)
	TUBAL LIGATION	1 (0.2%)	2 (0.4%)	3 (0.3%)
	URINARY TRACT OPERATION		1 (0.2%)	1 (0.1%)
	VAGINAL HYSTERECTOMY		1 (0.2%)	1 (0.1%)
	VAGOTOMY	1 (0.2%)		1 (0.1%)
	VARICOSE VEIN OPERATION		1 (0.2%)	1 (0.1%)
	VASCULAR BYPASS GRAFT	2 (0.4%)		2 (0.2%)
	VASECTOMY	1 (0.2%)		1 (0.1%)
VASCULAR DISORDERS	TOTAL	16 (3.5%)	16 (3.5%)	32 (3.5%)
	ANGIOPATHY	1 (0.2%)		1 (0.1%)
	AORTIC ANEURYSM	1 (0.2%)	1 (0.2%)	2 (0.2%)
	ARTERIAL DISORDER		1 (0.2%)	1 (0.1%)
	ARTERIAL THROMBOSIS		1 (0.2%)	1 (0.1%)
	ARTERITIS		1 (0.2%)	1 (0.1%)
	DEEP VEIN THROMBOSIS	1 (0.2%)		1 (0.1%)
	ESSENTIAL HYPERTENSION	1 (0.2%)		1 (0.1%)
	HYPERTENSION	5 (1.1%)	3 (0.7%)	8 (0.9%)
	INTERMITTENT CLAUDICATION		1 (0.2%)	1 (0.1%)
	PERIPHERAL EMBOLISM		1 (0.2%)	1 (0.1%)
	PERIPHERAL VASCULAR DISORDER	2 (0.4%)		2 (0.2%)
	SUBCLAVIAN STEAL SYNDROME		1 (0.2%)	1 (0.1%)
	THROMBOPHLEBITIS	1 (0.2%)	4 (0.9%)	5 (0.6%)
	THROMBOSIS	1 (0.2%)	2 (0.4%)	3 (0.3%)
	VARICOSE VEIN	2 (0.4%)		2 (0.2%)
	VASCULAR INSUFFICIENCY	1 (0.2%)		1 (0.1%)

1. PERCENTAGES ARE BASED ON NUMBER OF RANDOMIZED PATIENTS.
2. EXCLUSIVELY PRIOR CONDITIONS-ONGOING CONDITIONS SUMMARIZED IN TABLE 13.13B

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 13.13B

SUMMARY OF CURRENT/ACTIVE MEDICAL CONDITIONS AT SCREENING
BY DISEASE CODE LEVEL, MEDDRA PREFERRED TERM, AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

DISEASE CODE	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	TOTAL (N=907)
TOTAL	TOTAL	452 (100.0%)	455 (100.0%)	907 (100.0%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	TOTAL	10 (2.2%)	6 (1.3%)	16 (1.8%)
	ANAEMIA	5 (1.1%)	1 (0.2%)	6 (0.7%)
	LEUKOCYTOSIS	2 (0.4%)		2 (0.2%)
	MACROCYTOSIS		2 (0.4%)	2 (0.2%)
	MICROCYTIC ANAEMIA	1 (0.2%)		1 (0.1%)
	NEUTROPHILIA	1 (0.2%)		1 (0.1%)
	PERNICIOUS ANAEMIA	1 (0.2%)		1 (0.1%)
	POLYCYTHAEMIA		2 (0.4%)	2 (0.2%)
	STRESS POLYCYTHAEMIA	1 (0.2%)		1 (0.1%)
	THROMBOCYTOPENIA		1 (0.2%)	1 (0.1%)
CARDIAC DISORDERS	TOTAL	86 (19.0%)	98 (21.5%)	184 (20.3%)
	AGE INDETERMINATE MYOCARDIAL INFARCTION	1 (0.2%)	2 (0.4%)	3 (0.3%)
	ANGINA PECTORIS	13 (2.9%)	18 (4.0%)	31 (3.4%)
	AORTIC VALVE DISEASE	1 (0.2%)		1 (0.1%)
	AORTIC VALVE INCOMPETENCE		2 (0.4%)	2 (0.2%)
	ARRHYTHMIA	3 (0.7%)	2 (0.4%)	5 (0.6%)
	ATRIAL FIBRILLATION	12 (2.7%)	12 (2.6%)	24 (2.6%)
	ATRIAL HYPERTROPHY	2 (0.4%)	1 (0.2%)	3 (0.3%)
	ATRIOVENTRICULAR BLOCK FIRST DEGREE	2 (0.4%)	2 (0.4%)	4 (0.4%)
	ATRIOVENTRICULAR BLOCK SECOND DEGREE	1 (0.2%)		1 (0.1%)
	BUNDLE BRANCH BLOCK		1 (0.2%)	1 (0.1%)
	BUNDLE BRANCH BLOCK LEFT	3 (0.7%)	6 (1.3%)	9 (1.0%)
	BUNDLE BRANCH BLOCK RIGHT	3 (0.7%)	9 (2.0%)	12 (1.3%)
	CARDIAC DISORDER		1 (0.2%)	1 (0.1%)
	CARDIAC FAILURE	2 (0.4%)	5 (1.1%)	7 (0.8%)
	CARDIAC FAILURE CONGESTIVE	5 (1.1%)	1 (0.2%)	6 (0.7%)
	CARDIOMEGALY	3 (0.7%)		3 (0.3%)
	CARDIOMYOPATHY	2 (0.4%)	2 (0.4%)	4 (0.4%)
	CONDUCTION DISORDER	1 (0.2%)		1 (0.1%)
	COR PULMONALE	1 (0.2%)	1 (0.2%)	2 (0.2%)
	COR PULMONALE CHRONIC	1 (0.2%)	1 (0.2%)	2 (0.2%)
	CORONARY ARTERY ATHEROSCLEROSIS	5 (1.1%)	5 (1.1%)	10 (1.1%)
	CORONARY ARTERY DISEASE	13 (2.9%)	13 (2.9%)	26 (2.9%)
	CORONARY ARTERY INSUFFICIENCY		1 (0.2%)	1 (0.1%)
	CORONARY ARTERY OCCLUSION		1 (0.2%)	1 (0.1%)
	HYPERTENSIVE HEART DISEASE		2 (0.4%)	2 (0.2%)
	ISCHAEMIC CARDIOMYOPATHY	2 (0.4%)		2 (0.2%)
	LEFT VENTRICULAR FAILURE	1 (0.2%)	1 (0.2%)	2 (0.2%)

1. PERCENTAGES ARE BASED ON TOTAL NUMBER OF RANDOMIZED PATIENTS.
2. CURRENT/ACTIVE CONDITIONS - EXCLUSIVELY PRIOR CONDITIONS SUMMARIZED IN TABLE 13.13A

CONFIDENTIAL

SB 207499

TABLE 13.13B

SUMMARY OF CURRENT/ACTIVE MEDICAL CONDITIONS AT SCREENING
BY DISEASE CODE LEVEL, MEDDRA PREFERRED TERM, AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

DISEASE CODE	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	TOTAL (N=907)
CARDIAC DISORDERS	MITRAL VALVE INCOMPETENCE		1 (0.2%)	1 (0.1%)
	MITRAL VALVE STENOSIS		1 (0.2%)	1 (0.1%)
	MYOCARDIAL INFARCTION	1 (0.2%)		1 (0.1%)
	MYOCARDIAL ISCHAEMIA	19 (4.2%)	19 (4.2%)	38 (4.2%)
	PALPITATIONS	1 (0.2%)		1 (0.1%)
	PERICARDITIS		1 (0.2%)	1 (0.1%)
	RHEUMATIC HEART DISEASE		1 (0.2%)	1 (0.1%)
	SINUS BRADYCARDIA	2 (0.4%)	1 (0.2%)	3 (0.3%)
	SINUS TACHYCARDIA	2 (0.4%)	3 (0.7%)	5 (0.6%)
	SUPRAVENTRICULAR EXTRASYSTOLES		1 (0.2%)	1 (0.1%)
	SUPRAVENTRICULAR TACHYCARDIA		1 (0.2%)	1 (0.1%)
	TACHYCARDIA		1 (0.2%)	1 (0.1%)
	TACHYCARDIA PAROXYSMAL		1 (0.2%)	1 (0.1%)
	VENTRICULAR ARRHYTHMIA	1 (0.2%)		1 (0.1%)
	VENTRICULAR EXTRASYSTOLES		2 (0.4%)	2 (0.2%)
	VENTRICULAR FAILURE		1 (0.2%)	1 (0.1%)
	VENTRICULAR HYPERTROPHY	7 (1.5%)		7 (0.8%)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	TOTAL	3 (0.7%)	1 (0.2%)	4 (0.4%)
	ALPHA-1 ANTI-TRYPSIN DEFICIENCY	1 (0.2%)		1 (0.1%)
	CONGENITAL SCOLIOSIS	1 (0.2%)		1 (0.1%)
	EPIDERMAL NAEVUS		1 (0.2%)	1 (0.1%)
	HEART DISEASE CONGENITAL	1 (0.2%)		1 (0.1%)
EAR AND LABYRINTH DISORDERS	TOTAL	16 (3.5%)	6 (1.3%)	22 (2.4%)
	DEAFNESS	3 (0.7%)		3 (0.3%)
	DEAFNESS BILATERAL	1 (0.2%)		1 (0.1%)
	DEAFNESS PERMANENT PARTIAL	2 (0.4%)	1 (0.2%)	3 (0.3%)
	DEAFNESS UNILATERAL	1 (0.2%)	1 (0.2%)	2 (0.2%)
	EAR DISORDER	1 (0.2%)		1 (0.1%)
	HYPOACUSIS	4 (0.9%)	2 (0.4%)	6 (0.7%)
	PRESBYACUSIS	1 (0.2%)	1 (0.2%)	2 (0.2%)
	TINNITUS	1 (0.2%)		1 (0.1%)
	VERTIGO	2 (0.4%)	1 (0.2%)	3 (0.3%)
ENDOCRINE DISORDERS	TOTAL	22 (4.9%)	6 (1.3%)	28 (3.1%)
	ADRENAL DISORDER	1 (0.2%)		1 (0.1%)
	ADRENAL INSUFFICIENCY	1 (0.2%)		1 (0.1%)
	ENDOCRINE DISORDER	1 (0.2%)		1 (0.1%)
	GOITRE	3 (0.7%)	2 (0.4%)	5 (0.6%)
	HYPERTHYROIDISM	4 (0.9%)		4 (0.4%)

1. PERCENTAGES ARE BASED ON TOTAL NUMBER OF RANDOMIZED PATIENTS.
2. CURRENT/ACTIVE CONDITIONS - EXCLUSIVELY PRIOR CONDITIONS SUMMARIZED IN TABLE 13.13A

CONFIDENTIAL

SB 207499

TABLE 13.13B

SUMMARY OF CURRENT/ACTIVE MEDICAL CONDITIONS AT SCREENING
BY DISEASE CODE LEVEL, MEDDRA PREFERRED TERM, AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

DISEASE CODE	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	TOTAL (N=907)
ENDOCRINE DISORDERS	HYPOTHYROIDISM	11 (2.4%)	4 (0.9%)	15 (1.7%)
	OESTROGEN DEFICIENCY	1 (0.2%)		1 (0.1%)
	THYROID NODULE	1 (0.2%)		1 (0.1%)
	THYROTOXICOSIS	2 (0.4%)		2 (0.2%)
EYE DISORDERS	TOTAL	26 (5.8%)	23 (5.1%)	49 (5.4%)
	AMAUROSIS FUGAX	1 (0.2%)		1 (0.1%)
	ARCUS LIPOIDES		1 (0.2%)	1 (0.1%)
	ASTHENOPIA		1 (0.2%)	1 (0.1%)
	BLEPHAROSPASM		1 (0.2%)	1 (0.1%)
	BLINDNESS		1 (0.2%)	1 (0.1%)
	CATARACT	7 (1.5%)	2 (0.4%)	9 (1.0%)
	CHALAZION		1 (0.2%)	1 (0.1%)
	CONJUNCTIVITIS		2 (0.4%)	2 (0.2%)
	DIABETIC RETINOPATHY		1 (0.2%)	1 (0.1%)
	GLAUCOMA	9 (2.0%)	11 (2.4%)	20 (2.2%)
	HYPERMETROPIA		1 (0.2%)	1 (0.1%)
	IRIDOCYCLITIS	1 (0.2%)		1 (0.1%)
	KERATOCONJUNCTIVITIS SICCA	3 (0.7%)		3 (0.3%)
	MACULAR DEGENERATION	1 (0.2%)	1 (0.2%)	2 (0.2%)
	MACULAR HOLE	2 (0.4%)		2 (0.2%)
	MYOPIA	1 (0.2%)	1 (0.2%)	2 (0.2%)
	OCULAR HYPERTENSION	1 (0.2%)		1 (0.1%)
	OPEN ANGLE GLAUCOMA	1 (0.2%)		1 (0.1%)
	OPTIC NERVE CUPPING		1 (0.2%)	1 (0.1%)
	OPTIC NERVE DISORDER	1 (0.2%)		1 (0.1%)
	RETINOPATHY HYPERTENSIVE		1 (0.2%)	1 (0.1%)
	STRABISMUS	1 (0.2%)		1 (0.1%)
GASTROINTESTINAL DISORDERS	TOTAL	73 (16.2%)	85 (18.7%)	158 (17.4%)
	ABDOMINAL DISCOMFORT	1 (0.2%)		1 (0.1%)
	ABDOMINAL PAIN	1 (0.2%)	1 (0.2%)	2 (0.2%)
	ABDOMINAL PAIN UPPER	2 (0.4%)		2 (0.2%)
	COELIAC DISEASE		1 (0.2%)	1 (0.1%)
	COLITIS		1 (0.2%)	1 (0.1%)
	COLON SPASTIC		1 (0.2%)	1 (0.1%)
	COLONIC POLYP		1 (0.2%)	1 (0.1%)
	CONSTIPATION	7 (1.5%)	6 (1.3%)	13 (1.4%)
	DIARRHOEA	3 (0.7%)	1 (0.2%)	4 (0.4%)
	DIVERTICULITIS	1 (0.2%)		1 (0.1%)
	DIVERTICULUM	4 (0.9%)	2 (0.4%)	6 (0.7%)
	DUODENAL ULCER	4 (0.9%)	1 (0.2%)	5 (0.6%)

1. PERCENTAGES ARE BASED ON TOTAL NUMBER OF RANDOMIZED PATIENTS.
2. CURRENT/ACTIVE CONDITIONS - EXCLUSIVELY PRIOR CONDITIONS SUMMARIZED IN TABLE 13.13A

CONFIDENTIAL

SB 207499

TABLE 13.13B

SUMMARY OF CURRENT/ACTIVE MEDICAL CONDITIONS AT SCREENING
BY DISEASE CODE LEVEL, MEDDRA PREFERRED TERM, AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

DISEASE CODE	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	TOTAL (N=907)
GASTROINTESTINAL DISORDERS	DUODENITIS	1 (0.2%)		1 (0.1%)
	DYSPEPSIA	15 (3.3%)	13 (2.9%)	28 (3.1%)
	DYSPHAGIA	1 (0.2%)	2 (0.4%)	3 (0.3%)
	FREQUENT BOWEL MOVEMENTS		1 (0.2%)	1 (0.1%)
	GASTRIC DISORDER		1 (0.2%)	1 (0.1%)
	GASTRIC ULCER	3 (0.7%)	4 (0.9%)	7 (0.8%)
	GASTRITIS	7 (1.5%)	11 (2.4%)	18 (2.0%)
	GASTRITIS HYPERTROPHIC	1 (0.2%)		1 (0.1%)
	GASTROINTESTINAL DISORDER	1 (0.2%)		1 (0.1%)
	GASTROOESOPHAGEAL REFLUX DISEASE	10 (2.2%)	7 (1.5%)	17 (1.9%)
	GINGIVAL CYST		1 (0.2%)	1 (0.1%)
	GINGIVAL RECESSION		1 (0.2%)	1 (0.1%)
	HAEMORRHOIDAL HAEMORRHAGE		1 (0.2%)	1 (0.1%)
	HAEMORRHOIDS	6 (1.3%)	6 (1.3%)	12 (1.3%)
	HIATUS HERNIA	8 (1.8%)	19 (4.2%)	27 (3.0%)
	HYPERACIDITY		1 (0.2%)	1 (0.1%)
	INGUINAL HERNIA	2 (0.4%)	6 (1.3%)	8 (0.9%)
	IRRITABLE BOWEL SYNDROME	3 (0.7%)	3 (0.7%)	6 (0.7%)
	MALABSORPTION		1 (0.2%)	1 (0.1%)
	NAUSEA		1 (0.2%)	1 (0.1%)
	OESOPHAGEAL STENOSIS ACQUIRED		1 (0.2%)	1 (0.1%)
	OESOPHAGITIS		2 (0.4%)	2 (0.2%)
	ORAL LICHEN PLANUS	1 (0.2%)		1 (0.1%)
	PANCREATITIS	1 (0.2%)		1 (0.1%)
	PEPTIC ULCER	3 (0.7%)	4 (0.9%)	7 (0.8%)
	PEPTIC ULCER PERFORATION	1 (0.2%)		1 (0.1%)
	PROCTALGIA		1 (0.2%)	1 (0.1%)
	PRURITUS ANI		1 (0.2%)	1 (0.1%)
	REFLUX OESOPHAGITIS	6 (1.3%)	3 (0.7%)	9 (1.0%)
	SIGMOIDITIS	1 (0.2%)		1 (0.1%)
	UMBILICAL HERNIA	2 (0.4%)		2 (0.2%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	TOTAL	13 (2.9%)	7 (1.5%)	20 (2.2%)
	ASTHENIA	2 (0.4%)		2 (0.2%)
	ATROPHY	1 (0.2%)		1 (0.1%)
	CHEST PAIN	2 (0.4%)		2 (0.2%)
	FATIGUE	1 (0.2%)		1 (0.1%)
	FIBROSIS	1 (0.2%)		1 (0.1%)
	GRANULOMA	2 (0.4%)		2 (0.2%)
	HYPERPLASIA	1 (0.2%)		1 (0.1%)
	OEDEMA	2 (0.4%)	1 (0.2%)	3 (0.3%)

1. PERCENTAGES ARE BASED ON TOTAL NUMBER OF RANDOMIZED PATIENTS.
2. CURRENT/ACTIVE CONDITIONS - EXCLUSIVELY PRIOR CONDITIONS SUMMARIZED IN TABLE 13.13A

CONFIDENTIAL

SB 207499

TABLE 13.13B

SUMMARY OF CURRENT/ACTIVE MEDICAL CONDITIONS AT SCREENING
BY DISEASE CODE LEVEL, MEDDRA PREFERRED TERM, AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

DISEASE CODE	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	TOTAL (N=907)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	OEDEMA PERIPHERAL	1 (0.2%)	6 (1.3%)	7 (0.8%)
HEPATOBILIARY DISORDERS	TOTAL	18 (4.0%)	15 (3.3%)	33 (3.6%)
	CHOLECYSTITIS CHRONIC	3 (0.7%)	1 (0.2%)	4 (0.4%)
	CHOLELITHIASIS	4 (0.9%)	4 (0.9%)	8 (0.9%)
	CHOLESTASIS	1 (0.2%)		1 (0.1%)
	CHRONIC HEPATITIS	1 (0.2%)	1 (0.2%)	2 (0.2%)
	HEPATIC CIRRHOSIS	1 (0.2%)	1 (0.2%)	2 (0.2%)
	HEPATIC STEATOSIS	6 (1.3%)	5 (1.1%)	11 (1.2%)
	HEPATITIS		1 (0.2%)	1 (0.1%)
	HEPATITIS GRANULOMATOUS		1 (0.2%)	1 (0.1%)
	LIVER DISORDER	3 (0.7%)	2 (0.4%)	5 (0.6%)
IMMUNE SYSTEM DISORDERS	TOTAL	24 (5.3%)	18 (4.0%)	42 (4.6%)
	ALLERGY TO PLANTS	2 (0.4%)		2 (0.2%)
	DRUG HYPERSENSITIVITY	13 (2.9%)	10 (2.2%)	23 (2.5%)
	FOOD ALLERGY	1 (0.2%)	1 (0.2%)	2 (0.2%)
	HOUSE DUST ALLERGY	2 (0.4%)		2 (0.2%)
	HYPERSENSITIVITY	3 (0.7%)	3 (0.7%)	6 (0.7%)
	NICKEL SENSITIVITY	1 (0.2%)		1 (0.1%)
	SEASONAL ALLERGY	3 (0.7%)	4 (0.9%)	7 (0.8%)
INFECTIONS AND INFESTATIONS	TOTAL	213 (47.1%)	184 (40.4%)	397 (43.8%)
	BLADDER INFECTION	1 (0.2%)		1 (0.1%)
	BRONCHITIS	3 (0.7%)	3 (0.7%)	6 (0.7%)
	BRONCHITIS CHRONIC	199 (44.0%)	169 (37.1%)	368 (40.6%)
	CELLULITIS	2 (0.4%)	1 (0.2%)	3 (0.3%)
	CHRONIC SINUSITIS	4 (0.9%)	2 (0.4%)	6 (0.7%)
	CYSTITIS	1 (0.2%)		1 (0.1%)
	DENTAL CARIES		1 (0.2%)	1 (0.1%)
	FUNGAL INFECTION		1 (0.2%)	1 (0.1%)
	HEPATITIS B		1 (0.2%)	1 (0.1%)
	HIV INFECTION		1 (0.2%)	1 (0.1%)
	LARYNGITIS		1 (0.2%)	1 (0.1%)
	LARYNGOTRACHEITIS		1 (0.2%)	1 (0.1%)
	ONYCHOMYCOSIS	1 (0.2%)		1 (0.1%)
	ORAL CANDIDIASIS		2 (0.4%)	2 (0.2%)
	OTITIS EXTERNA	1 (0.2%)		1 (0.1%)
	OTITIS MEDIA		1 (0.2%)	1 (0.1%)
	PHARYNGITIS	2 (0.4%)		2 (0.2%)
	PULMONARY TUBERCULOSIS	1 (0.2%)		1 (0.1%)

1. PERCENTAGES ARE BASED ON TOTAL NUMBER OF RANDOMIZED PATIENTS.
2. CURRENT/ACTIVE CONDITIONS - EXCLUSIVELY PRIOR CONDITIONS SUMMARIZED IN TABLE 13.13A

CONFIDENTIAL

SB 207499

TABLE 13.13B

SUMMARY OF CURRENT/ACTIVE MEDICAL CONDITIONS AT SCREENING
BY DISEASE CODE LEVEL, MEDDRA PREFERRED TERM, AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

DISEASE CODE	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	TOTAL (N=907)
INFECTIONS AND INFESTATIONS	PYELONEPHRITIS	1 (0.2%)	1 (0.2%)	2 (0.2%)
	PYELONEPHRITIS CHRONIC		1 (0.2%)	1 (0.1%)
	RHINITIS INFECTIVE	1 (0.2%)		1 (0.1%)
	SALPINGITIS	1 (0.2%)		1 (0.1%)
	SINUSITIS	4 (0.9%)	6 (1.3%)	10 (1.1%)
	TINEA PEDIS		1 (0.2%)	1 (0.1%)
	TRICHOPHYTON INFECTION	1 (0.2%)		1 (0.1%)
	TUBERCULOSIS		1 (0.2%)	1 (0.1%)
	VAGINAL CANDIDIASIS	1 (0.2%)		1 (0.1%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	TOTAL	11 (2.4%)	3 (0.7%)	14 (1.5%)
	BACK CRUSHING	1 (0.2%)		1 (0.1%)
	BACK INJURY	1 (0.2%)		1 (0.1%)
	CATARACT TRAUMATIC	1 (0.2%)		1 (0.1%)
	CORNEAL EROSION	1 (0.2%)		1 (0.1%)
	EPICONDYLITIS	1 (0.2%)		1 (0.1%)
	INCISIONAL HERNIA	1 (0.2%)		1 (0.1%)
	JOINT INJURY	1 (0.2%)		1 (0.1%)
	LIMB INJURY	1 (0.2%)		1 (0.1%)
	MUSCLE STRAIN	1 (0.2%)		1 (0.1%)
	POST GASTRIC SURGERY SYNDROME		1 (0.2%)	1 (0.1%)
	SPINAL CORD INJURY		1 (0.2%)	1 (0.1%)
	TENDON RUPTURE	1 (0.2%)		1 (0.1%)
	THERMAL BURN	1 (0.2%)		1 (0.1%)
	UPPER LIMB FRACTURE	1 (0.2%)		1 (0.1%)
	WRIST FRACTURE		1 (0.2%)	1 (0.1%)
INVESTIGATIONS	TOTAL	16 (3.5%)	20 (4.4%)	36 (4.0%)
	ALANINE AMINOTRANSFERASE INCREASED		1 (0.2%)	1 (0.1%)
	ASPARTATE AMINOTRANSFERASE INCREASED		1 (0.2%)	1 (0.1%)
	BLEEDING TIME PROLONGED	1 (0.2%)		1 (0.1%)
	BLOOD BILIRUBIN INCREASED	1 (0.2%)	1 (0.2%)	2 (0.2%)
	BLOOD GLUCOSE INCREASED		1 (0.2%)	1 (0.1%)
	BLOOD OESTROGEN DECREASED	1 (0.2%)		1 (0.1%)
	BLOOD SODIUM DECREASED		1 (0.2%)	1 (0.1%)
	CARDIAC MURMUR		1 (0.2%)	1 (0.1%)
	CAROTID BRUIT		1 (0.2%)	1 (0.1%)
	CHEST X-RAY ABNORMAL		1 (0.2%)	1 (0.1%)
	ECG SIGNS OF VENTRICULAR HYPERTROPHY		1 (0.2%)	1 (0.1%)
	ELECTROCARDIOGRAM ABNORMAL		1 (0.2%)	1 (0.1%)
	ELECTROCARDIOGRAM ST SEGMENT DEPRESSION	1 (0.2%)	1 (0.2%)	2 (0.2%)

1. PERCENTAGES ARE BASED ON TOTAL NUMBER OF RANDOMIZED PATIENTS.
2. CURRENT/ACTIVE CONDITIONS - EXCLUSIVELY PRIOR CONDITIONS SUMMARIZED IN TABLE 13.13A

CONFIDENTIAL

SB 207499

TABLE 13.13B

SUMMARY OF CURRENT/ACTIVE MEDICAL CONDITIONS AT SCREENING
BY DISEASE CODE LEVEL, MEDDRA PREFERRED TERM, AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

DISEASE CODE	MEDDRA PREFERRED TERM	PLACEBO (N=452)	TREATMENT GROUP SB 207499 (N=455)	TOTAL (N=907)
INVESTIGATIONS	ELECTROCARDIOGRAM ST-T CHANGE	1 (0.2%)		1 (0.1%)
	GAMMA-GLUTAMYLTRANSFERASE INCREASED	1 (0.2%)	2 (0.4%)	3 (0.3%)
	HAEMATOCRIT INCREASED	1 (0.2%)		1 (0.1%)
	HAEMOGLOBIN DECREASED		1 (0.2%)	1 (0.1%)
	HEART RATE IRREGULAR		2 (0.4%)	2 (0.2%)
	HEPATIC ENZYME INCREASED	1 (0.2%)		1 (0.1%)
	MEAN CELL VOLUME DECREASED	1 (0.2%)		1 (0.1%)
	MONOCYTE COUNT DECREASED	1 (0.2%)		1 (0.1%)
	PLATELET COUNT DECREASED	1 (0.2%)		1 (0.1%)
	PLATELET COUNT INCREASED		2 (0.4%)	2 (0.2%)
	PROTEIN URINE PRESENT	3 (0.7%)	2 (0.4%)	5 (0.6%)
	QRS AXIS ABNORMAL		1 (0.2%)	1 (0.1%)
	SPUTUM INCREASED	1 (0.2%)		1 (0.1%)
	TUBERCULIN TEST POSITIVE	1 (0.2%)		1 (0.1%)
	URINARY OCCULT BLOOD POSITIVE	1 (0.2%)	1 (0.2%)	2 (0.2%)
	WEIGHT DECREASED		1 (0.2%)	1 (0.1%)
	WHITE BLOOD CELL COUNT INCREASED	1 (0.2%)	1 (0.2%)	2 (0.2%)
	X-RAY ABNORMAL		1 (0.2%)	1 (0.1%)
METABOLISM AND NUTRITION DISORDERS	TOTAL	100 (22.1%)	95 (20.9%)	195 (21.5%)
	ANOREXIA		1 (0.2%)	1 (0.1%)
	DECREASED APPETITE		1 (0.2%)	1 (0.1%)
	DIABETES MELLITUS	34 (7.5%)	19 (4.2%)	53 (5.8%)
	DIABETES MELLITUS NON-INSULIN-DEPENDENT	8 (1.8%)	7 (1.5%)	15 (1.7%)
	DYSLIPIDAEMIA	1 (0.2%)	1 (0.2%)	2 (0.2%)
	FLUID RETENTION	2 (0.4%)		2 (0.2%)
	FOLATE DEFICIENCY	1 (0.2%)		1 (0.1%)
	GLUCOSE TOLERANCE IMPAIRED		2 (0.4%)	2 (0.2%)
	GOUT	1 (0.2%)	8 (1.8%)	9 (1.0%)
	HAEMOSIDEROSIS		1 (0.2%)	1 (0.1%)
	HYPERCHOLESTEROLAEMIA	33 (7.3%)	31 (6.8%)	64 (7.1%)
	HYPERGLYCAEMIA	2 (0.4%)	1 (0.2%)	3 (0.3%)
	HYPERKALAEMIA	1 (0.2%)		1 (0.1%)
	HYPERLIPIDAEMIA	16 (3.5%)	13 (2.9%)	29 (3.2%)
	HYPERTRIGLYCERIDAEMIA	2 (0.4%)	1 (0.2%)	3 (0.3%)
	HYPERURICAEMIA	12 (2.7%)	11 (2.4%)	23 (2.5%)
	HYPOKALAEMIA	1 (0.2%)		1 (0.1%)
	LACTOSE INTOLERANCE		1 (0.2%)	1 (0.1%)
	LIPID METABOLISM DISORDER	1 (0.2%)		1 (0.1%)
	LIPOMATOSIS	1 (0.2%)	1 (0.2%)	2 (0.2%)
	MALNUTRITION	1 (0.2%)		1 (0.1%)

1. PERCENTAGES ARE BASED ON TOTAL NUMBER OF RANDOMIZED PATIENTS.
2. CURRENT/ACTIVE CONDITIONS - EXCLUSIVELY PRIOR CONDITIONS SUMMARIZED IN TABLE 13.13A

CONFIDENTIAL

SB 207499

TABLE 13.13B

SUMMARY OF CURRENT/ACTIVE MEDICAL CONDITIONS AT SCREENING
BY DISEASE CODE LEVEL, MEDDRA PREFERRED TERM, AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

DISEASE CODE	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	TOTAL (N=907)
METABOLISM AND NUTRITION DISORDERS	OBESITY	10 (2.2%)	8 (1.8%)	18 (2.0%)
	VITAMIN B12 DEFICIENCY	1 (0.2%)		1 (0.1%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	TOTAL	98 (21.7%)	91 (20.0%)	189 (20.8%)
	ANKYLOSING SPONDYLITIS	1 (0.2%)		1 (0.1%)
	ARTHRALGIA	7 (1.5%)	5 (1.1%)	12 (1.3%)
	ARTHRITIS	12 (2.7%)	7 (1.5%)	19 (2.1%)
	ARTHROPATHY		1 (0.2%)	1 (0.1%)
	BACK PAIN	11 (2.4%)	17 (3.7%)	28 (3.1%)
	BONE PAIN	1 (0.2%)		1 (0.1%)
	FIBROMYALGIA	2 (0.4%)	1 (0.2%)	3 (0.3%)
	GOUTY ARTHRITIS	2 (0.4%)	3 (0.7%)	5 (0.6%)
	INTERVERTEBRAL DISC DEGENERATION		1 (0.2%)	1 (0.1%)
	INTERVERTEBRAL DISC PROTRUSION	2 (0.4%)	2 (0.4%)	4 (0.4%)
	LOCAL SWELLING		1 (0.2%)	1 (0.1%)
	LOCALISED OSTEOARTHRITIS	6 (1.3%)	5 (1.1%)	11 (1.2%)
	MONOARTHRITIS		1 (0.2%)	1 (0.1%)
	MUSCLE CRAMP	1 (0.2%)	3 (0.7%)	4 (0.4%)
	MYALGIA	2 (0.4%)		2 (0.2%)
	NECK MASS	1 (0.2%)		1 (0.1%)
	NECK PAIN	3 (0.7%)	3 (0.7%)	6 (0.7%)
	NIGHT CRAMPS	2 (0.4%)		2 (0.2%)
	OSTEOARTHRITIS	20 (4.4%)	19 (4.2%)	39 (4.3%)
	OSTEOARTHRITIS GENERALISED	6 (1.3%)	5 (1.1%)	11 (1.2%)
	OSTEOCHONDROSIS	2 (0.4%)		2 (0.2%)
	OSTEOPENIA		1 (0.2%)	1 (0.1%)
	OSTEOPOROSIS	15 (3.3%)	8 (1.8%)	23 (2.5%)
	PAIN IN EXTREMITY	1 (0.2%)	2 (0.4%)	3 (0.3%)
	PERIARTHRITIS		2 (0.4%)	2 (0.2%)
	RENAL OSTEODYSTROPHY		1 (0.2%)	1 (0.1%)
	RHEUMATOID ARTHRITIS	3 (0.7%)	3 (0.7%)	6 (0.7%)
	SHOULDER BLADE PAIN	1 (0.2%)		1 (0.1%)
	SJOGREN'S SYNDROME		1 (0.2%)	1 (0.1%)
	SPINAL DISORDER	6 (1.3%)	5 (1.1%)	11 (1.2%)
	SPINAL OSTEOARTHRITIS		2 (0.4%)	2 (0.2%)
	SPONDYLOSIS	7 (1.5%)	6 (1.3%)	13 (1.4%)
	SYSTEMIC LUPUS ERYTHEMATOSUS		1 (0.2%)	1 (0.1%)
	TENOSYNOVITIS STENOSANS		1 (0.2%)	1 (0.1%)
	TRIGGER FINGER		1 (0.2%)	1 (0.1%)

1. PERCENTAGES ARE BASED ON TOTAL NUMBER OF RANDOMIZED PATIENTS.
2. CURRENT/ACTIVE CONDITIONS - EXCLUSIVELY PRIOR CONDITIONS SUMMARIZED IN TABLE 13.13A

CONFIDENTIAL

SB 207499

TABLE 13.13B

SUMMARY OF CURRENT/ACTIVE MEDICAL CONDITIONS AT SCREENING
BY DISEASE CODE LEVEL, MEDDRA PREFERRED TERM, AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

DISEASE CODE	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	TOTAL (N=907)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	TOTAL	10 (2.2%)	11 (2.4%)	21 (2.3%)
	BASAL CELL CARCINOMA		3 (0.7%)	3 (0.3%)
	HAEMANGIOMA ACQUIRED	1 (0.2%)		1 (0.1%)
	KERATOACANTHOMA		1 (0.2%)	1 (0.1%)
	LUNG NEOPLASM MALIGNANT	1 (0.2%)		1 (0.1%)
	LUNG NODULE		1 (0.2%)	1 (0.1%)
	MALIGNANT MELANOMA	1 (0.2%)		1 (0.1%)
	NEOPLASM		1 (0.2%)	1 (0.1%)
	PROSTATE CANCER	2 (0.4%)		2 (0.2%)
	PROSTATIC ADENOMA	4 (0.9%)	3 (0.7%)	7 (0.8%)
	SKIN CARCINOMA	1 (0.2%)		1 (0.1%)
	SKIN PAPILLOMA		1 (0.2%)	1 (0.1%)
	SQUAMOUS CELL CARCINOMA OF SKIN		1 (0.2%)	1 (0.1%)
NERVOUS SYSTEM DISORDERS	TOTAL	30 (6.6%)	36 (7.9%)	66 (7.3%)
	AMNESIA	1 (0.2%)		1 (0.1%)
	CAROTID ARTERY DISEASE		1 (0.2%)	1 (0.1%)
	CAROTID ARTERY STENOSIS	1 (0.2%)		1 (0.1%)
	CEREBELLAR ATROPHY		1 (0.2%)	1 (0.1%)
	CEREBRAL ATHEROSCLEROSIS		1 (0.2%)	1 (0.1%)
	CEREBROVASCULAR ACCIDENT		1 (0.2%)	1 (0.1%)
	CEREBROVASCULAR DISORDER	1 (0.2%)	1 (0.2%)	2 (0.2%)
	CEREBROVASCULAR INSUFFICIENCY		1 (0.2%)	1 (0.1%)
	DIZZINESS		1 (0.2%)	1 (0.1%)
	DYSARTHRIA		1 (0.2%)	1 (0.1%)
	EPILEPSY	1 (0.2%)	1 (0.2%)	2 (0.2%)
	ESSENTIAL TREMOR		2 (0.4%)	2 (0.2%)
	HEADACHE	9 (2.0%)	8 (1.8%)	17 (1.9%)
	HEMIPARESIS		1 (0.2%)	1 (0.1%)
	HYPERTONIA	6 (1.3%)	4 (0.9%)	10 (1.1%)
	HYPOAESTHESIA	2 (0.4%)		2 (0.2%)
	INTERCOSTAL NEURALGIA		1 (0.2%)	1 (0.1%)
	LOSS OF CONSCIOUSNESS	1 (0.2%)		1 (0.1%)
	MIGRAINE	3 (0.7%)	2 (0.4%)	5 (0.6%)
	NEURITIS	1 (0.2%)		1 (0.1%)
	NEUROPATHY PERIPHERAL		1 (0.2%)	1 (0.1%)
	PARAESTHESIA		1 (0.2%)	1 (0.1%)
	PARALYSIS		2 (0.4%)	2 (0.2%)
	PARKINSON'S DISEASE		3 (0.7%)	3 (0.3%)
	PARKINSONISM	1 (0.2%)		1 (0.1%)

1. PERCENTAGES ARE BASED ON TOTAL NUMBER OF RANDOMIZED PATIENTS.
2. CURRENT/ACTIVE CONDITIONS - EXCLUSIVELY PRIOR CONDITIONS SUMMARIZED IN TABLE 13.13A

CONFIDENTIAL

SB 207499

TABLE 13.13B

SUMMARY OF CURRENT/ACTIVE MEDICAL CONDITIONS AT SCREENING
BY DISEASE CODE LEVEL, MEDDRA PREFERRED TERM, AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

DISEASE CODE	MEDDRA PREFERRED TERM	PLACEBO (N=452)	TREATMENT GROUP SB 207499 (N=455)	TOTAL (N=907)
NERVOUS SYSTEM DISORDERS	PERONEAL NERVE PALSY		1 (0.2%)	1 (0.1%)
	POLYNEUROPATHY		1 (0.2%)	1 (0.1%)
	SENSORY LOSS	1 (0.2%)		1 (0.1%)
	SPINAL COLUMN STENOSIS		1 (0.2%)	1 (0.1%)
	SPINAL CORD COMPRESSION		1 (0.2%)	1 (0.1%)
	SYNCOPE		1 (0.2%)	1 (0.1%)
	TRANSIENT ISCHAEMIC ATTACK	1 (0.2%)	1 (0.2%)	2 (0.2%)
	TREMOR	2 (0.4%)	1 (0.2%)	3 (0.3%)
PSYCHIATRIC DISORDERS	TOTAL	44 (9.7%)	28 (6.2%)	72 (7.9%)
	AFFECT LABILITY	1 (0.2%)		1 (0.1%)
	ALCOHOL WITHDRAWAL SYNDROME	1 (0.2%)		1 (0.1%)
	ANXIETY	14 (3.1%)	10 (2.2%)	24 (2.6%)
	DEPRESSION	16 (3.5%)	10 (2.2%)	26 (2.9%)
	INSOMNIA	16 (3.5%)	13 (2.9%)	29 (3.2%)
	MOOD ALTERED		1 (0.2%)	1 (0.1%)
	NIGHTMARE	1 (0.2%)	1 (0.2%)	2 (0.2%)
	PANIC ATTACK		1 (0.2%)	1 (0.1%)
	RESTLESSNESS	1 (0.2%)		1 (0.1%)
	SCHIZOPHRENIA	1 (0.2%)		1 (0.1%)
	SLEEP DISORDER		2 (0.4%)	2 (0.2%)
	TENSION	1 (0.2%)		1 (0.1%)
RENAL AND URINARY DISORDERS	TOTAL	12 (2.7%)	13 (2.9%)	25 (2.8%)
	ATONIC URINARY BLADDER		1 (0.2%)	1 (0.1%)
	CALCULUS URINARY	3 (0.7%)	1 (0.2%)	4 (0.4%)
	HAEMATURIA	1 (0.2%)	1 (0.2%)	2 (0.2%)
	HYPERTONIC BLADDER		1 (0.2%)	1 (0.1%)
	NEPHROCALCINOSIS		1 (0.2%)	1 (0.1%)
	NEPHROLITHIASIS	1 (0.2%)	1 (0.2%)	2 (0.2%)
	NEPHROPATHY	1 (0.2%)		1 (0.1%)
	NOCTURIA	1 (0.2%)	1 (0.2%)	2 (0.2%)
	PROTEINURIA		1 (0.2%)	1 (0.1%)
	RENAL COLIC	1 (0.2%)		1 (0.1%)
	RENAL DISORDER	1 (0.2%)		1 (0.1%)
	RENAL FAILURE CHRONIC		1 (0.2%)	1 (0.1%)
	RENAL INSUFFICIENCY	1 (0.2%)	1 (0.2%)	2 (0.2%)
	RENAL VESSEL DISORDER	1 (0.2%)		1 (0.1%)
	STRESS INCONTINENCE		1 (0.2%)	1 (0.1%)
	URGE INCONTINENCE		1 (0.2%)	1 (0.1%)
	URINARY INCONTINENCE	1 (0.2%)		1 (0.1%)
	URINARY RETENTION		1 (0.2%)	1 (0.1%)

1. PERCENTAGES ARE BASED ON TOTAL NUMBER OF RANDOMIZED PATIENTS.
2. CURRENT/ACTIVE CONDITIONS - EXCLUSIVELY PRIOR CONDITIONS SUMMARIZED IN TABLE 13.13A

CONFIDENTIAL

SB 207499

TABLE 13.13B

SUMMARY OF CURRENT/ACTIVE MEDICAL CONDITIONS AT SCREENING
BY DISEASE CODE LEVEL, MEDDRA PREFERRED TERM, AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

DISEASE CODE	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	TOTAL (N=907)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	TOTAL	31 (6.9%)	41 (9.0%)	72 (7.9%)
	BENIGN PROSTATIC HYPERPLASIA	7 (1.5%)	15 (3.3%)	22 (2.4%)
	BREAST DISORDER		1 (0.2%)	1 (0.1%)
	BREAST MASS		1 (0.2%)	1 (0.1%)
	ERECTILE DYSFUNCTION	3 (0.7%)	3 (0.7%)	6 (0.7%)
	GALACTORRHOEA	1 (0.2%)		1 (0.1%)
	GYNAECOMASTIA	1 (0.2%)		1 (0.1%)
	MENOPAUSAL SYMPTOMS	2 (0.4%)	2 (0.4%)	4 (0.4%)
	PROSTATIC DISORDER	1 (0.2%)	2 (0.4%)	3 (0.3%)
	PROSTATIC HYPERTROPHY	10 (2.2%)	15 (3.3%)	25 (2.8%)
	PROSTATISM	4 (0.9%)	2 (0.4%)	6 (0.7%)
	PROSTATITIS	2 (0.4%)	1 (0.2%)	3 (0.3%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	TOTAL	452 (100.0%)	455 (100.0%)	907 (100.0%)
	ADDUCTOR VOCAL CORD WEAKNESS	1 (0.2%)		1 (0.1%)
	ASTHMA	3 (0.7%)	1 (0.2%)	4 (0.4%)
	ATELECTASIS	1 (0.2%)		1 (0.1%)
	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE	452 (100.0%)	455 (100.0%)	907 (100.0%)
	CHRONIC RESPIRATORY FAILURE		1 (0.2%)	1 (0.1%)
	COUGH	3 (0.7%)	2 (0.4%)	5 (0.6%)
	DIAPHRAGMATIC HERNIA		1 (0.2%)	1 (0.1%)
	DIAPHRAGMATIC PARALYSIS	1 (0.2%)	1 (0.2%)	2 (0.2%)
	DYSPNOEA	1 (0.2%)		1 (0.1%)
	EMPHYSEMA	5 (1.1%)	7 (1.5%)	12 (1.3%)
	EMPHYSEMATOUS BULLA		1 (0.2%)	1 (0.1%)
	EPISTAXIS		1 (0.2%)	1 (0.1%)
	LUNG DISORDER	3 (0.7%)		3 (0.3%)
	NASAL CONGESTION	2 (0.4%)	4 (0.9%)	6 (0.7%)
	NASAL DRYNESS	1 (0.2%)		1 (0.1%)
	NASAL POLYPS		1 (0.2%)	1 (0.1%)
	NASAL SEPTUM DEVIATION	4 (0.9%)	2 (0.4%)	6 (0.7%)
	PLEURAL FIBROSIS		3 (0.7%)	3 (0.3%)
	PLEURISY	1 (0.2%)	1 (0.2%)	2 (0.2%)
	POSTNASAL DRIP	2 (0.4%)	1 (0.2%)	3 (0.3%)
	PRODUCTIVE COUGH	1 (0.2%)	1 (0.2%)	2 (0.2%)
	PULMONARY FIBROSIS	2 (0.4%)	1 (0.2%)	3 (0.3%)
	PULMONARY GRANULOMA		3 (0.7%)	3 (0.3%)
	PULMONARY HYPERTENSION	1 (0.2%)	2 (0.4%)	3 (0.3%)
	RHINITIS	11 (2.4%)	5 (1.1%)	16 (1.8%)
	RHINITIS ALLERGIC	6 (1.3%)	6 (1.3%)	12 (1.3%)

1. PERCENTAGES ARE BASED ON TOTAL NUMBER OF RANDOMIZED PATIENTS.
2. CURRENT/ACTIVE CONDITIONS - EXCLUSIVELY PRIOR CONDITIONS SUMMARIZED IN TABLE 13.13A

CONFIDENTIAL

SB 207499

TABLE 13.13B

SUMMARY OF CURRENT/ACTIVE MEDICAL CONDITIONS AT SCREENING
BY DISEASE CODE LEVEL, MEDDRA PREFERRED TERM, AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

DISEASE CODE	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	TOTAL (N=907)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	RHINITIS PERENNIAL	1 (0.2%)	1 (0.2%)	2 (0.2%)
	RHINORRHOEA		2 (0.4%)	2 (0.2%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	TOTAL	17 (3.8%)	19 (4.2%)	36 (4.0%)
	ACTINIC KERATOSIS	1 (0.2%)	1 (0.2%)	2 (0.2%)
	CUTANEOUS LUPUS ERYTHEMATOSUS		1 (0.2%)	1 (0.1%)
	DERMAL CYST		1 (0.2%)	1 (0.1%)
	DERMATITIS		3 (0.7%)	3 (0.3%)
	DERMATITIS ALLERGIC		1 (0.2%)	1 (0.1%)
	DERMATITIS CONTACT	1 (0.2%)	1 (0.2%)	2 (0.2%)
	ECZEMA	4 (0.9%)	1 (0.2%)	5 (0.6%)
	INTERTRIGO		1 (0.2%)	1 (0.1%)
	NIGHT SWEATS		1 (0.2%)	1 (0.1%)
	PHOTODERMATOSIS	1 (0.2%)		1 (0.1%)
	PRURIGO		1 (0.2%)	1 (0.1%)
	PRURITUS	1 (0.2%)		1 (0.1%)
	PSORIASIS	3 (0.7%)	3 (0.7%)	6 (0.7%)
	RASH	1 (0.2%)	1 (0.2%)	2 (0.2%)
	ROSACEA	1 (0.2%)		1 (0.1%)
	SEBORRHOEIC DERMATITIS		1 (0.2%)	1 (0.1%)
	SKIN BLEEDING		1 (0.2%)	1 (0.1%)
	SKIN ULCER	1 (0.2%)		1 (0.1%)
	STASIS DERMATITIS		2 (0.4%)	2 (0.2%)
	SUBCUTANEOUS NODULE	1 (0.2%)		1 (0.1%)
	URTICARIA	2 (0.4%)	1 (0.2%)	3 (0.3%)
	URTICARIA CHRONIC	1 (0.2%)		1 (0.1%)
	VITILIGO	1 (0.2%)		1 (0.1%)
SOCIAL CIRCUMSTANCES	TOTAL	12 (2.7%)	4 (0.9%)	16 (1.8%)
	EYE PROSTHESIS USER	1 (0.2%)		1 (0.1%)
	HEARING AID USER	1 (0.2%)		1 (0.1%)
	MENOPAUSE	4 (0.9%)	1 (0.2%)	5 (0.6%)
	POSTMENOPAUSE	3 (0.7%)		3 (0.3%)
	TOBACCO ABUSE	3 (0.7%)	3 (0.7%)	6 (0.7%)
SURGICAL AND MEDICAL PROCEDURES	TOTAL	8 (1.8%)	7 (1.5%)	15 (1.7%)
	APPENDICECTOMY	1 (0.2%)	1 (0.2%)	2 (0.2%)
	ARTERIAL BYPASS OPERATION	1 (0.2%)		1 (0.1%)
	ARTHRODESIS	1 (0.2%)		1 (0.1%)

1. PERCENTAGES ARE BASED ON TOTAL NUMBER OF RANDOMIZED PATIENTS.
2. CURRENT/ACTIVE CONDITIONS - EXCLUSIVELY PRIOR CONDITIONS SUMMARIZED IN TABLE 13.13A

CONFIDENTIAL

SB 207499

TABLE 13.13B

SUMMARY OF CURRENT/ACTIVE MEDICAL CONDITIONS AT SCREENING
BY DISEASE CODE LEVEL, MEDDRA PREFERRED TERM, AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

DISEASE CODE	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	TOTAL (N=907)
SURGICAL AND MEDICAL PROCEDURES	COLOSTOMY	1 (0.2%)		1 (0.1%)
	CORNEAL TRANSPLANT		1 (0.2%)	1 (0.1%)
	EAR TUBE INSERTION		1 (0.2%)	1 (0.1%)
	EYE EXCISION		1 (0.2%)	1 (0.1%)
	HIP ARTHROPLASTY	1 (0.2%)	3 (0.7%)	4 (0.4%)
	HYSTERECTOMY	2 (0.4%)		2 (0.2%)
	KNEE ARTHROPLASTY	1 (0.2%)		1 (0.1%)
	STERILISATION	1 (0.2%)	1 (0.2%)	2 (0.2%)
	VASODILATION PROCEDURE	1 (0.2%)		1 (0.1%)
VASCULAR DISORDERS	TOTAL	170 (37.6%)	178 (39.1%)	348 (38.4%)
	ANGIOPATHY	2 (0.4%)	1 (0.2%)	3 (0.3%)
	AORTIC ANEURYSM		1 (0.2%)	1 (0.1%)
	AORTIC ATHEROSCLEROSIS		2 (0.4%)	2 (0.2%)
	AORTIC DISORDER		1 (0.2%)	1 (0.1%)
	ARTERIAL OCCLUSIVE DISEASE	1 (0.2%)	2 (0.4%)	3 (0.3%)
	ARTERIOPATHIC DISEASE		1 (0.2%)	1 (0.1%)
	ARTERIOSCLEROSIS		2 (0.4%)	2 (0.2%)
	ARTERITIS	1 (0.2%)		1 (0.1%)
	ATHEROSCLEROSIS	1 (0.2%)	2 (0.4%)	3 (0.3%)
	ATHEROSCLEROSIS OBLITERANS	1 (0.2%)		1 (0.1%)
	DEEP VEIN THROMBOSIS		1 (0.2%)	1 (0.1%)
	ESSENTIAL HYPERTENSION	7 (1.5%)	9 (2.0%)	16 (1.8%)
	HYPERTENSION	148 (32.7%)	150 (33.0%)	298 (32.9%)
	HYPERTENSIVE CARDIOMYOPATHY		2 (0.4%)	2 (0.2%)
	HYPOTENSION	2 (0.4%)	1 (0.2%)	3 (0.3%)
	INTERMITTENT CLAUDICATION	1 (0.2%)	2 (0.4%)	3 (0.3%)
	LERICHE SYNDROME	1 (0.2%)		1 (0.1%)
	LYMPHOEDEMA	1 (0.2%)	1 (0.2%)	2 (0.2%)
	PERIPHERAL ISCHAEMIA		2 (0.4%)	2 (0.2%)
	PERIPHERAL OCCLUSIVE DISEASE	1 (0.2%)		1 (0.1%)
	PERIPHERAL VASCULAR DISORDER	4 (0.9%)	7 (1.5%)	11 (1.2%)
	POOR PERIPHERAL CIRCULATION	1 (0.2%)		1 (0.1%)
	RAYNAUD'S PHENOMENON	1 (0.2%)	2 (0.4%)	3 (0.3%)
	SYSTOLIC HYPERTENSION	1 (0.2%)		1 (0.1%)
	THROMBOANGIITIS OBLITERANS		2 (0.4%)	2 (0.2%)
	VARICOSE VEIN	9 (2.0%)	4 (0.9%)	13 (1.4%)
	VASCULAR INSUFFICIENCY	1 (0.2%)	2 (0.4%)	3 (0.3%)
	VASCULITIS		1 (0.2%)	1 (0.1%)
	VENOUS INSUFFICIENCY	2 (0.4%)	2 (0.4%)	4 (0.4%)

1. PERCENTAGES ARE BASED ON TOTAL NUMBER OF RANDOMIZED PATIENTS.
2. CURRENT/ACTIVE CONDITIONS - EXCLUSIVELY PRIOR CONDITIONS SUMMARIZED IN TABLE 13.13A

CONFIDENTIAL

SB 207499

TABLE 13.14

SUMMARY OF BASELINE SIGNS AND SYMPTOMS BY MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM

PROTOCOL 157

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=454)	SB 207499 (N=456)	NON-RAND. (N=480)	Total (N=1390)
TOTAL	TOTAL	93 (20.5%)	97 (21.3%)	149 (31.0%)	339 (24.4%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	TOTAL	26 (5.7%)	27 (5.9%)	86 (17.9%)	139 (10.0%)
	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE EXACERBATED	13 (2.9%)	15 (3.3%)	70 (14.6%)	98 (7.1%)
	COUGH	4 (0.9%)	3 (0.7%)	8 (1.7%)	15 (1.1%)
	PHARYNGOLARYNGEAL PAIN	4 (0.9%)	1 (0.2%)	3 (0.6%)	8 (0.6%)
	DYSPNOEA	2 (0.4%)	2 (0.4%)	2 (0.4%)	6 (0.4%)
	RHINITIS	1 (0.2%)	4 (0.9%)	0 .	5 (0.4%)
	DYSPNOEA EXACERBATED	1 (0.2%)	0 .	3 (0.6%)	4 (0.3%)
	ABNORMAL CHEST SOUND	0 .	0 .	1 (0.2%)	1 (0.1%)
	CHRONIC RESPIRATORY FAILURE	0 .	1 (0.2%)	0 .	1 (0.1%)
	DYSPNOEA EXERTIONAL	1 (0.2%)	0 .	0 .	1 (0.1%)
	EPISTAXIS	0 .	0 .	1 (0.2%)	1 (0.1%)
	HAEMOPTYSIS	0 .	1 (0.2%)	0 .	1 (0.1%)
	HYPOXIA	0 .	1 (0.2%)	0 .	1 (0.1%)
	PRODUCTIVE COUGH	1 (0.2%)	0 .	0 .	1 (0.1%)
	RHINORRHOEA	0 .	0 .	1 (0.2%)	1 (0.1%)
	SPUTUM DISCOLOURED	0 .	0 .	1 (0.2%)	1 (0.1%)
	THROAT TIGHTNESS	0 .	0 .	1 (0.2%)	1 (0.1%)
	WHEEZING	0 .	0 .	1 (0.2%)	1 (0.1%)
GASTROINTESTINAL DISORDERS	TOTAL	17 (3.7%)	16 (3.5%)	32 (6.7%)	65 (4.7%)
	DIARRHOEA	4 (0.9%)	1 (0.2%)	7 (1.5%)	12 (0.9%)
	NAUSEA	3 (0.7%)	2 (0.4%)	6 (1.3%)	11 (0.8%)
	ABDOMINAL PAIN UPPER	1 (0.2%)	2 (0.4%)	6 (1.3%)	9 (0.6%)
	LOOSE STOOLS	2 (0.4%)	1 (0.2%)	3 (0.6%)	6 (0.4%)
	ABDOMINAL PAIN	2 (0.4%)	1 (0.2%)	2 (0.4%)	5 (0.4%)
	DRY MOUTH	1 (0.2%)	1 (0.2%)	2 (0.4%)	4 (0.3%)
	VOMITING	2 (0.4%)	0 .	2 (0.4%)	4 (0.3%)
	ABDOMINAL DISCOMFORT	0 .	1 (0.2%)	2 (0.4%)	3 (0.2%)
	DYSPEPSIA	1 (0.2%)	1 (0.2%)	1 (0.2%)	3 (0.2%)
	CONSTIPATION	0 .	1 (0.2%)	1 (0.2%)	2 (0.1%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA PREFERRED TERM
2. TOTAL ROWS REPRESENT TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED FOR PLACEBO AND SB207499 COLUMNS AND ON TOTAL NUMBER OF PATIENTS ENTERING RUN-IN FOR TOTAL COLUMN

CONFIDENTIAL

SB 207499

TABLE 13.14

SUMMARY OF BASELINE SIGNS AND SYMPTOMS BY MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM

PROTOCOL 157

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=454)	SB 207499 (N=456)	NON-RAND. (N=480)	Total (N=1390)
GASTROINTESTINAL DISORDERS	FLATULENCE	1 (0.2%)	1 (0.2%)	0 .	2 (0.1%)
	HAEMORRHOIDS	1 (0.2%)	0 .	1 (0.2%)	2 (0.1%)
	ABDOMINAL PAIN LOWER	1 (0.2%)	0 .	0 .	1 (0.1%)
	AEROPHAGIA	0 .	1 (0.2%)	0 .	1 (0.1%)
	COLONIC POLYP	0 .	0 .	1 (0.2%)	1 (0.1%)
	DUODENITIS	0 .	0 .	1 (0.2%)	1 (0.1%)
	GASTROINTESTINAL DISORDER	1 (0.2%)	0 .	0 .	1 (0.1%)
	GASTROINTESTINAL UPSET	0 .	1 (0.2%)	0 .	1 (0.1%)
	GASTROOESOPHAGEAL REFLUX DISEASE	0 .	1 (0.2%)	0 .	1 (0.1%)
	GINGIVAL CYST	0 .	1 (0.2%)	0 .	1 (0.1%)
	GLOSSODYNIA	1 (0.2%)	0 .	0 .	1 (0.1%)
	INGUINAL HERNIA	0 .	1 (0.2%)	0 .	1 (0.1%)
	IRRITABLE BOWEL SYNDROME	1 (0.2%)	0 .	0 .	1 (0.1%)
	RECTAL HAEMORRHAGE	0 .	0 .	1 (0.2%)	1 (0.1%)
	STOMATITIS	0 .	1 (0.2%)	0 .	1 (0.1%)
	TONGUE DISCOLOURATION	0 .	0 .	1 (0.2%)	1 (0.1%)
	TOOTHACHE	0 .	0 .	1 (0.2%)	1 (0.1%)
INFECTIONS AND INFESTATIONS	TOTAL	19 (4.2%)	24 (5.3%)	24 (5.0%)	67 (4.8%)
	NASOPHARYNGITIS	5 (1.1%)	8 (1.8%)	6 (1.3%)	19 (1.4%)
	GASTROENTERITIS	2 (0.4%)	0 .	4 (0.8%)	6 (0.4%)
	BRONCHITIS	1 (0.2%)	2 (0.4%)	2 (0.4%)	5 (0.4%)
	LOWER RESPIRATORY TRACT INFECTION	0 .	3 (0.7%)	2 (0.4%)	5 (0.4%)
	PHARYNGITIS	2 (0.4%)	2 (0.4%)	0 .	4 (0.3%)
	SINUSITIS	2 (0.4%)	2 (0.4%)	0 .	4 (0.3%)
	UPPER RESPIRATORY TRACT INFECTION	2 (0.4%)	1 (0.2%)	1 (0.2%)	4 (0.3%)
	INFLUENZA	1 (0.2%)	1 (0.2%)	1 (0.2%)	3 (0.2%)
	RESPIRATORY TRACT INFECTION	0 .	1 (0.2%)	2 (0.4%)	3 (0.2%)
	CELLULITIS	1 (0.2%)	1 (0.2%)	0 .	2 (0.1%)
	ORAL CANDIDIASIS	0 .	1 (0.2%)	1 (0.2%)	2 (0.1%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA PREFERRED TERM
2. TOTAL ROWS REPRESENT TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED FOR PLACEBO AND SB207499 COLUMNS AND ON TOTAL NUMBER OF PATIENTS ENTERING RUN-IN FOR TOTAL COLUMN

CONFIDENTIAL

SB 207499

TABLE 13.14

SUMMARY OF BASELINE SIGNS AND SYMPTOMS BY MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM

PROTOCOL 157

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=454)	SB 207499 (N=456)	NON-RAND. (N=480)	Total (N=1390)
INFECTIONS AND INFESTATIONS	BRONCHITIS ACUTE	0 .	0 .	1 (0.2%)	1 (0.1%)
	CYSTITIS ACUTE	0 .	0 .	1 (0.2%)	1 (0.1%)
	DENTAL CARIES	1 (0.2%)	0 .	0 .	1 (0.1%)
	EAR INFECTION	0 .	1 (0.2%)	0 .	1 (0.1%)
	EYE INFECTION	0 .	1 (0.2%)	0 .	1 (0.1%)
	GASTROINTESTINAL INFECTION	0 .	0 .	1 (0.2%)	1 (0.1%)
	INFECTED SEBACEOUS CYST	0 .	0 .	1 (0.2%)	1 (0.1%)
	LICE INFESTATION	1 (0.2%)	0 .	0 .	1 (0.1%)
	LOCALISED INFECTION	0 .	1 (0.2%)	0 .	1 (0.1%)
	ONYCHOMYCOSIS	0 .	1 (0.2%)	0 .	1 (0.1%)
	OROPHARYNGEAL CANDIDIASIS	1 (0.2%)	0 .	0 .	1 (0.1%)
	PYELONEPHRITIS CHRONIC	0 .	0 .	1 (0.2%)	1 (0.1%)
	SKIN INFECTION	0 .	1 (0.2%)	0 .	1 (0.1%)
	URINARY TRACT INFECTION	1 (0.2%)	0 .	0 .	1 (0.1%)
	WOUND INFECTION	0 .	0 .	1 (0.2%)	1 (0.1%)
NERVOUS SYSTEM DISORDERS	TOTAL	13 (2.9%)	13 (2.9%)	13 (2.7%)	39 (2.8%)
	HEADACHE	12 (2.6%)	6 (1.3%)	7 (1.5%)	25 (1.8%)
	DIZZINESS	0 .	2 (0.4%)	4 (0.8%)	6 (0.4%)
	PARAESTHESIA	0 .	2 (0.4%)	0 .	2 (0.1%)
	SOMNOLENCE	0 .	2 (0.4%)	0 .	2 (0.1%)
	MIGRAINE	0 .	0 .	1 (0.2%)	1 (0.1%)
	SYNCOPE	1 (0.2%)	0 .	0 .	1 (0.1%)
	TORTICOLLIS	0 .	1 (0.2%)	0 .	1 (0.1%)
	TRANSIENT ISCHAEMIC ATTACK	0 .	0 .	1 (0.2%)	1 (0.1%)
	TREMOR	0 .	1 (0.2%)	0 .	1 (0.1%)
INVESTIGATIONS	TOTAL	9 (2.0%)	10 (2.2%)	11 (2.3%)	30 (2.2%)
	BLOOD GLUCOSE INCREASED	1 (0.2%)	0 .	4 (0.8%)	5 (0.4%)
	C-REACTIVE PROTEIN INCREASED	3 (0.7%)	1 (0.2%)	0 .	4 (0.3%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA PREFERRED TERM
2. TOTAL ROWS REPRESENT TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED FOR PLACEBO AND SB207499 COLUMNS AND ON TOTAL NUMBER OF PATIENTS ENTERING RUN-IN FOR TOTAL COLUMN

CONFIDENTIAL

SB 207499

TABLE 13.14

SUMMARY OF BASELINE SIGNS AND SYMPTOMS BY MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM

PROTOCOL 157

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=454)	SB 207499 (N=456)	NON-RAND. (N=480)	Total (N=1390)
INVESTIGATIONS	WHITE BLOOD CELL COUNT INCREASED	2 (0.4%)	2 (0.4%)	0 .	4 (0.3%)
	GAMMA-GLUTAMYLTRANSFERASE INCREASED	1 (0.2%)	1 (0.2%)	1 (0.2%)	3 (0.2%)
	FAECAL OCCULT BLOOD POSITIVE	0 .	0 .	2 (0.4%)	2 (0.1%)
	BACTERIA SPUTUM IDENTIFIED	0 .	1 (0.2%)	0 .	1 (0.1%)
	BLOOD ALKALINE PHOSPHATASE INCREASED	0 .	1 (0.2%)	0 .	1 (0.1%)
	BLOOD BILIRUBIN INCREASED	1 (0.2%)	0 .	0 .	1 (0.1%)
	BLOOD CREATININE INCREASED	1 (0.2%)	0 .	0 .	1 (0.1%)
	BLOOD IN STOOL	0 .	0 .	1 (0.2%)	1 (0.1%)
	BLOOD TEST ABNORMAL	0 .	0 .	1 (0.2%)	1 (0.1%)
	BLOOD UREA INCREASED	0 .	1 (0.2%)	0 .	1 (0.1%)
	BLOOD URIC ACID INCREASED	1 (0.2%)	0 .	0 .	1 (0.1%)
	HAEMATOCRIT DECREASED	0 .	0 .	1 (0.2%)	1 (0.1%)
	HAEMOGLOBIN DECREASED	0 .	0 .	1 (0.2%)	1 (0.1%)
	LYMPHOCYTE COUNT INCREASED	1 (0.2%)	0 .	0 .	1 (0.1%)
	MONOCYTE COUNT INCREASED	1 (0.2%)	0 .	0 .	1 (0.1%)
	NEUTROPHIL COUNT INCREASED	0 .	1 (0.2%)	0 .	1 (0.1%)
	SPUTUM ABNORMAL	0 .	0 .	1 (0.2%)	1 (0.1%)
	SPUTUM TEST	0 .	1 (0.2%)	0 .	1 (0.1%)
	T-LYMPHOCYTE COUNT INCREASED	0 .	1 (0.2%)	0 .	1 (0.1%)
	WEIGHT DECREASED	0 .	1 (0.2%)	0 .	1 (0.1%)
	WEIGHT INCREASED	0 .	1 (0.2%)	0 .	1 (0.1%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	TOTAL	8 (1.8%)	7 (1.5%)	8 (1.7%)	23 (1.7%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA PREFERRED TERM
2. TOTAL ROWS REPRESENT TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED FOR PLACEBO AND SB207499 COLUMNS AND ON TOTAL NUMBER OF PATIENTS ENTERING RUN-IN FOR TOTAL COLUMN

CONFIDENTIAL

SB 207499

TABLE 13.14

SUMMARY OF BASELINE SIGNS AND SYMPTOMS BY MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM

PROTOCOL 157

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=454)	SB 207499 (N=456)	NON-RAND. (N=480)	Total (N=1390)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	OEDEMA PERIPHERAL	3 (0.7%)	2 (0.4%)	3 (0.6%)	8 (0.6%)
	FATIGUE	4 (0.9%)	1 (0.2%)	0 .	5 (0.4%)
	PYREXIA	0 .	3 (0.7%)	0 .	3 (0.2%)
	CHEST PAIN	0 .	0 .	2 (0.4%)	2 (0.1%)
	INFLUENZA LIKE ILLNESS	1 (0.2%)	0 .	1 (0.2%)	2 (0.1%)
	ASTHENIA	0 .	0 .	1 (0.2%)	1 (0.1%)
	MUCOSA VESICLE	0 .	0 .	1 (0.2%)	1 (0.1%)
	VENIPUNCTURE SITE HAEMORRHAGE	0 .	1 (0.2%)	0 .	1 (0.1%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	TOTAL	5 (1.1%)	6 (1.3%)	3 (0.6%)	14 (1.0%)
	BACK PAIN	2 (0.4%)	2 (0.4%)	1 (0.2%)	5 (0.4%)
	ARTHRALGIA	2 (0.4%)	0 .	1 (0.2%)	3 (0.2%)
	JOINT EFFUSION	1 (0.2%)	1 (0.2%)	0 .	2 (0.1%)
	JOINT SWELLING	0 .	1 (0.2%)	0 .	1 (0.1%)
	MUSCULOSKELETAL CHEST PAIN	0 .	1 (0.2%)	0 .	1 (0.1%)
	MYALGIA	0 .	0 .	1 (0.2%)	1 (0.1%)
	NECK PAIN	0 .	1 (0.2%)	0 .	1 (0.1%)
METABOLISM AND NUTRITION DISORDERS	TOTAL	3 (0.7%)	4 (0.9%)	3 (0.6%)	10 (0.7%)
	ANOREXIA	0 .	2 (0.4%)	1 (0.2%)	3 (0.2%)
	GLUCOSE TOLERANCE IMPAIRED	0 .	1 (0.2%)	0 .	1 (0.1%)
	GOUT	1 (0.2%)	0 .	0 .	1 (0.1%)
	HYPERGLYCAEMIA	0 .	1 (0.2%)	0 .	1 (0.1%)
	HYPERKALAEMIA	1 (0.2%)	0 .	0 .	1 (0.1%)
	HYPERLIPIDAEMIA	0 .	0 .	1 (0.2%)	1 (0.1%)
	HYPERURICAEMIA	0 .	0 .	1 (0.2%)	1 (0.1%)
	HYPOGLYCAEMIA	1 (0.2%)	0 .	0 .	1 (0.1%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	TOTAL	4 (0.9%)	4 (0.9%)	1 (0.2%)	9 (0.6%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA PREFERRED TERM
2. TOTAL ROWS REPRESENT TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED FOR PLACEBO AND SB207499 COLUMNS AND ON TOTAL NUMBER OF PATIENTS ENTERING RUN-IN FOR TOTAL COLUMN

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 13.14

SUMMARY OF BASELINE SIGNS AND SYMPTOMS BY MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM

PROTOCOL 157

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=454)	SB 207499 (N=456)	NON-RAND. (N=480)	Total (N=1390)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	DRY SKIN	0 .	2 (0.4%)	0 .	2 (0.1%)
	ACTINIC KERATOSIS	1 (0.2%)	0 .	0 .	1 (0.1%)
	DERMATITIS	0 .	1 (0.2%)	0 .	1 (0.1%)
	DYSHIDROSIS	1 (0.2%)	0 .	0 .	1 (0.1%)
	ECZEMA	0 .	0 .	1 (0.2%)	1 (0.1%)
	ICHTHYOSIS ACQUIRED	0 .	1 (0.2%)	0 .	1 (0.1%)
	RASH	1 (0.2%)	0 .	0 .	1 (0.1%)
	ROSACEA	1 (0.2%)	0 .	0 .	1 (0.1%)
	URTICARIA	1 (0.2%)	0 .	0 .	1 (0.1%)
PSYCHIATRIC DISORDERS	TOTAL	2 (0.4%)	3 (0.7%)	3 (0.6%)	8 (0.6%)
	INSOMNIA	1 (0.2%)	1 (0.2%)	1 (0.2%)	3 (0.2%)
	DEPRESSION	0 .	1 (0.2%)	1 (0.2%)	2 (0.1%)
	ANXIETY	1 (0.2%)	0 .	0 .	1 (0.1%)
	DYSTHYMIC DISORDER	0 .	1 (0.2%)	0 .	1 (0.1%)
	MIDDLE INSOMNIA	0 .	1 (0.2%)	0 .	1 (0.1%)
	SLEEP DISORDER	0 .	0 .	1 (0.2%)	1 (0.1%)
VASCULAR DISORDERS	TOTAL	4 (0.9%)	1 (0.2%)	1 (0.2%)	6 (0.4%)
	HYPERTENSION	4 (0.9%)	1 (0.2%)	1 (0.2%)	6 (0.4%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	TOTAL	2 (0.4%)	2 (0.4%)	0 .	4 (0.3%)
	ARTHROPOD BITE	1 (0.2%)	0 .	0 .	1 (0.1%)
	LIMB INJURY	0 .	1 (0.2%)	0 .	1 (0.1%)
	MUSCLE INJURY	1 (0.2%)	0 .	0 .	1 (0.1%)
	NECK INJURY	0 .	1 (0.2%)	0 .	1 (0.1%)
	RIB FRACTURE	0 .	1 (0.2%)	0 .	1 (0.1%)
CARDIAC DISORDERS	TOTAL	1 (0.2%)	2 (0.4%)	1 (0.2%)	4 (0.3%)
	ARRHYTHMIA	0 .	0 .	1 (0.2%)	1 (0.1%)
	ATRIOVENTRICULAR BLOCK FIRST DEGREE	1 (0.2%)	0 .	0 .	1 (0.1%)
	SINUS TACHYCARDIA	0 .	1 (0.2%)	0 .	1 (0.1%)
	SUPRAVENTRICULAR TACHYCARDIA	0 .	1 (0.2%)	0 .	1 (0.1%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA PREFERRED TERM
2. TOTAL ROWS REPRESENT TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED FOR PLACEBO AND SB207499 COLUMNS AND ON TOTAL NUMBER OF PATIENTS ENTERING RUN-IN FOR TOTAL COLUMN

CONFIDENTIAL

SB 207499

TABLE 13.14

SUMMARY OF BASELINE SIGNS AND SYMPTOMS BY MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM

PROTOCOL 157

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=454)	SB 207499 (N=456)	NON-RAND. (N=480)	Total (N=1390)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	TOTAL	1 (0.2%)	1 (0.2%)	1 (0.2%)	3 (0.2%)
	ANAEMIA	1 (0.2%)	0 .	0 .	1 (0.1%)
	POLYCYTHAEMIA	0 .	0 .	1 (0.2%)	1 (0.1%)
	SECONDARY POLYCYTHAEMIA	0 .	1 (0.2%)	0 .	1 (0.1%)
EAR AND LABYRINTH DISORDERS	TOTAL	2 (0.4%)	1 (0.2%)	0 .	3 (0.2%)
	VERTIGO	2 (0.4%)	1 (0.2%)	0 .	3 (0.2%)
RENAL AND URINARY DISORDERS	TOTAL	1 (0.2%)	0 .	2 (0.4%)	3 (0.2%)
	CALCULUS URINARY	0 .	0 .	1 (0.2%)	1 (0.1%)
	NOCTURIA	1 (0.2%)	0 .	0 .	1 (0.1%)
	RENAL INSUFFICIENCY	0 .	0 .	1 (0.2%)	1 (0.1%)
EYE DISORDERS	TOTAL	0 .	2 (0.4%)	0 .	2 (0.1%)
	DIPLOPIA	0 .	1 (0.2%)	0 .	1 (0.1%)
	VISUAL DISTURBANCE	0 .	1 (0.2%)	0 .	1 (0.1%)
HEPATOBILIARY DISORDERS	TOTAL	0 .	2 (0.4%)	0 .	2 (0.1%)
	BILIARY COLIC	0 .	1 (0.2%)	0 .	1 (0.1%)
	CHOLELITHIASIS	0 .	1 (0.2%)	0 .	1 (0.1%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	TOTAL	1 (0.2%)	0 .	0 .	1 (0.1%)
	EYELID TUMOUR	1 (0.2%)	0 .	0 .	1 (0.1%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	TOTAL	1 (0.2%)	0 .	0 .	1 (0.1%)
	OVARIAN DISORDER	1 (0.2%)	0 .	0 .	1 (0.1%)
SURGICAL AND MEDICAL PROCEDURES	TOTAL	1 (0.2%)	0 .	0 .	1 (0.1%)
	CATARACT EXTRACTION	1 (0.2%)	0 .	0 .	1 (0.1%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA PREFERRED TERM
2. TOTAL ROWS REPRESENT TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED FOR PLACEBO AND SB207499 COLUMNS AND ON TOTAL NUMBER OF PATIENTS ENTERING RUN-IN FOR TOTAL COLUMN

CONFIDENTIAL

SB 207499

TABLE 13.15A

SUMMARY OF PRIOR MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
TOTAL	451 (99.8%)	455 (100.0%)	906 (99.9%)
SALBUTAMOL	444 (98.2%)	450 (98.9%)	894 (98.6%)
IPRATROPIUM BROMIDE	243 (53.8%)	244 (53.6%)	487 (53.7%)
FLUTICASONE PROPIONATE	92 (20.4%)	116 (25.5%)	208 (22.9%)
SALMETEROL XINAFOATE	92 (20.4%)	112 (24.6%)	204 (22.5%)
THEOPHYLLINE	67 (14.8%)	76 (16.7%)	143 (15.8%)
BUDESONIDE	61 (13.5%)	67 (14.7%)	128 (14.1%)
ACETYLSALICYLIC ACID	64 (14.2%)	56 (12.3%)	120 (13.2%)
FENOTEROL HYDROBROMIDE	43 (9.5%)	50 (11.0%)	93 (10.3%)
EFORMOTEROL FUMARATE	41 (9.1%)	47 (10.3%)	88 (9.7%)
OXITROPIUM BROMIDE	26 (5.8%)	39 (8.6%)	65 (7.2%)
PARACETAMOL	38 (8.4%)	35 (7.7%)	73 (8.0%)
BECLOMETASONE DIPROPIONATE	30 (6.6%)	25 (5.5%)	55 (6.1%)
SALBUTAMOL SULFATE	40 (8.8%)	25 (5.5%)	65 (7.2%)
ACETYLCYSTEINE	14 (3.1%)	24 (5.3%)	38 (4.2%)
HYDROCHLOROTHIAZIDE	29 (6.4%)	24 (5.3%)	53 (5.8%)
OMEPRAZOLE	21 (4.6%)	22 (4.8%)	43 (4.7%)
FUROSEMIDE	22 (4.9%)	21 (4.6%)	43 (4.7%)
AMLODIPINE BESILATE	16 (3.5%)	19 (4.2%)	35 (3.9%)
SALMETEROL	11 (2.4%)	19 (4.2%)	30 (3.3%)
ENALAPRIL	10 (2.2%)	16 (3.5%)	26 (2.9%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR PRIOR MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED POST-RANDOMIZATION AND MEDICATIONS DISCONTINUED PRIOR TO RANDOMIZATION
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15A

SUMMARY OF PRIOR MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
RAMIPRIL	8 (1.8%)	16 (3.5%)	24 (2.6%)
ALLOPURINOL	10 (2.2%)	15 (3.3%)	25 (2.8%)
ISOSORBIDE MONONITRATE	12 (2.7%)	15 (3.3%)	27 (3.0%)
SIMVASTATIN	16 (3.5%)	15 (3.3%)	31 (3.4%)
DIGOXIN	11 (2.4%)	14 (3.1%)	25 (2.8%)
GLYCERYL TRINITRATE	16 (3.5%)	14 (3.1%)	30 (3.3%)
ISOSORBIDE DINITRATE	8 (1.8%)	14 (3.1%)	22 (2.4%)
IPRATROPIUM	13 (2.9%)	12 (2.6%)	25 (2.8%)
CODEINE PHOSPHATE	13 (2.9%)	11 (2.4%)	24 (2.6%)
DILTIAZEM HYDROCHLORIDE	8 (1.8%)	11 (2.4%)	19 (2.1%)
VERAPAMIL HYDROCHLORIDE	8 (1.8%)	11 (2.4%)	19 (2.1%)
AMINOPHYLLINE	13 (2.9%)	10 (2.2%)	23 (2.5%)
ATORVASTATIN CALCIUM	13 (2.9%)	10 (2.2%)	23 (2.5%)
DEXTROPROPOXYPHENE HYDROCHLORIDE	5 (1.1%)	10 (2.2%)	15 (1.7%)
ENALAPRIL MALEATE	13 (2.9%)	10 (2.2%)	23 (2.5%)
FORMOTEROL	14 (3.1%)	10 (2.2%)	24 (2.6%)
LISINOPRIL	9 (2.0%)	10 (2.2%)	19 (2.1%)
BENDROFLUMETHIAZIDE	7 (1.5%)	9 (2.0%)	16 (1.8%)
INDAPAMIDE	3 (0.7%)	9 (2.0%)	12 (1.3%)
TERBUTALINE	12 (2.7%)	9 (2.0%)	21 (2.3%)
AMILORIDE HYDROCHLORIDE	7 (1.5%)	8 (1.8%)	15 (1.7%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR PRIOR MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED POST-RANDOMIZATION AND MEDICATIONS DISCONTINUED PRIOR TO RANDOMIZATION
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 13.15A

SUMMARY OF PRIOR MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
ASCORBIC ACID	2 (0.4%)	8 (1.8%)	10 (1.1%)
DICLOFENAC SODIUM	3 (0.7%)	8 (1.8%)	11 (1.2%)
FELODIPINE	7 (1.5%)	8 (1.8%)	15 (1.7%)
IBUPROFEN	5 (1.1%)	8 (1.8%)	13 (1.4%)
LORATADINE	3 (0.7%)	8 (1.8%)	11 (1.2%)
NIFEDIPINE	7 (1.5%)	8 (1.8%)	15 (1.7%)
POTASSIUM CHLORIDE	3 (0.7%)	8 (1.8%)	11 (1.2%)
ACETYLSALICYLATE LYSINE	5 (1.1%)	7 (1.5%)	12 (1.3%)
ALFUZOSIN HYDROCHLORIDE	0 .	7 (1.5%)	7 (0.8%)
CAPTOPRIL	12 (2.7%)	7 (1.5%)	19 (2.1%)
PENTOXIFYLLINE	4 (0.9%)	7 (1.5%)	11 (1.2%)
AMLODIPINE	4 (0.9%)	6 (1.3%)	10 (1.1%)
AMOXICILLIN TRIHYDRATE	4 (0.9%)	6 (1.3%)	10 (1.1%)
DOXAZOSIN MESILATE	5 (1.1%)	6 (1.3%)	11 (1.2%)
GLIBENCLAMIDE	7 (1.5%)	6 (1.3%)	13 (1.4%)
PREDNISONE	9 (2.0%)	6 (1.3%)	15 (1.7%)
TAMSULOSIN HYDROCHLORIDE	4 (0.9%)	6 (1.3%)	10 (1.1%)
TERAZOSIN HYDROCHLORIDE	4 (0.9%)	6 (1.3%)	10 (1.1%)
VALSARTAN	4 (0.9%)	6 (1.3%)	10 (1.1%)
VERAPAMIL	5 (1.1%)	6 (1.3%)	11 (1.2%)
AMOXICILLIN	6 (1.3%)	5 (1.1%)	11 (1.2%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR PRIOR MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED POST-RANDOMIZATION AND MEDICATIONS DISCONTINUED PRIOR TO RANDOMIZATION
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15A

SUMMARY OF PRIOR MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
ATENOLOL	6 (1.3%)	5 (1.1%)	11 (1.2%)
CELECOXIB	6 (1.3%)	5 (1.1%)	11 (1.2%)
DIAZEPAM	7 (1.5%)	5 (1.1%)	12 (1.3%)
DILTIAZEM	3 (0.7%)	5 (1.1%)	8 (0.9%)
IRBESARTAN	8 (1.8%)	5 (1.1%)	13 (1.4%)
LANSOPRAZOLE	2 (0.4%)	5 (1.1%)	7 (0.8%)
METFORMIN HYDROCHLORIDE	6 (1.3%)	5 (1.1%)	11 (1.2%)
NICOUMALONE	2 (0.4%)	5 (1.1%)	7 (0.8%)
PANTOPRAZOLE SODIUM	2 (0.4%)	5 (1.1%)	7 (0.8%)
QUINAPRIL	3 (0.7%)	5 (1.1%)	8 (0.9%)
RANITIDINE	4 (0.9%)	5 (1.1%)	9 (1.0%)
TORASEMIDE	1 (0.2%)	5 (1.1%)	6 (0.7%)
VITAMINS NOS	1 (0.2%)	5 (1.1%)	6 (0.7%)
ALENDRONATE SODIUM	5 (1.1%)	4 (0.9%)	9 (1.0%)
AMBROXOL HYDROCHLORIDE	8 (1.8%)	4 (0.9%)	12 (1.3%)
AMIODARONE HYDROCHLORIDE	2 (0.4%)	4 (0.9%)	6 (0.7%)
BECLOMETASONE	9 (2.0%)	4 (0.9%)	13 (1.4%)
CALCIUM CARBONATE	5 (1.1%)	4 (0.9%)	9 (1.0%)
CANDESARTAN CILEXETIL	2 (0.4%)	4 (0.9%)	6 (0.7%)
CLAVULANATE POTASSIUM	5 (1.1%)	4 (0.9%)	9 (1.0%)
DOXYCYCLINE	1 (0.2%)	4 (0.9%)	5 (0.6%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR PRIOR MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED POST-RANDOMIZATION AND MEDICATIONS DISCONTINUED PRIOR TO RANDOMIZATION
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15A

SUMMARY OF PRIOR MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
FINASTERIDE	1 (0.2%)	4 (0.9%)	5 (0.6%)
GAVISCON NOS	2 (0.4%)	4 (0.9%)	6 (0.7%)
GLICLAZIDE	8 (1.8%)	4 (0.9%)	12 (1.3%)
LACIDIPINE	2 (0.4%)	4 (0.9%)	6 (0.7%)
LORMETAZEPAM	1 (0.2%)	4 (0.9%)	5 (0.6%)
METOPROLOL TARTRATE	3 (0.7%)	4 (0.9%)	7 (0.8%)
MINERALS NOS	1 (0.2%)	4 (0.9%)	5 (0.6%)
MISOPROSTOL	1 (0.2%)	4 (0.9%)	5 (0.6%)
PREDNISOLONE	9 (2.0%)	4 (0.9%)	13 (1.4%)
RANITIDINE HYDROCHLORIDE	8 (1.8%)	4 (0.9%)	12 (1.3%)
SPIRONOLACTONE	4 (0.9%)	4 (0.9%)	8 (0.9%)
TERBUTALINE SULFATE	1 (0.2%)	4 (0.9%)	5 (0.6%)
TIMOLOL MALEATE	1 (0.2%)	4 (0.9%)	5 (0.6%)
TIOTROPIUM BROMIDE	5 (1.1%)	4 (0.9%)	9 (1.0%)
TRIFLUSAL	1 (0.2%)	4 (0.9%)	5 (0.6%)
ACARBOSE	0 .	3 (0.7%)	3 (0.3%)
ALPRAZOLAM	2 (0.4%)	3 (0.7%)	5 (0.6%)
BISOPROLOL FUMARATE	3 (0.7%)	3 (0.7%)	6 (0.7%)
BROMHEXINE	0 .	3 (0.7%)	3 (0.3%)
CAFFEINE	7 (1.5%)	3 (0.7%)	10 (1.1%)
CEFAZOLIN	0 .	3 (0.7%)	3 (0.3%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR PRIOR MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED POST-RANDOMIZATION AND MEDICATIONS DISCONTINUED PRIOR TO RANDOMIZATION
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15A

SUMMARY OF PRIOR MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
CIMETIDINE	4 (0.9%)	3 (0.7%)	7 (0.8%)
CLENBUTEROL HYDROCHLORIDE	2 (0.4%)	3 (0.7%)	5 (0.6%)
DICLOFENAC	2 (0.4%)	3 (0.7%)	5 (0.6%)
DIHYDROCODEINE BITARTRATE	1 (0.2%)	3 (0.7%)	4 (0.4%)
FAMOTIDINE	2 (0.4%)	3 (0.7%)	5 (0.6%)
FENOTEROL	1 (0.2%)	3 (0.7%)	4 (0.4%)
FLUDIAZEPAM	0 .	3 (0.7%)	3 (0.3%)
FLUTICASONE	2 (0.4%)	3 (0.7%)	5 (0.6%)
INFLUENZA VACCINE	1 (0.2%)	3 (0.7%)	4 (0.4%)
INSULIN HUMAN	3 (0.7%)	3 (0.7%)	6 (0.7%)
LACTULOSE	3 (0.7%)	3 (0.7%)	6 (0.7%)
LEVOTHYROXINE SODIUM	10 (2.2%)	3 (0.7%)	13 (1.4%)
MELOXICAM	1 (0.2%)	3 (0.7%)	4 (0.4%)
METAMIZOLE SODIUM	0 .	3 (0.7%)	3 (0.3%)
METHYLPREDNISOLONE	1 (0.2%)	3 (0.7%)	4 (0.4%)
NIMESULIDE	0 .	3 (0.7%)	3 (0.3%)
NITRENDIPINE	0 .	3 (0.7%)	3 (0.3%)
NYSTATIN	1 (0.2%)	3 (0.7%)	4 (0.4%)
PERINDOPRIL	4 (0.9%)	3 (0.7%)	7 (0.8%)
PLANTAGO OVATA	2 (0.4%)	3 (0.7%)	5 (0.6%)
PNEUMOCOCCAL VACCINE	4 (0.9%)	3 (0.7%)	7 (0.8%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR PRIOR MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED POST-RANDOMIZATION AND MEDICATIONS DISCONTINUED PRIOR TO RANDOMIZATION
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15A

SUMMARY OF PRIOR MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
PROPRANOLOL HYDROCHLORIDE	0 .	3 (0.7%)	3 (0.3%)
PYRIDOXINE HYDROCHLORIDE	1 (0.2%)	3 (0.7%)	4 (0.4%)
SODIUM CHLORIDE	2 (0.4%)	3 (0.7%)	5 (0.6%)
TEMAZEPAM	1 (0.2%)	3 (0.7%)	4 (0.4%)
TICLOPIDINE HYDROCHLORIDE	2 (0.4%)	3 (0.7%)	5 (0.6%)
VITAMIN B SUBSTANCES NOS	0 .	3 (0.7%)	3 (0.3%)
WARFARIN	5 (1.1%)	3 (0.7%)	8 (0.9%)
ACETYLDIGOXIN	1 (0.2%)	2 (0.4%)	3 (0.3%)
ALMAGATE	1 (0.2%)	2 (0.4%)	3 (0.3%)
ALTHAEA OFFICINALIS	1 (0.2%)	2 (0.4%)	3 (0.3%)
ANTIMONY POTASSIUM TARTRATE	0 .	2 (0.4%)	2 (0.2%)
ARMENIACA VULGARIS	2 (0.4%)	2 (0.4%)	4 (0.4%)
BENZOIC ACID	0 .	2 (0.4%)	2 (0.2%)
BENZONATATE	1 (0.2%)	2 (0.4%)	3 (0.3%)
BENZYDAMINE HYDROCHLORIDE	1 (0.2%)	2 (0.4%)	3 (0.3%)
BEZAFIBRATE	1 (0.2%)	2 (0.4%)	3 (0.3%)
BISOPROLOL	0 .	2 (0.4%)	2 (0.2%)
BUPROPION HYDROCHLORIDE	2 (0.4%)	2 (0.4%)	4 (0.4%)
CAMPHOR	0 .	2 (0.4%)	2 (0.2%)
CARBAMAZEPINE	0 .	2 (0.4%)	2 (0.2%)
CARTEOLOL HYDROCHLORIDE	0 .	2 (0.4%)	2 (0.2%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR PRIOR MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED POST-RANDOMIZATION AND MEDICATIONS DISCONTINUED PRIOR TO RANDOMIZATION
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15A

SUMMARY OF PRIOR MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
CHLORPHENAMINE MALEATE	0 .	2 (0.4%)	2 (0.2%)
CILAZAPRIL	3 (0.7%)	2 (0.4%)	5 (0.6%)
CLOPIDOGREL SULFATE	2 (0.4%)	2 (0.4%)	4 (0.4%)
COLCHICINE	0 .	2 (0.4%)	2 (0.2%)
COLECALCIFEROL	1 (0.2%)	2 (0.4%)	3 (0.3%)
CROMOGLICATE SODIUM	1 (0.2%)	2 (0.4%)	3 (0.3%)
DEXTROMETHORPHAN HYDROBROMIDE	2 (0.4%)	2 (0.4%)	4 (0.4%)
DICLOFENAC DIETHYLAMINE	1 (0.2%)	2 (0.4%)	3 (0.3%)
DIHYDROCODEINE	3 (0.7%)	2 (0.4%)	5 (0.6%)
DIPYRIDAMOLE	3 (0.7%)	2 (0.4%)	5 (0.6%)
DORZOLAMIDE HYDROCHLORIDE	1 (0.2%)	2 (0.4%)	3 (0.3%)
ESOMEPRAZOLE MAGNESIUM	0 .	2 (0.4%)	2 (0.2%)
ESTRADIOL	6 (1.3%)	2 (0.4%)	8 (0.9%)
ETHANOL	0 .	2 (0.4%)	2 (0.2%)
FENOFIBRATE	4 (0.9%)	2 (0.4%)	6 (0.7%)
FERROUS SULPHATE	0 .	2 (0.4%)	2 (0.2%)
FLUCLOXACILLIN	0 .	2 (0.4%)	2 (0.2%)
FLUOXETINE HYDROCHLORIDE	5 (1.1%)	2 (0.4%)	7 (0.8%)
FLUVASTATIN SODIUM	1 (0.2%)	2 (0.4%)	3 (0.3%)
FOSFOMYCIN CALCIUM	2 (0.4%)	2 (0.4%)	4 (0.4%)
GLIPIZIDE	0 .	2 (0.4%)	2 (0.2%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR PRIOR MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED POST-RANDOMIZATION AND MEDICATIONS DISCONTINUED PRIOR TO RANDOMIZATION
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15A

SUMMARY OF PRIOR MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
HEDERA HELIX	0 .	2 (0.4%)	2 (0.2%)
HYDROCORTISONE	1 (0.2%)	2 (0.4%)	3 (0.3%)
HYDROTALCITE	2 (0.4%)	2 (0.4%)	4 (0.4%)
HYDROXYZINE	1 (0.2%)	2 (0.4%)	3 (0.3%)
HYOSCINE BUTYLBROMIDE	0 .	2 (0.4%)	2 (0.2%)
INSULIN HUMAN INJECTION, ISOPHANE	2 (0.4%)	2 (0.4%)	4 (0.4%)
ISONIAZID	0 .	2 (0.4%)	2 (0.2%)
ISRADIPINE	0 .	2 (0.4%)	2 (0.2%)
LEVODOPA	0 .	2 (0.4%)	2 (0.2%)
LEVONORGESTREL	0 .	2 (0.4%)	2 (0.2%)
LEVOTHYROXINE	7 (1.5%)	2 (0.4%)	9 (1.0%)
LIQUORICE LIQUID EXTRACT	0 .	2 (0.4%)	2 (0.2%)
LOSARTAN POTASSIUM	9 (2.0%)	2 (0.4%)	11 (1.2%)
MEDICATION UNKNOWN	1 (0.2%)	2 (0.4%)	3 (0.3%)
METHYLEPHEDRINE HYDROCHLORIDE	0 .	2 (0.4%)	2 (0.2%)
METOCLOPRAMIDE	2 (0.4%)	2 (0.4%)	4 (0.4%)
METOPROLOL SUCCINATE	3 (0.7%)	2 (0.4%)	5 (0.6%)
MOMETASONE FUROATE	1 (0.2%)	2 (0.4%)	3 (0.3%)
NAPROXEN	5 (1.1%)	2 (0.4%)	7 (0.8%)
NICORANDIL	1 (0.2%)	2 (0.4%)	3 (0.3%)
OXYGEN	0 .	2 (0.4%)	2 (0.2%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR PRIOR MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED POST-RANDOMIZATION AND MEDICATIONS DISCONTINUED PRIOR TO RANDOMIZATION
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15A

SUMMARY OF PRIOR MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
PAPAVER SOMNIFERUM	0 .	2 (0.4%)	2 (0.2%)
PIMPINELLA ANISUM	0 .	2 (0.4%)	2 (0.2%)
PIOGLITAZONE HYDROCHLORIDE	1 (0.2%)	2 (0.4%)	3 (0.3%)
PIRETANIDE	0 .	2 (0.4%)	2 (0.2%)
PRAVASTATIN SODIUM	3 (0.7%)	2 (0.4%)	5 (0.6%)
QUININE SULPHATE	0 .	2 (0.4%)	2 (0.2%)
SERTRALINE HYDROCHLORIDE	1 (0.2%)	2 (0.4%)	3 (0.3%)
SILYMARIN	1 (0.2%)	2 (0.4%)	3 (0.3%)
SODIUM CITRATE	2 (0.4%)	2 (0.4%)	4 (0.4%)
TELMISARTAN	4 (0.9%)	2 (0.4%)	6 (0.7%)
TERAZOSIN	0 .	2 (0.4%)	2 (0.2%)
THEOPHEDRIN (NOS)	1 (0.2%)	2 (0.4%)	3 (0.3%)
THIOCTIC ACID	0 .	2 (0.4%)	2 (0.2%)
TRAMADOL HYDROCHLORIDE	1 (0.2%)	2 (0.4%)	3 (0.3%)
TRIAMTERENE	4 (0.9%)	2 (0.4%)	6 (0.7%)
TRIMETHOPRIM	2 (0.4%)	2 (0.4%)	4 (0.4%)
VENLAFAXINE HYDROCHLORIDE	1 (0.2%)	2 (0.4%)	3 (0.3%)
VINPOCETINE	0 .	2 (0.4%)	2 (0.2%)
ZAFIRLUKAST	0 .	2 (0.4%)	2 (0.2%)
ACCUPRIN (NOS)	0 .	1 (0.2%)	1 (0.1%)
ACEDIUR (NOS)	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR PRIOR MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED POST-RANDOMIZATION AND MEDICATIONS DISCONTINUED PRIOR TO RANDOMIZATION
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15A

SUMMARY OF PRIOR MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
ALGINIC ACID	0 .	1 (0.2%)	1 (0.1%)
ALMITRINE DIMESILATE	0 .	1 (0.2%)	1 (0.1%)
AMBROXOL	1 (0.2%)	1 (0.2%)	2 (0.2%)
AMBUPHYLLINE	0 .	1 (0.2%)	1 (0.1%)
AMCINONIDE	0 .	1 (0.2%)	1 (0.1%)
AMINOPHENAZONE	0 .	1 (0.2%)	1 (0.1%)
AMITRIPTYLINE	5 (1.1%)	1 (0.2%)	6 (0.7%)
AMMONIUM BICARBONATE	0 .	1 (0.2%)	1 (0.1%)
ANTIBIOTICS NOS	0 .	1 (0.2%)	1 (0.1%)
ASPARAGINE	0 .	1 (0.2%)	1 (0.1%)
BAMBUTEROL	0 .	1 (0.2%)	1 (0.1%)
BAMBUTEROL HYDROCHLORIDE	1 (0.2%)	1 (0.2%)	2 (0.2%)
BEE VENOM, STANDARD	0 .	1 (0.2%)	1 (0.1%)
BENADRYL (NOS)	0 .	1 (0.2%)	1 (0.1%)
BENSERAZIDE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
BENTONITE	0 .	1 (0.2%)	1 (0.1%)
BENZBROMARONE	0 .	1 (0.2%)	1 (0.1%)
BEPANTHEN (NOS)	0 .	1 (0.2%)	1 (0.1%)
BETAMETHASONE SODIUM PHOSPHATE	1 (0.2%)	1 (0.2%)	2 (0.2%)
BRIMONIDINE	0 .	1 (0.2%)	1 (0.1%)
BROMHEXINE HYDROCHLORIDE	3 (0.7%)	1 (0.2%)	4 (0.4%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR PRIOR MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED POST-RANDOMIZATION AND MEDICATIONS DISCONTINUED PRIOR TO RANDOMIZATION
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15A

SUMMARY OF PRIOR MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
BUFLOMEDIL HYDROCHLORIDE	1 (0.2%)	1 (0.2%)	2 (0.2%)
BUMETANIDE	1 (0.2%)	1 (0.2%)	2 (0.2%)
BUPHENINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
CALAMINE	0 .	1 (0.2%)	1 (0.1%)
CALCITRIOL	0 .	1 (0.2%)	1 (0.1%)
CALCIUM	1 (0.2%)	1 (0.2%)	2 (0.2%)
CALCIUM DOBESILATE	0 .	1 (0.2%)	1 (0.1%)
CALCIUM INOSITOL HEXAPHOSPHATE	0 .	1 (0.2%)	1 (0.1%)
CALCIUM PHOSPHATE	0 .	1 (0.2%)	1 (0.1%)
CARBASALATE CALCIUM	2 (0.4%)	1 (0.2%)	3 (0.3%)
CARBIDOPA	0 .	1 (0.2%)	1 (0.1%)
CARBOMER	0 .	1 (0.2%)	1 (0.1%)
CARISOPRODOL	0 .	1 (0.2%)	1 (0.1%)
CEFACLOR	1 (0.2%)	1 (0.2%)	2 (0.2%)
CEFALEXIN MONOHYDRATE	0 .	1 (0.2%)	1 (0.1%)
CERIVASTATIN SODIUM	0 .	1 (0.2%)	1 (0.1%)
CETIRIZINE HYDROCHLORIDE	3 (0.7%)	1 (0.2%)	4 (0.4%)
CHLORAMPHENICOL	2 (0.4%)	1 (0.2%)	3 (0.3%)
CIBENZOLINE	0 .	1 (0.2%)	1 (0.1%)
CINNAMIC ESTER	0 .	1 (0.2%)	1 (0.1%)
CIPROFLOXACIN	2 (0.4%)	1 (0.2%)	3 (0.3%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR PRIOR MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED POST-RANDOMIZATION AND MEDICATIONS DISCONTINUED PRIOR TO RANDOMIZATION
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15A

SUMMARY OF PRIOR MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
CITALOPRAM	1 (0.2%)	1 (0.2%)	2 (0.2%)
CITALOPRAM HYDROBROMIDE	1 (0.2%)	1 (0.2%)	2 (0.2%)
CITRIC ACID	0 .	1 (0.2%)	1 (0.1%)
CLARITHROMYCIN	2 (0.4%)	1 (0.2%)	3 (0.3%)
CLEBOPRIDE	0 .	1 (0.2%)	1 (0.1%)
CLEBOPRIDE HYDROGEN MALEATE	0 .	1 (0.2%)	1 (0.1%)
CLONAZEPAM	0 .	1 (0.2%)	1 (0.1%)
CLOPIDOGREL	2 (0.4%)	1 (0.2%)	3 (0.3%)
CLOPREDNOL	0 .	1 (0.2%)	1 (0.1%)
CLOTRIMAZOLE	0 .	1 (0.2%)	1 (0.1%)
COD-LIVER OIL	3 (0.7%)	1 (0.2%)	4 (0.4%)
CODEINE	0 .	1 (0.2%)	1 (0.1%)
CODEINE PHOSPHATE HEMIHYDRATE	0 .	1 (0.2%)	1 (0.1%)
CORTISONE	0 .	1 (0.2%)	1 (0.1%)
CORVASAL NOS	0 .	1 (0.2%)	1 (0.1%)
CREOSOTE	0 .	1 (0.2%)	1 (0.1%)
CRESOLSULFONIC ACID	1 (0.2%)	1 (0.2%)	2 (0.2%)
CYPROHEPTADINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
DAFLON NOS	1 (0.2%)	1 (0.2%)	2 (0.2%)
DEFLAZACORT	0 .	1 (0.2%)	1 (0.1%)
DELAPRIL	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR PRIOR MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED POST-RANDOMIZATION AND MEDICATIONS DISCONTINUED PRIOR TO RANDOMIZATION
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 13.15A

SUMMARY OF PRIOR MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
DESIPRAMINE HYDROCHLORIDE	2 (0.4%)	1 (0.2%)	3 (0.3%)
DESOXIMETASONE	0 .	1 (0.2%)	1 (0.1%)
DEXTROPROPOXYPHENE NAPSILATE	2 (0.4%)	1 (0.2%)	3 (0.3%)
DIBENZOYLMETHANE	0 .	1 (0.2%)	1 (0.1%)
DICLOFENAC RESINATE	0 .	1 (0.2%)	1 (0.1%)
DIGITOXIN	0 .	1 (0.2%)	1 (0.1%)
DIMETICONE	0 .	1 (0.2%)	1 (0.1%)
DIOXIDINE	1 (0.2%)	1 (0.2%)	2 (0.2%)
DIPHENHYDRAMINE HYDROCHLORIDE	2 (0.4%)	1 (0.2%)	3 (0.3%)
DIPHENYLPYRALINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
DIPROPHYLLINE	0 .	1 (0.2%)	1 (0.1%)
DITOPAX (NOS)	0 .	1 (0.2%)	1 (0.1%)
DOSULEPIN	0 .	1 (0.2%)	1 (0.1%)
DOXAZOSIN	1 (0.2%)	1 (0.2%)	2 (0.2%)
DOXEPIN HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
DOXYLAMINE SUCCINATE	1 (0.2%)	1 (0.2%)	2 (0.2%)
ELECTROLYTES NOS	0 .	1 (0.2%)	1 (0.1%)
EMULSIFYING WAX	0 .	1 (0.2%)	1 (0.1%)
ERYTHROMYCIN	2 (0.4%)	1 (0.2%)	3 (0.3%)
ESTRADIOL VALERATE	0 .	1 (0.2%)	1 (0.1%)
ESTRIOL	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR PRIOR MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED POST-RANDOMIZATION AND MEDICATIONS DISCONTINUED PRIOR TO RANDOMIZATION
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15A

SUMMARY OF PRIOR MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
ESTROGENS CONJUGATED	7 (1.5%)	1 (0.2%)	8 (0.9%)
ETAFEDRINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
ETHENZAMIDE	0 .	1 (0.2%)	1 (0.1%)
ETHINYLOESTRADIOL	2 (0.4%)	1 (0.2%)	3 (0.3%)
ETOFYLLINE	0 .	1 (0.2%)	1 (0.1%)
EUCALYPTUS GLOBULUS OIL	1 (0.2%)	1 (0.2%)	2 (0.2%)
FENIPENTOL	0 .	1 (0.2%)	1 (0.1%)
FEXOFENADINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
FLAVOXATE	0 .	1 (0.2%)	1 (0.1%)
FLAVOXATE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
FLECAINIDE	0 .	1 (0.2%)	1 (0.1%)
FLUCLOXACILLIN SODIUM	0 .	1 (0.2%)	1 (0.1%)
FLUCONAZOLE	1 (0.2%)	1 (0.2%)	2 (0.2%)
FLUDROCORTISONE ACETATE	0 .	1 (0.2%)	1 (0.1%)
FLUOROURACIL	0 .	1 (0.2%)	1 (0.1%)
FOLIC ACID	2 (0.4%)	1 (0.2%)	3 (0.3%)
FUSAFUNGINE	0 .	1 (0.2%)	1 (0.1%)
FYTIC ACID	0 .	1 (0.2%)	1 (0.1%)
GATIFLOXACIN	0 .	1 (0.2%)	1 (0.1%)
GELUSIL NOS	1 (0.2%)	1 (0.2%)	2 (0.2%)
GEMFIBROZIL	1 (0.2%)	1 (0.2%)	2 (0.2%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR PRIOR MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED POST-RANDOMIZATION AND MEDICATIONS DISCONTINUED PRIOR TO RANDOMIZATION
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15A

SUMMARY OF PRIOR MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
GENTAMICIN	0 .	1 (0.2%)	1 (0.1%)
GENTAMICIN SULFATE	0 .	1 (0.2%)	1 (0.1%)
GINSENG	0 .	1 (0.2%)	1 (0.1%)
GLUCOSAMINE	0 .	1 (0.2%)	1 (0.1%)
GLUTATHIONE	0 .	1 (0.2%)	1 (0.1%)
GLYCEROL	0 .	1 (0.2%)	1 (0.1%)
GUAIFENESIN	1 (0.2%)	1 (0.2%)	2 (0.2%)
HAEMOGLOBIN	0 .	1 (0.2%)	1 (0.1%)
HEPARINOID	0 .	1 (0.2%)	1 (0.1%)
HERBALS NOS	0 .	1 (0.2%)	1 (0.1%)
HESPERIDIN	1 (0.2%)	1 (0.2%)	2 (0.2%)
HESPERIDIN METHYL CHALCONE	0 .	1 (0.2%)	1 (0.1%)
HEXETIDINE	0 .	1 (0.2%)	1 (0.1%)
HONEY	0 .	1 (0.2%)	1 (0.1%)
HYDROCORTISONE BUTYRATE	1 (0.2%)	1 (0.2%)	2 (0.2%)
HYDROXYCARBAMIDE	0 .	1 (0.2%)	1 (0.1%)
HYDROXYCHLOROQUINE SULFATE	0 .	1 (0.2%)	1 (0.1%)
HYDROXYZINE EMBONATE	0 .	1 (0.2%)	1 (0.1%)
HYDROXYZINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
INDOMETACIN	1 (0.2%)	1 (0.2%)	2 (0.2%)
ISOPHANE INSULIN	1 (0.2%)	1 (0.2%)	2 (0.2%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR PRIOR MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED POST-RANDOMIZATION AND MEDICATIONS DISCONTINUED PRIOR TO RANDOMIZATION
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15A

SUMMARY OF PRIOR MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
LAMIVUDINE	0 .	1 (0.2%)	1 (0.1%)
LATANOPROST	5 (1.1%)	1 (0.2%)	6 (0.7%)
LECITHIN	0 .	1 (0.2%)	1 (0.1%)
LEVODROPROPIZINE	0 .	1 (0.2%)	1 (0.1%)
LEVOFLOXACIN	2 (0.4%)	1 (0.2%)	3 (0.3%)
LIDOCAINE	1 (0.2%)	1 (0.2%)	2 (0.2%)
LIDOCAINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
LINUM USITATISSIMUM OIL	0 .	1 (0.2%)	1 (0.1%)
LIOTHYRONINE	0 .	1 (0.2%)	1 (0.1%)
LOFEPRAMINE	0 .	1 (0.2%)	1 (0.1%)
LOPERAMIDE	0 .	1 (0.2%)	1 (0.1%)
LOPRAZOLAM	0 .	1 (0.2%)	1 (0.1%)
LORAZEPAM	3 (0.7%)	1 (0.2%)	4 (0.4%)
LOSARTAN	1 (0.2%)	1 (0.2%)	2 (0.2%)
LOVASTATIN	1 (0.2%)	1 (0.2%)	2 (0.2%)
LYMECYCLINE	0 .	1 (0.2%)	1 (0.1%)
LYSOZYME HYDROCHLORIDE	1 (0.2%)	1 (0.2%)	2 (0.2%)
MACROGOL	0 .	1 (0.2%)	1 (0.1%)
MAGALDRATE	0 .	1 (0.2%)	1 (0.1%)
MAGNESIUM	1 (0.2%)	1 (0.2%)	2 (0.2%)
MAGNESIUM CARBONATE	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR PRIOR MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED POST-RANDOMIZATION AND MEDICATIONS DISCONTINUED PRIOR TO RANDOMIZATION
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15A

SUMMARY OF PRIOR MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
MAGNESIUM OXIDE	3 (0.7%)	1 (0.2%)	4 (0.4%)
MEDROXYPROGESTERONE ACETATE	4 (0.9%)	1 (0.2%)	5 (0.6%)
MENTHOL	1 (0.2%)	1 (0.2%)	2 (0.2%)
MEPROBAMATE	0 .	1 (0.2%)	1 (0.1%)
MESNA	1 (0.2%)	1 (0.2%)	2 (0.2%)
METFORMIN	2 (0.4%)	1 (0.2%)	3 (0.3%)
METHYLDOPA	0 .	1 (0.2%)	1 (0.1%)
METOPROLOL	2 (0.4%)	1 (0.2%)	3 (0.3%)
MICONAZOLE NITRATE	0 .	1 (0.2%)	1 (0.1%)
MIZOLASTINE	0 .	1 (0.2%)	1 (0.1%)
MONTELUKAST SODIUM	4 (0.9%)	1 (0.2%)	5 (0.6%)
MOXIFLOXACIN	1 (0.2%)	1 (0.2%)	2 (0.2%)
MOXONIDINE	1 (0.2%)	1 (0.2%)	2 (0.2%)
NAPHAZOLINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
NEFAZODONE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
NEOMYCIN SULFATE	1 (0.2%)	1 (0.2%)	2 (0.2%)
NICOTINIC ACID	0 .	1 (0.2%)	1 (0.1%)
NITRAZEPAM	2 (0.4%)	1 (0.2%)	3 (0.3%)
NITROFURANTOIN	0 .	1 (0.2%)	1 (0.1%)
NORETHISTERONE	4 (0.9%)	1 (0.2%)	5 (0.6%)
NORETHISTERONE ACETATE	3 (0.7%)	1 (0.2%)	4 (0.4%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR PRIOR MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED POST-RANDOMIZATION AND MEDICATIONS DISCONTINUED PRIOR TO RANDOMIZATION
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15A

SUMMARY OF PRIOR MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
NUTRITIONAL SUPPLEMENT NOS	0 .	1 (0.2%)	1 (0.1%)
OFLOXACIN	0 .	1 (0.2%)	1 (0.1%)
OLEUM PINI SYLVESTRIS	0 .	1 (0.2%)	1 (0.1%)
OMEGA-3 TRIGLYCERIDES	0 .	1 (0.2%)	1 (0.1%)
ORLISTAT	0 .	1 (0.2%)	1 (0.1%)
ORPHENADRINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
OXYBUTYNIN HYDROCHLORIDE	1 (0.2%)	1 (0.2%)	2 (0.2%)
PANTOPRAZOLE	0 .	1 (0.2%)	1 (0.1%)
PARAFFIN, LIQUID	1 (0.2%)	1 (0.2%)	2 (0.2%)
PAROXETINE	1 (0.2%)	1 (0.2%)	2 (0.2%)
PHENACETIN	0 .	1 (0.2%)	1 (0.1%)
PHENOL, LIQUEFIED	0 .	1 (0.2%)	1 (0.1%)
PHENOXYETHANOL	0 .	1 (0.2%)	1 (0.1%)
PHENPROCOUMON	1 (0.2%)	1 (0.2%)	2 (0.2%)
PHENYLEPHRINE HYDROCHLORIDE	1 (0.2%)	1 (0.2%)	2 (0.2%)
PHOLCODINE	0 .	1 (0.2%)	1 (0.1%)
PILOCARPINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
PINAVERIUM	0 .	1 (0.2%)	1 (0.1%)
PIRACETAM	0 .	1 (0.2%)	1 (0.1%)
PIROXICAM	1 (0.2%)	1 (0.2%)	2 (0.2%)
PIZOTIFEN MALATE	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR PRIOR MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED POST-RANDOMIZATION AND MEDICATIONS DISCONTINUED PRIOR TO RANDOMIZATION
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 13.15A

SUMMARY OF PRIOR MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
POLYMYXIN B SULFATE	1 (0.2%)	1 (0.2%)	2 (0.2%)
POTASSIUM ASCORBATE	1 (0.2%)	1 (0.2%)	2 (0.2%)
PRAMIPEXOLE	0 .	1 (0.2%)	1 (0.1%)
PRAZOSIN HYDROCHLORIDE	3 (0.7%)	1 (0.2%)	4 (0.4%)
PROCHLORPERAZINE MALEATE	0 .	1 (0.2%)	1 (0.1%)
PROPIOMAZINE MALEATE	0 .	1 (0.2%)	1 (0.1%)
PROXYPHYLLINE	0 .	1 (0.2%)	1 (0.1%)
PSEUDOEPHEDRINE SULFATE	1 (0.2%)	1 (0.2%)	2 (0.2%)
PUMILIO PINE OIL	0 .	1 (0.2%)	1 (0.1%)
REPAGLINIDE	0 .	1 (0.2%)	1 (0.1%)
REPROTEROL HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
RIFAMPICIN	0 .	1 (0.2%)	1 (0.1%)
RUSCUS ACULEATUS	0 .	1 (0.2%)	1 (0.1%)
RUTOSIDE	1 (0.2%)	1 (0.2%)	2 (0.2%)
SALICYLIC ACID	0 .	1 (0.2%)	1 (0.1%)
SENEGA	0 .	1 (0.2%)	1 (0.1%)
SENNA	1 (0.2%)	1 (0.2%)	2 (0.2%)
SENNOSIDE A+B CALCIUM	0 .	1 (0.2%)	1 (0.1%)
SERENOA REPENS	2 (0.4%)	1 (0.2%)	3 (0.3%)
SIMETICONE	3 (0.7%)	1 (0.2%)	4 (0.4%)
SODIUM ADENOSINE TRIPHOSPHATE	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR PRIOR MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED POST-RANDOMIZATION AND MEDICATIONS DISCONTINUED PRIOR TO RANDOMIZATION
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 13.15A

SUMMARY OF PRIOR MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
SODIUM BICARBONATE	0 .	1 (0.2%)	1 (0.1%)
SOTALOL	1 (0.2%)	1 (0.2%)	2 (0.2%)
SOTALOL HYDROCHLORIDE	1 (0.2%)	1 (0.2%)	2 (0.2%)
STAVUDINE	0 .	1 (0.2%)	1 (0.1%)
STOPAYNE (NOS)	0 .	1 (0.2%)	1 (0.1%)
SULFAMETHOXAZOLE	1 (0.2%)	1 (0.2%)	2 (0.2%)
SULPIRIDE	0 .	1 (0.2%)	1 (0.1%)
SYNDOL (NOS)	0 .	1 (0.2%)	1 (0.1%)
TAMOXIFEN CITRATE	0 .	1 (0.2%)	1 (0.1%)
TAMSULOSIN	0 .	1 (0.2%)	1 (0.1%)
TERBINAFINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
THEBACON HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
THIAMINE	0 .	1 (0.2%)	1 (0.1%)
THIAMINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
THYMOL	0 .	1 (0.2%)	1 (0.1%)
TILIDINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
TITANIUM DIOXIDE	0 .	1 (0.2%)	1 (0.1%)
TRANEXAMIC ACID	0 .	1 (0.2%)	1 (0.1%)
TRIAMCINOLONE ACETONIDE	0 .	1 (0.2%)	1 (0.1%)
TRIMETAZIDINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
TRIPELENNAMINE	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR PRIOR MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED POST-RANDOMIZATION AND MEDICATIONS DISCONTINUED PRIOR TO RANDOMIZATION
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15A

SUMMARY OF PRIOR MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
URAPIDIL	0 .	1 (0.2%)	1 (0.1%)
WARFARIN SODIUM	1 (0.2%)	1 (0.2%)	2 (0.2%)
XYLOPROCT (NOS)	0 .	1 (0.2%)	1 (0.1%)
ZINC OXIDE	0 .	1 (0.2%)	1 (0.1%)
ZOLPIDEM TARTRATE	1 (0.2%)	1 (0.2%)	2 (0.2%)
ZUCLOPENTHIXOL	1 (0.2%)	1 (0.2%)	2 (0.2%)
3-BENZHYDRYLOXY-8-ISOPROPYLNORTROPANE MESILATE	1 (0.2%)	0 .	1 (0.1%)
ACEPROMAZINE	1 (0.2%)	0 .	1 (0.1%)
ACEPROMETAZINE	1 (0.2%)	0 .	1 (0.1%)
ACETAZOLAMIDE	1 (0.2%)	0 .	1 (0.1%)
ALANINE	2 (0.4%)	0 .	2 (0.2%)
ALDIOXA	1 (0.2%)	0 .	1 (0.1%)
ALPROSTADIL	1 (0.2%)	0 .	1 (0.1%)
ALTIZIDE	2 (0.4%)	0 .	2 (0.2%)
ALUMINIUM HYDROXIDE	1 (0.2%)	0 .	1 (0.1%)
ALUMINIUM HYDROXIDE GEL	1 (0.2%)	0 .	1 (0.1%)
ALUMINIUM HYDROXIDE GEL, DRIED	3 (0.7%)	0 .	3 (0.3%)
AMILORIDE	1 (0.2%)	0 .	1 (0.1%)
AMINOACETIC ACID	2 (0.4%)	0 .	2 (0.2%)
AMITRIPTYLINE HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR PRIOR MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED POST-RANDOMIZATION AND MEDICATIONS DISCONTINUED PRIOR TO RANDOMIZATION
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15A

SUMMARY OF PRIOR MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
AMMONIUM CHLORIDE	1 (0.2%)	0 .	1 (0.1%)
AMPICILLIN	1 (0.2%)	0 .	1 (0.1%)
ANASTROZOLE	1 (0.2%)	0 .	1 (0.1%)
ATORVASTATIN	4 (0.9%)	0 .	4 (0.4%)
ATROPINE SULFATE	2 (0.4%)	0 .	2 (0.2%)
AZITHROMYCIN	2 (0.4%)	0 .	2 (0.2%)
BENAZEPRIL HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
BENTAZEPAM	1 (0.2%)	0 .	1 (0.1%)
BENZYLPENICILLIN	1 (0.2%)	0 .	1 (0.1%)
BETAMETHASONE	1 (0.2%)	0 .	1 (0.1%)
BETAMETHASONE VALERATE	1 (0.2%)	0 .	1 (0.1%)
BETAMOX (NOS)	1 (0.2%)	0 .	1 (0.1%)
BETAXOLOL	1 (0.2%)	0 .	1 (0.1%)
BETAXOLOL HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
BIPERIDEN HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
BLINDED TRIAL MEDICATION	1 (0.2%)	0 .	1 (0.1%)
BRIMONIDINE TARTRATE	1 (0.2%)	0 .	1 (0.1%)
BRINZOLAMIDE	1 (0.2%)	0 .	1 (0.1%)
BROMAZEPAM	1 (0.2%)	0 .	1 (0.1%)
BRONCHOSAN (NOS)	1 (0.2%)	0 .	1 (0.1%)
BROTIZOLAM	1 (0.2%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR PRIOR MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED POST-RANDOMIZATION AND MEDICATIONS DISCONTINUED PRIOR TO RANDOMIZATION
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15A

SUMMARY OF PRIOR MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
BUPIVACAINE HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
CALCIUM CHLORIDE	1 (0.2%)	0 .	1 (0.1%)
CANRENONE	3 (0.7%)	0 .	3 (0.3%)
CARBIMAZOLE	1 (0.2%)	0 .	1 (0.1%)
CARBOCISTEINE	1 (0.2%)	0 .	1 (0.1%)
CARVEDILOL	2 (0.4%)	0 .	2 (0.2%)
CEFPODOXIME PROXETIL	1 (0.2%)	0 .	1 (0.1%)
CELIPROLOL HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
CEPACOL LOZENGES NOS	1 (0.2%)	0 .	1 (0.1%)
CETYLPYRIDINIUM CHLORIDE	1 (0.2%)	0 .	1 (0.1%)
CHLORHEXIDINE HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
CHLORTALIDONE	1 (0.2%)	0 .	1 (0.1%)
CINCHOCAINE HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
CINNARIZINE	2 (0.4%)	0 .	2 (0.2%)
CISAPRIDE	2 (0.4%)	0 .	2 (0.2%)
CLOBUTINOL HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
CLONIDINE	1 (0.2%)	0 .	1 (0.1%)
CLONIDINE HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
CLOPAMIDE	1 (0.2%)	0 .	1 (0.1%)
CLOTIAPINE	1 (0.2%)	0 .	1 (0.1%)
COLCAPS (NOS)	1 (0.2%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR PRIOR MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED POST-RANDOMIZATION AND MEDICATIONS DISCONTINUED PRIOR TO RANDOMIZATION
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15A

SUMMARY OF PRIOR MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
COLCHIMAX (NOS)	1 (0.2%)	0 .	1 (0.1%)
CYANOCOBALAMIN	1 (0.2%)	0 .	1 (0.1%)
CYCLOPENTHIAZIDE	1 (0.2%)	0 .	1 (0.1%)
CYCLOPENTOLATE HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
DEHYDROCHOLIC ACID	1 (0.2%)	0 .	1 (0.1%)
DESOGESTREL	1 (0.2%)	0 .	1 (0.1%)
DEXAMETHASONE	3 (0.7%)	0 .	3 (0.3%)
DIHYDROERGOCRISTINE MESILATE	2 (0.4%)	0 .	2 (0.2%)
DIHYDROERGOTOXINE MESILATE	1 (0.2%)	0 .	1 (0.1%)
DIMEMORFAN PHOSPHATE	1 (0.2%)	0 .	1 (0.1%)
DIOSMIN	1 (0.2%)	0 .	1 (0.1%)
DIPHENOXYLATE HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
DIPOTASSIUM CLORAZEPATE	2 (0.4%)	0 .	2 (0.2%)
DOXOFYLLINE	1 (0.2%)	0 .	1 (0.1%)
DOXYCYCLINE HYCLATE	1 (0.2%)	0 .	1 (0.1%)
DROSPIRENONE	1 (0.2%)	0 .	1 (0.1%)
EPRAZINONE	1 (0.2%)	0 .	1 (0.1%)
ERGOTAMINE TARTRATE	1 (0.2%)	0 .	1 (0.1%)
ESTAZOLAM	1 (0.2%)	0 .	1 (0.1%)
ESTRAMUSTINE	1 (0.2%)	0 .	1 (0.1%)
FENSPIRIDE HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR PRIOR MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED POST-RANDOMIZATION AND MEDICATIONS DISCONTINUED PRIOR TO RANDOMIZATION
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 13.15A

SUMMARY OF PRIOR MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
FIBER	1 (0.2%)	0 .	1 (0.1%)
FLECAINIDE ACETATE	1 (0.2%)	0 .	1 (0.1%)
FLUINDIONE	1 (0.2%)	0 .	1 (0.1%)
FLUNISOLIDE	1 (0.2%)	0 .	1 (0.1%)
FLUOROMETHOLONE	1 (0.2%)	0 .	1 (0.1%)
FLUOXETINE	1 (0.2%)	0 .	1 (0.1%)
FLUTAMIDE	1 (0.2%)	0 .	1 (0.1%)
FUSIDIC ACID	2 (0.4%)	0 .	2 (0.2%)
GLIMEPIRIDE	8 (1.8%)	0 .	8 (0.9%)
GLUCOSAMINE SULFATE	2 (0.4%)	0 .	2 (0.2%)
GLUTAMIC ACID	2 (0.4%)	0 .	2 (0.2%)
GRISEOFULVIN	1 (0.2%)	0 .	1 (0.1%)
HOMEOPATHIC MEDICATION (NOS)	1 (0.2%)	0 .	1 (0.1%)
HYALURONIDASE	1 (0.2%)	0 .	1 (0.1%)
HYDROXYAPATITE	1 (0.2%)	0 .	1 (0.1%)
HYPROMELLOSE	2 (0.4%)	0 .	2 (0.2%)
IMIPRAMINE	1 (0.2%)	0 .	1 (0.1%)
INFLUENZA VIRUS VACCINE INACTIVATED	2 (0.4%)	0 .	2 (0.2%)
INSULIN ASPART	1 (0.2%)	0 .	1 (0.1%)
INSULIN GLARGINE	1 (0.2%)	0 .	1 (0.1%)
INSULIN NOS	1 (0.2%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR PRIOR MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED POST-RANDOMIZATION AND MEDICATIONS DISCONTINUED PRIOR TO RANDOMIZATION
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15A

SUMMARY OF PRIOR MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
IRON	1 (0.2%)	0 .	1 (0.1%)
KETOPROFEN	2 (0.4%)	0 .	2 (0.2%)
LACTIC ACID	1 (0.2%)	0 .	1 (0.1%)
LERCANIDIPINE HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
LEVOCABASTINE	1 (0.2%)	0 .	1 (0.1%)
LEVOMEPROMAZINE	1 (0.2%)	0 .	1 (0.1%)
LIPEX (NOS)	1 (0.2%)	0 .	1 (0.1%)
LIVER EXTRACT	1 (0.2%)	0 .	1 (0.1%)
LOPERAMIDE HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
MAGNESIUM CHLORIDE	1 (0.2%)	0 .	1 (0.1%)
MAGNESIUM HYDROXIDE	4 (0.9%)	0 .	4 (0.4%)
MAGNESIUM PYRIDOXAL PHOSPHATE GLUTAMINATE	1 (0.2%)	0 .	1 (0.1%)
MANIDIPINE HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
MEBEVERINE	1 (0.2%)	0 .	1 (0.1%)
MEDRYSONE	1 (0.2%)	0 .	1 (0.1%)
MENTHA PIPERITA	1 (0.2%)	0 .	1 (0.1%)
METHADONE HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
METHYL HYDROXYBENZOATE	1 (0.2%)	0 .	1 (0.1%)
METILDIGOXIN	3 (0.7%)	0 .	3 (0.3%)
MICONAZOLE	1 (0.2%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR PRIOR MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED POST-RANDOMIZATION AND MEDICATIONS DISCONTINUED PRIOR TO RANDOMIZATION
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 13.15A

SUMMARY OF PRIOR MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
MIDAZOLAM MALEATE	1 (0.2%)	0 .	1 (0.1%)
MIRTAZAPINE	1 (0.2%)	0 .	1 (0.1%)
MORPHINE SULFATE	1 (0.2%)	0 .	1 (0.1%)
MOXIFLOXACIN HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
MYRTOL	2 (0.4%)	0 .	2 (0.2%)
NAFTIDROFURYL OXALATE	1 (0.2%)	0 .	1 (0.1%)
NALTREXONE HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
NEBIVOLOL HYDROCHLORIDE	2 (0.4%)	0 .	2 (0.2%)
NICARDIPINE HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
NICERGOLINE	1 (0.2%)	0 .	1 (0.1%)
NICOTINE	2 (0.4%)	0 .	2 (0.2%)
NORFLOXACIN	1 (0.2%)	0 .	1 (0.1%)
OLANZAPINE	1 (0.2%)	0 .	1 (0.1%)
OMEPRAZOLE MAGNESIUM	1 (0.2%)	0 .	1 (0.1%)
OPIPRAMOL HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
ORTHOSIPHON STAMINEUS	1 (0.2%)	0 .	1 (0.1%)
OXAZEPAM	1 (0.2%)	0 .	1 (0.1%)
OXETACAINE	1 (0.2%)	0 .	1 (0.1%)
OXYMETAZOLINE HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
PANCREATIN	1 (0.2%)	0 .	1 (0.1%)
PAROXETINE HYDROCHLORIDE	3 (0.7%)	0 .	3 (0.3%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR PRIOR MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED POST-RANDOMIZATION AND MEDICATIONS DISCONTINUED PRIOR TO RANDOMIZATION
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 13.15A

SUMMARY OF PRIOR MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
PETHIDINE	1 (0.2%)	0 .	1 (0.1%)
PHENOBARBITAL	1 (0.2%)	0 .	1 (0.1%)
PHENOXYMETHYLPENICILLIN POTASSIUM	1 (0.2%)	0 .	1 (0.1%)
PHENYLEPHRINE	1 (0.2%)	0 .	1 (0.1%)
PHOSPHORUS	1 (0.2%)	0 .	1 (0.1%)
PINDOLOL	1 (0.2%)	0 .	1 (0.1%)
PIRITRAMIDE	1 (0.2%)	0 .	1 (0.1%)
PLATYCODON GRANDIFLORUM	2 (0.4%)	0 .	2 (0.2%)
PREDNISOLONE CAPROATE	1 (0.2%)	0 .	1 (0.1%)
PROCATEROL	2 (0.4%)	0 .	2 (0.2%)
PROCATEROL HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
PROCTOSEDYL NOS	1 (0.2%)	0 .	1 (0.1%)
PROPRANOLOL	1 (0.2%)	0 .	1 (0.1%)
PROPYL PARABEN	1 (0.2%)	0 .	1 (0.1%)
PYGEUM AFRICANUM	3 (0.7%)	0 .	3 (0.3%)
PYRETHRINS	1 (0.2%)	0 .	1 (0.1%)
QUINAPRIL HYDROCHLORIDE	3 (0.7%)	0 .	3 (0.3%)
QUININE	1 (0.2%)	0 .	1 (0.1%)
QUININE HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
RABEPRAZOLE SODIUM	1 (0.2%)	0 .	1 (0.1%)
RESERPINE	1 (0.2%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR PRIOR MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED POST-RANDOMIZATION AND MEDICATIONS DISCONTINUED PRIOR TO RANDOMIZATION
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15A

SUMMARY OF PRIOR MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
RETINOL	1 (0.2%)	0 .	1 (0.1%)
ROFECOXIB	3 (0.7%)	0 .	3 (0.3%)
ROXITHROMYCIN	3 (0.7%)	0 .	3 (0.3%)
SELEGILINE HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
SERTRALINE	1 (0.2%)	0 .	1 (0.1%)
SITOSTEROL	1 (0.2%)	0 .	1 (0.1%)
STERCULIA	1 (0.2%)	0 .	1 (0.1%)
SULFASALAZINE	1 (0.2%)	0 .	1 (0.1%)
TAMOXIFEN	1 (0.2%)	0 .	1 (0.1%)
THIAMAZOLE	1 (0.2%)	0 .	1 (0.1%)
TIBOLONE	1 (0.2%)	0 .	1 (0.1%)
TIOTROPIUM	1 (0.2%)	0 .	1 (0.1%)
TOCOPHEROL	2 (0.4%)	0 .	2 (0.2%)
TRANDOLAPRIL	1 (0.2%)	0 .	1 (0.1%)
TRIAZOLAM	1 (0.2%)	0 .	1 (0.1%)
TRIFLUOPERAZINE HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
TRIMIPRAMINE	1 (0.2%)	0 .	1 (0.1%)
TRINOVIN (NOS)	1 (0.2%)	0 .	1 (0.1%)
TROXERUTIN	1 (0.2%)	0 .	1 (0.1%)
TYROTHRICIN	1 (0.2%)	0 .	1 (0.1%)
UNASYN (NOS)	1 (0.2%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR PRIOR MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED POST-RANDOMIZATION AND MEDICATIONS DISCONTINUED PRIOR TO RANDOMIZATION
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 13.15A

SUMMARY OF PRIOR MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
UNOPROST (NOS)	1 (0.2%)	0 .	1 (0.1%)
UREA	1 (0.2%)	0 .	1 (0.1%)
URTICA DIOICA	1 (0.2%)	0 .	1 (0.1%)
VALPROATE SODIUM	1 (0.2%)	0 .	1 (0.1%)
VITAMIN B NOS	2 (0.4%)	0 .	2 (0.2%)
WHITE PETROLEUM	1 (0.2%)	0 .	1 (0.1%)
WOOL FAT	1 (0.2%)	0 .	1 (0.1%)
XANTHINE	1 (0.2%)	0 .	1 (0.1%)
ZOPICLONE	4 (0.9%)	0 .	4 (0.4%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR PRIOR MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED POST-RANDOMIZATION AND MEDICATIONS DISCONTINUED PRIOR TO RANDOMIZATION
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 13.15B

SUMMARY OF CONCOMITANT MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
TOTAL	452 (100.0%)	452 (99.3%)	904 (99.7%)
SALBUTAMOL	439 (97.1%)	440 (96.7%)	879 (96.9%)
IPRATROPIUM BROMIDE	230 (50.9%)	208 (45.7%)	438 (48.3%)
PARACETAMOL	89 (19.7%)	79 (17.4%)	168 (18.5%)
ACETYLSALICYLIC ACID	77 (17.0%)	69 (15.2%)	146 (16.1%)
AMOXICILLIN	37 (8.2%)	48 (10.5%)	85 (9.4%)
PREDNISONE	34 (7.5%)	48 (10.5%)	82 (9.0%)
CLAVULANATE POTASSIUM	26 (5.8%)	40 (8.8%)	66 (7.3%)
OMEPRAZOLE	30 (6.6%)	40 (8.8%)	70 (7.7%)
AMOXICILLIN TRIHYDRATE	29 (6.4%)	39 (8.6%)	68 (7.5%)
PREDNISOLONE	51 (11.3%)	39 (8.6%)	90 (9.9%)
OXITROPIUM BROMIDE	25 (5.5%)	32 (7.0%)	57 (6.3%)
HYDROCHLOROTHIAZIDE	32 (7.1%)	29 (6.4%)	61 (6.7%)
FUROSEMIDE	28 (6.2%)	27 (5.9%)	55 (6.1%)
ACETYLCYSTEINE	21 (4.6%)	25 (5.5%)	46 (5.1%)
AMLODIPINE BESILATE	19 (4.2%)	20 (4.4%)	39 (4.3%)
CLARITHROMYCIN	18 (4.0%)	20 (4.4%)	38 (4.2%)
GLYCERYL TRINITRATE	20 (4.4%)	19 (4.2%)	39 (4.3%)
ASCORBIC ACID	9 (2.0%)	18 (4.0%)	27 (3.0%)
CODEINE PHOSPHATE	29 (6.4%)	17 (3.7%)	46 (5.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMIZATION AND MEDICATIONS INITIATED POST-RANDOMIZATION
4. TABLE INCLUDES CONCOMITANT MEDICATIONS USED FOR COPD EXACERBATIONS
5. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15B

SUMMARY OF CONCOMITANT MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
DOXYCYCLINE	18 (4.0%)	17 (3.7%)	35 (3.9%)
ISOSORBIDE MONONITRATE	12 (2.7%)	17 (3.7%)	29 (3.2%)
RAMIPRIL	12 (2.7%)	17 (3.7%)	29 (3.2%)
SIMVASTATIN	21 (4.6%)	17 (3.7%)	38 (4.2%)
ALLOPURINOL	11 (2.4%)	16 (3.5%)	27 (3.0%)
DIGOXIN	14 (3.1%)	16 (3.5%)	30 (3.3%)
ISOSORBIDE DINITRATE	11 (2.4%)	16 (3.5%)	27 (3.0%)
AZITHROMYCIN	13 (2.9%)	15 (3.3%)	28 (3.1%)
CIPROFLOXACIN	21 (4.6%)	15 (3.3%)	36 (4.0%)
ENALAPRIL	11 (2.4%)	15 (3.3%)	26 (2.9%)
SALBUTAMOL SULFATE	17 (3.8%)	15 (3.3%)	32 (3.5%)
DICLOFENAC SODIUM	11 (2.4%)	14 (3.1%)	25 (2.8%)
POTASSIUM CHLORIDE	7 (1.5%)	14 (3.1%)	21 (2.3%)
IBUPROFEN	19 (4.2%)	13 (2.9%)	32 (3.5%)
LEVOFLOXACIN	15 (3.3%)	13 (2.9%)	28 (3.1%)
LORATADINE	7 (1.5%)	13 (2.9%)	20 (2.2%)
AMBROXOL HYDROCHLORIDE	6 (1.3%)	12 (2.6%)	18 (2.0%)
IPRATROPIUM	13 (2.9%)	12 (2.6%)	25 (2.8%)
MOXIFLOXACIN HYDROCHLORIDE	13 (2.9%)	12 (2.6%)	25 (2.8%)
VERAPAMIL HYDROCHLORIDE	10 (2.2%)	12 (2.6%)	22 (2.4%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMIZATION AND MEDICATIONS INITIATED POST-RANDOMIZATION
4. TABLE INCLUDES CONCOMITANT MEDICATIONS USED FOR COPD EXACERBATIONS
5. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15B

SUMMARY OF CONCOMITANT MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
ATORVASTATIN CALCIUM	16 (3.5%)	11 (2.4%)	27 (3.0%)
DILTIAZEM HYDROCHLORIDE	9 (2.0%)	11 (2.4%)	20 (2.2%)
FLUTICASONE PROPIONATE	7 (1.5%)	11 (2.4%)	18 (2.0%)
RANITIDINE HYDROCHLORIDE	10 (2.2%)	11 (2.4%)	21 (2.3%)
VITAMINS NOS	5 (1.1%)	11 (2.4%)	16 (1.8%)
BENDROFLUMETHIAZIDE	9 (2.0%)	10 (2.2%)	19 (2.1%)
CLAVULANIC ACID	6 (1.3%)	10 (2.2%)	16 (1.8%)
DEXTROPROPOXYPHENE HYDROCHLORIDE	13 (2.9%)	10 (2.2%)	23 (2.5%)
DICLOFENAC	6 (1.3%)	10 (2.2%)	16 (1.8%)
ENALAPRIL MALEATE	15 (3.3%)	10 (2.2%)	25 (2.8%)
INDAPAMIDE	6 (1.3%)	10 (2.2%)	16 (1.8%)
LISINOPRIL	9 (2.0%)	10 (2.2%)	19 (2.1%)
METHYLPREDNISOLONE	16 (3.5%)	10 (2.2%)	26 (2.9%)
PANTOPRAZOLE SODIUM	4 (0.9%)	10 (2.2%)	14 (1.5%)
ROXITHROMYCIN	13 (2.9%)	10 (2.2%)	23 (2.5%)
SODIUM CHLORIDE	6 (1.3%)	10 (2.2%)	16 (1.8%)
AMILORIDE HYDROCHLORIDE	7 (1.5%)	9 (2.0%)	16 (1.8%)
BUDESONIDE	14 (3.1%)	9 (2.0%)	23 (2.5%)
CAPTOPRIL	12 (2.7%)	9 (2.0%)	21 (2.3%)
CEFUROXIME	7 (1.5%)	9 (2.0%)	16 (1.8%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMIZATION AND MEDICATIONS INITIATED POST-RANDOMIZATION
4. TABLE INCLUDES CONCOMITANT MEDICATIONS USED FOR COPD EXACERBATIONS
5. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15B

SUMMARY OF CONCOMITANT MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
TELITHROMYCIN	3 (0.7%)	9 (2.0%)	12 (1.3%)
THEOPHYLLINE	10 (2.2%)	9 (2.0%)	19 (2.1%)
CAFFEINE	9 (2.0%)	8 (1.8%)	17 (1.9%)
CALCIUM CARBONATE	8 (1.8%)	8 (1.8%)	16 (1.8%)
DOXAZOSIN MESILATE	5 (1.1%)	8 (1.8%)	13 (1.4%)
FELODIPINE	7 (1.5%)	8 (1.8%)	15 (1.7%)
GUAIFENESIN	7 (1.5%)	8 (1.8%)	15 (1.7%)
METAMIZOLE SODIUM	5 (1.1%)	8 (1.8%)	13 (1.4%)
NIFEDIPINE	10 (2.2%)	8 (1.8%)	18 (2.0%)
OXYGEN	2 (0.4%)	8 (1.8%)	10 (1.1%)
VERAPAMIL	6 (1.3%)	8 (1.8%)	14 (1.5%)
ACETYLSALICYLATE LYSINE	7 (1.5%)	7 (1.5%)	14 (1.5%)
ALFUZOSIN HYDROCHLORIDE	0 .	7 (1.5%)	7 (0.8%)
AMIODARONE HYDROCHLORIDE	2 (0.4%)	7 (1.5%)	9 (1.0%)
CHLORPHENAMINE MALEATE	5 (1.1%)	7 (1.5%)	12 (1.3%)
DIAZEPAM	9 (2.0%)	7 (1.5%)	16 (1.8%)
GAVISCON NOS	3 (0.7%)	7 (1.5%)	10 (1.1%)
HYDROCORTISONE	5 (1.1%)	7 (1.5%)	12 (1.3%)
INFLUENZA VACCINE	12 (2.7%)	7 (1.5%)	19 (2.1%)
IRBESARTAN	8 (1.8%)	7 (1.5%)	15 (1.7%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMIZATION AND MEDICATIONS INITIATED POST-RANDOMIZATION
4. TABLE INCLUDES CONCOMITANT MEDICATIONS USED FOR COPD EXACERBATIONS
5. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 13.15B

SUMMARY OF CONCOMITANT MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
METFORMIN HYDROCHLORIDE	9 (2.0%)	7 (1.5%)	16 (1.8%)
RANITIDINE	4 (0.9%)	7 (1.5%)	11 (1.2%)
TAMSULOSIN HYDROCHLORIDE	4 (0.9%)	7 (1.5%)	11 (1.2%)
TERAZOSIN HYDROCHLORIDE	4 (0.9%)	7 (1.5%)	11 (1.2%)
TIOTROPIUM BROMIDE	5 (1.1%)	7 (1.5%)	12 (1.3%)
TRIMETHOPRIM	8 (1.8%)	7 (1.5%)	15 (1.7%)
VITAMIN B SUBSTANCES NOS	3 (0.7%)	7 (1.5%)	10 (1.1%)
AMLODIPINE	5 (1.1%)	6 (1.3%)	11 (1.2%)
BECLOMETASONE DIPROPIONATE	11 (2.4%)	6 (1.3%)	17 (1.9%)
GLIBENCLAMIDE	8 (1.8%)	6 (1.3%)	14 (1.5%)
INFLUENZA VIRUS VACCINE INACTIVATED	7 (1.5%)	6 (1.3%)	13 (1.4%)
LANSOPRAZOLE	5 (1.1%)	6 (1.3%)	11 (1.2%)
PENTOXIFYLLINE	5 (1.1%)	6 (1.3%)	11 (1.2%)
PNEUMOCOCCAL VACCINE	8 (1.8%)	6 (1.3%)	14 (1.5%)
TORASEMIDE	2 (0.4%)	6 (1.3%)	8 (0.9%)
VALSARTAN	4 (0.9%)	6 (1.3%)	10 (1.1%)
ALMAGATE	3 (0.7%)	5 (1.1%)	8 (0.9%)
ATENOLOL	5 (1.1%)	5 (1.1%)	10 (1.1%)
BROMHEXINE HYDROCHLORIDE	5 (1.1%)	5 (1.1%)	10 (1.1%)
CELECOXIB	7 (1.5%)	5 (1.1%)	12 (1.3%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMIZATION AND MEDICATIONS INITIATED POST-RANDOMIZATION
4. TABLE INCLUDES CONCOMITANT MEDICATIONS USED FOR COPD EXACERBATIONS
5. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15B

SUMMARY OF CONCOMITANT MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
CHLORAMPHENICOL	5 (1.1%)	5 (1.1%)	10 (1.1%)
CLOPIDOGREL SULFATE	2 (0.4%)	5 (1.1%)	7 (0.8%)
DEXAMETHASONE	9 (2.0%)	5 (1.1%)	14 (1.5%)
DILTIAZEM	4 (0.9%)	5 (1.1%)	9 (1.0%)
FINASTERIDE	1 (0.2%)	5 (1.1%)	6 (0.7%)
LACIDIPINE	2 (0.4%)	5 (1.1%)	7 (0.8%)
METHYLPREDNISOLONE SODIUM SUCCINATE	7 (1.5%)	5 (1.1%)	12 (1.3%)
MINERALS NOS	3 (0.7%)	5 (1.1%)	8 (0.9%)
MISOPROSTOL	0 .	5 (1.1%)	5 (0.6%)
MOXIFLOXACIN	6 (1.3%)	5 (1.1%)	11 (1.2%)
NICOUMALONE	2 (0.4%)	5 (1.1%)	7 (0.8%)
NYSTATIN	1 (0.2%)	5 (1.1%)	6 (0.7%)
PLANTAGO OVATA	3 (0.7%)	5 (1.1%)	8 (0.9%)
PROCHLORPERAZINE	2 (0.4%)	5 (1.1%)	7 (0.8%)
QUINAPRIL	4 (0.9%)	5 (1.1%)	9 (1.0%)
SALMETEROL XINAFOATE	7 (1.5%)	5 (1.1%)	12 (1.3%)
SPIRONOLACTONE	4 (0.9%)	5 (1.1%)	9 (1.0%)
SULFAMETHOXAZOLE	6 (1.3%)	5 (1.1%)	11 (1.2%)
TRIFLUSAL	2 (0.4%)	5 (1.1%)	7 (0.8%)
ALENDRONATE SODIUM	7 (1.5%)	4 (0.9%)	11 (1.2%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMIZATION AND MEDICATIONS INITIATED POST-RANDOMIZATION
4. TABLE INCLUDES CONCOMITANT MEDICATIONS USED FOR COPD EXACERBATIONS
5. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15B

SUMMARY OF CONCOMITANT MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
BETAMETHASONE SODIUM PHOSPHATE	6 (1.3%)	4 (0.9%)	10 (1.1%)
BISOPROLOL FUMARATE	3 (0.7%)	4 (0.9%)	7 (0.8%)
CANDESARTAN CILEXETIL	3 (0.7%)	4 (0.9%)	7 (0.8%)
CEFACLOR	6 (1.3%)	4 (0.9%)	10 (1.1%)
CEFIXIME	7 (1.5%)	4 (0.9%)	11 (1.2%)
CEFTRIAXONE SODIUM	2 (0.4%)	4 (0.9%)	6 (0.7%)
CITALOPRAM	2 (0.4%)	4 (0.9%)	6 (0.7%)
CLOPERASTINE	1 (0.2%)	4 (0.9%)	5 (0.6%)
CYANOCOBALAMIN	4 (0.9%)	4 (0.9%)	8 (0.9%)
DEXTROMETHORPHAN HYDROBROMIDE	2 (0.4%)	4 (0.9%)	6 (0.7%)
DIPYRIDAMOLE	5 (1.1%)	4 (0.9%)	9 (1.0%)
DOXYCYCLINE HYCLATE	0 .	4 (0.9%)	4 (0.4%)
EFORMOTEROL FUMARATE	3 (0.7%)	4 (0.9%)	7 (0.8%)
EPHEDRINE HYDROCHLORIDE	4 (0.9%)	4 (0.9%)	8 (0.9%)
ESOMEPRAZOLE MAGNESIUM	3 (0.7%)	4 (0.9%)	7 (0.8%)
ETHENZAMIDE	3 (0.7%)	4 (0.9%)	7 (0.8%)
FAMOTIDINE	2 (0.4%)	4 (0.9%)	6 (0.7%)
FERROUS SULPHATE	5 (1.1%)	4 (0.9%)	9 (1.0%)
GLICLAZIDE	8 (1.8%)	4 (0.9%)	12 (1.3%)
HERBALS NOS	1 (0.2%)	4 (0.9%)	5 (0.6%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMIZATION AND MEDICATIONS INITIATED POST-RANDOMIZATION
4. TABLE INCLUDES CONCOMITANT MEDICATIONS USED FOR COPD EXACERBATIONS
5. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15B

SUMMARY OF CONCOMITANT MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
HESPERIDIN	4 (0.9%)	4 (0.9%)	8 (0.9%)
HYOSCINE BUTYLBROMIDE	3 (0.7%)	4 (0.9%)	7 (0.8%)
LACTULOSE	3 (0.7%)	4 (0.9%)	7 (0.8%)
LOPERAMIDE HYDROCHLORIDE	3 (0.7%)	4 (0.9%)	7 (0.8%)
METHYLEPHEDRINE HYDROCHLORIDE	4 (0.9%)	4 (0.9%)	8 (0.9%)
METOCLOPRAMIDE	1 (0.2%)	4 (0.9%)	5 (0.6%)
NEOMYCIN SULFATE	4 (0.9%)	4 (0.9%)	8 (0.9%)
NICOTINE	8 (1.8%)	4 (0.9%)	12 (1.3%)
NIMESULIDE	2 (0.4%)	4 (0.9%)	6 (0.7%)
PHENACETIN	4 (0.9%)	4 (0.9%)	8 (0.9%)
PRAVASTATIN SODIUM	3 (0.7%)	4 (0.9%)	7 (0.8%)
PROMETHAZINE HYDROCHLORIDE	1 (0.2%)	4 (0.9%)	5 (0.6%)
PROPRANOLOL HYDROCHLORIDE	0 .	4 (0.9%)	4 (0.4%)
PSEUDOEPHEDRINE HYDROCHLORIDE	6 (1.3%)	4 (0.9%)	10 (1.1%)
SILYMARIN	1 (0.2%)	4 (0.9%)	5 (0.6%)
SIMETICONE	3 (0.7%)	4 (0.9%)	7 (0.8%)
SODIUM BICARBONATE	1 (0.2%)	4 (0.9%)	5 (0.6%)
TEMAZEPAM	3 (0.7%)	4 (0.9%)	7 (0.8%)
TIMOLOL MALEATE	1 (0.2%)	4 (0.9%)	5 (0.6%)
TRIPELENNAMINE	3 (0.7%)	4 (0.9%)	7 (0.8%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMIZATION AND MEDICATIONS INITIATED POST-RANDOMIZATION
4. TABLE INCLUDES CONCOMITANT MEDICATIONS USED FOR COPD EXACERBATIONS
5. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 13.15B

SUMMARY OF CONCOMITANT MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
WARFARIN	5 (1.1%)	4 (0.9%)	9 (1.0%)
ACARBOSE	0 .	3 (0.7%)	3 (0.3%)
AMINOPHYLLINE	5 (1.1%)	3 (0.7%)	8 (0.9%)
AMPICILLIN	4 (0.9%)	3 (0.7%)	7 (0.8%)
BETAMETHASONE	4 (0.9%)	3 (0.7%)	7 (0.8%)
BETAMETHASONE DIPROPIONATE	0 .	3 (0.7%)	3 (0.3%)
BETAMETHASONE VALERATE	5 (1.1%)	3 (0.7%)	8 (0.9%)
BROMHEXINE	3 (0.7%)	3 (0.7%)	6 (0.7%)
BUPROPION HYDROCHLORIDE	3 (0.7%)	3 (0.7%)	6 (0.7%)
CALCIUM	1 (0.2%)	3 (0.7%)	4 (0.4%)
CARBOCISTEINE	5 (1.1%)	3 (0.7%)	8 (0.9%)
CEFPODOXIME PROXETIL	1 (0.2%)	3 (0.7%)	4 (0.4%)
CETIRIZINE HYDROCHLORIDE	6 (1.3%)	3 (0.7%)	9 (1.0%)
CIMETIDINE	4 (0.9%)	3 (0.7%)	7 (0.8%)
CLOTRIMAZOLE	1 (0.2%)	3 (0.7%)	4 (0.4%)
COLCHICINE	0 .	3 (0.7%)	3 (0.3%)
COLECALCIFEROL	3 (0.7%)	3 (0.7%)	6 (0.7%)
DICLOFENAC DIETHYLAMINE	1 (0.2%)	3 (0.7%)	4 (0.4%)
DIHYDROCODEINE BITARTRATE	1 (0.2%)	3 (0.7%)	4 (0.4%)
DIPHENYLPYRALINE HYDROCHLORIDE	1 (0.2%)	3 (0.7%)	4 (0.4%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMIZATION AND MEDICATIONS INITIATED POST-RANDOMIZATION
4. TABLE INCLUDES CONCOMITANT MEDICATIONS USED FOR COPD EXACERBATIONS
5. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15B

SUMMARY OF CONCOMITANT MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
ERYTHROMYCIN	8 (1.8%)	3 (0.7%)	11 (1.2%)
ETHANOL	1 (0.2%)	3 (0.7%)	4 (0.4%)
FEXOFENADINE HYDROCHLORIDE	3 (0.7%)	3 (0.7%)	6 (0.7%)
FLUCLOXACILLIN	5 (1.1%)	3 (0.7%)	8 (0.9%)
FLUDIAZEPAM	1 (0.2%)	3 (0.7%)	4 (0.4%)
FLUOXETINE	2 (0.4%)	3 (0.7%)	5 (0.6%)
FOLIC ACID	3 (0.7%)	3 (0.7%)	6 (0.7%)
FUSIDIC ACID	5 (1.1%)	3 (0.7%)	8 (0.9%)
GLUCOSE	1 (0.2%)	3 (0.7%)	4 (0.4%)
HEPARIN	1 (0.2%)	3 (0.7%)	4 (0.4%)
HYDROXYZINE	2 (0.4%)	3 (0.7%)	5 (0.6%)
INDOMETACIN	2 (0.4%)	3 (0.7%)	5 (0.6%)
INSULIN HUMAN	3 (0.7%)	3 (0.7%)	6 (0.7%)
ITRACONAZOLE	0 .	3 (0.7%)	3 (0.3%)
LEVODROPROPIZINE	0 .	3 (0.7%)	3 (0.3%)
LEVOTHYROXINE SODIUM	10 (2.2%)	3 (0.7%)	13 (1.4%)
LORMETAZEPAM	1 (0.2%)	3 (0.7%)	4 (0.4%)
MAGNESIUM	2 (0.4%)	3 (0.7%)	5 (0.6%)
MAGNESIUM CARBONATE	1 (0.2%)	3 (0.7%)	4 (0.4%)
MAGNESIUM HYDROXIDE	5 (1.1%)	3 (0.7%)	8 (0.9%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMIZATION AND MEDICATIONS INITIATED POST-RANDOMIZATION
4. TABLE INCLUDES CONCOMITANT MEDICATIONS USED FOR COPD EXACERBATIONS
5. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 13.15B

SUMMARY OF CONCOMITANT MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
MAGNESIUM OXIDE	2 (0.4%)	3 (0.7%)	5 (0.6%)
MELOXICAM	2 (0.4%)	3 (0.7%)	5 (0.6%)
MENTHOL	3 (0.7%)	3 (0.7%)	6 (0.7%)
METAMIZOLE MAGNESIUM	2 (0.4%)	3 (0.7%)	5 (0.6%)
METOCLOPRAMIDE HYDROCHLORIDE	5 (1.1%)	3 (0.7%)	8 (0.9%)
METOPROLOL TARTRATE	3 (0.7%)	3 (0.7%)	6 (0.7%)
NAPROXEN	5 (1.1%)	3 (0.7%)	8 (0.9%)
NICORANDIL	1 (0.2%)	3 (0.7%)	4 (0.4%)
NITRENDIPINE	0 .	3 (0.7%)	3 (0.3%)
OFLOXACIN	3 (0.7%)	3 (0.7%)	6 (0.7%)
ORCIPRENALINE SULFATE	0 .	3 (0.7%)	3 (0.3%)
PERINDOPRIL	5 (1.1%)	3 (0.7%)	8 (0.9%)
PHENYLEPHRINE	2 (0.4%)	3 (0.7%)	5 (0.6%)
PHENYLEPHRINE HYDROCHLORIDE	3 (0.7%)	3 (0.7%)	6 (0.7%)
PSEUDOEPHEDRINE SULFATE	2 (0.4%)	3 (0.7%)	5 (0.6%)
PYRIDOXINE HYDROCHLORIDE	5 (1.1%)	3 (0.7%)	8 (0.9%)
SERTRALINE HYDROCHLORIDE	1 (0.2%)	3 (0.7%)	4 (0.4%)
TELMISARTAN	4 (0.9%)	3 (0.7%)	7 (0.8%)
TERBINAFINE HYDROCHLORIDE	0 .	3 (0.7%)	3 (0.3%)
TICLOPIDINE HYDROCHLORIDE	2 (0.4%)	3 (0.7%)	5 (0.6%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMIZATION AND MEDICATIONS INITIATED POST-RANDOMIZATION
4. TABLE INCLUDES CONCOMITANT MEDICATIONS USED FOR COPD EXACERBATIONS
5. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 13.15B

SUMMARY OF CONCOMITANT MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
TRIAMTERENE	4 (0.9%)	3 (0.7%)	7 (0.8%)
ACETYLDIGOXIN	1 (0.2%)	2 (0.4%)	3 (0.3%)
ALUMINIUM HYDROXIDE GEL, DRIED	3 (0.7%)	2 (0.4%)	5 (0.6%)
AMITRIPTYLINE	6 (1.3%)	2 (0.4%)	8 (0.9%)
AMYLMETACRESOL	0 .	2 (0.4%)	2 (0.2%)
ANTIMONY POTASSIUM TARTRATE	1 (0.2%)	2 (0.4%)	3 (0.3%)
ATROPINE SULFATE	3 (0.7%)	2 (0.4%)	5 (0.6%)
BENADRYL (NOS)	0 .	2 (0.4%)	2 (0.2%)
BENZOIC ACID	1 (0.2%)	2 (0.4%)	3 (0.3%)
BENZYDAMINE HYDROCHLORIDE	2 (0.4%)	2 (0.4%)	4 (0.4%)
BEZAFIBRATE	1 (0.2%)	2 (0.4%)	3 (0.3%)
BISOPROLOL	0 .	2 (0.4%)	2 (0.2%)
BUMETANIDE	2 (0.4%)	2 (0.4%)	4 (0.4%)
CAMPHOR	1 (0.2%)	2 (0.4%)	3 (0.3%)
CARBAMAZEPINE	1 (0.2%)	2 (0.4%)	3 (0.3%)
CARTEOLOL HYDROCHLORIDE	0 .	2 (0.4%)	2 (0.2%)
CEFALEXIN MONOHYDRATE	2 (0.4%)	2 (0.4%)	4 (0.4%)
CEFAZOLIN	0 .	2 (0.4%)	2 (0.2%)
CETIRIZINE	2 (0.4%)	2 (0.4%)	4 (0.4%)
CILAZAPRIL	3 (0.7%)	2 (0.4%)	5 (0.6%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMIZATION AND MEDICATIONS INITIATED POST-RANDOMIZATION
4. TABLE INCLUDES CONCOMITANT MEDICATIONS USED FOR COPD EXACERBATIONS
5. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15B

SUMMARY OF CONCOMITANT MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
CITALOPRAM HYDROBROMIDE	1 (0.2%)	2 (0.4%)	3 (0.3%)
CITRIC ACID	2 (0.4%)	2 (0.4%)	4 (0.4%)
COCILLANA	3 (0.7%)	2 (0.4%)	5 (0.6%)
CRESOLSULFONIC ACID	0 .	2 (0.4%)	2 (0.2%)
CYPROHEPTADINE HYDROCHLORIDE	0 .	2 (0.4%)	2 (0.2%)
DAFLON NOS	1 (0.2%)	2 (0.4%)	3 (0.3%)
DESLORATADINE	2 (0.4%)	2 (0.4%)	4 (0.4%)
DICHLOROBENZYL ALCOHOL	0 .	2 (0.4%)	2 (0.2%)
DIHYDROCODEINE	3 (0.7%)	2 (0.4%)	5 (0.6%)
DIMEMORFAN PHOSPHATE	3 (0.7%)	2 (0.4%)	5 (0.6%)
DIMETICONE	0 .	2 (0.4%)	2 (0.2%)
DIPHENOXYLATE HYDROCHLORIDE	2 (0.4%)	2 (0.4%)	4 (0.4%)
DORZOLAMIDE HYDROCHLORIDE	1 (0.2%)	2 (0.4%)	3 (0.3%)
DOXYLAMINE SUCCINATE	4 (0.9%)	2 (0.4%)	6 (0.7%)
EMULSIFYING WAX	0 .	2 (0.4%)	2 (0.2%)
EPRAZINONE	3 (0.7%)	2 (0.4%)	5 (0.6%)
ESTRADIOL	6 (1.3%)	2 (0.4%)	8 (0.9%)
ETHYLMORPHINE HYDROCHLORIDE	0 .	2 (0.4%)	2 (0.2%)
FENOFIBRATE	4 (0.9%)	2 (0.4%)	6 (0.7%)
FENOTEROL HYDROBROMIDE	3 (0.7%)	2 (0.4%)	5 (0.6%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMIZATION AND MEDICATIONS INITIATED POST-RANDOMIZATION
4. TABLE INCLUDES CONCOMITANT MEDICATIONS USED FOR COPD EXACERBATIONS
5. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15B

SUMMARY OF CONCOMITANT MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
FLAVOXATE HYDROCHLORIDE	0 .	2 (0.4%)	2 (0.2%)
FLUNISOLIDE	1 (0.2%)	2 (0.4%)	3 (0.3%)
FLUOXETINE HYDROCHLORIDE	5 (1.1%)	2 (0.4%)	7 (0.8%)
FLUVASTATIN SODIUM	1 (0.2%)	2 (0.4%)	3 (0.3%)
FRAMYCETIN SULFATE	2 (0.4%)	2 (0.4%)	4 (0.4%)
GLIPIZIDE	0 .	2 (0.4%)	2 (0.2%)
GRAMICIDIN	1 (0.2%)	2 (0.4%)	3 (0.3%)
HYDROCORTISONE BUTYRATE	2 (0.4%)	2 (0.4%)	4 (0.4%)
HYDROCORTISONE SODIUM SUCCINATE	1 (0.2%)	2 (0.4%)	3 (0.3%)
HYDROTALCITE	3 (0.7%)	2 (0.4%)	5 (0.6%)
HYDROXYZINE HYDROCHLORIDE	0 .	2 (0.4%)	2 (0.2%)
INSULIN HUMAN INJECTION, ISOPHANE	3 (0.7%)	2 (0.4%)	5 (0.6%)
ISRADIPINE	0 .	2 (0.4%)	2 (0.2%)
LACTOBACILLUS ACIDOPHILUS	0 .	2 (0.4%)	2 (0.2%)
LEVODOPA	0 .	2 (0.4%)	2 (0.2%)
LEVONORGESTREL	0 .	2 (0.4%)	2 (0.2%)
LEVOTHYROXINE	7 (1.5%)	2 (0.4%)	9 (1.0%)
LIDOCAINE HYDROCHLORIDE	3 (0.7%)	2 (0.4%)	5 (0.6%)
LIQUORICE LIQUID EXTRACT	1 (0.2%)	2 (0.4%)	3 (0.3%)
LOFEPRAMINE	0 .	2 (0.4%)	2 (0.2%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMIZATION AND MEDICATIONS INITIATED POST-RANDOMIZATION
4. TABLE INCLUDES CONCOMITANT MEDICATIONS USED FOR COPD EXACERBATIONS
5. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15B

SUMMARY OF CONCOMITANT MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
LOPERAMIDE	0 .	2 (0.4%)	2 (0.2%)
LORAZEPAM	5 (1.1%)	2 (0.4%)	7 (0.8%)
LOSARTAN POTASSIUM	10 (2.2%)	2 (0.4%)	12 (1.3%)
LYSOZYME HYDROCHLORIDE	0 .	2 (0.4%)	2 (0.2%)
MEDROXYPROGESTERONE ACETATE	5 (1.1%)	2 (0.4%)	7 (0.8%)
METOPROLOL SUCCINATE	3 (0.7%)	2 (0.4%)	5 (0.6%)
MICONAZOLE NITRATE	1 (0.2%)	2 (0.4%)	3 (0.3%)
MOMETASONE FUROATE	4 (0.9%)	2 (0.4%)	6 (0.7%)
NADROPARIN CALCIUM	1 (0.2%)	2 (0.4%)	3 (0.3%)
NIMODIPINE	0 .	2 (0.4%)	2 (0.2%)
NITRAZEPAM	3 (0.7%)	2 (0.4%)	5 (0.6%)
NUTRITIONAL SUPPLEMENT NOS	1 (0.2%)	2 (0.4%)	3 (0.3%)
OXAZEPAM	1 (0.2%)	2 (0.4%)	3 (0.3%)
OXYMETAZOLINE HYDROCHLORIDE	1 (0.2%)	2 (0.4%)	3 (0.3%)
PANTOPRAZOLE	1 (0.2%)	2 (0.4%)	3 (0.3%)
PAPAVER SOMNIFERUM	1 (0.2%)	2 (0.4%)	3 (0.3%)
PHENOXYETHANOL	0 .	2 (0.4%)	2 (0.2%)
PHENOXYMETHYLPENICILLIN POTASSIUM	4 (0.9%)	2 (0.4%)	6 (0.7%)
PIMPINELLA ANISUM	1 (0.2%)	2 (0.4%)	3 (0.3%)
PIOGLITAZONE HYDROCHLORIDE	1 (0.2%)	2 (0.4%)	3 (0.3%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMIZATION AND MEDICATIONS INITIATED POST-RANDOMIZATION
4. TABLE INCLUDES CONCOMITANT MEDICATIONS USED FOR COPD EXACERBATIONS
5. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15B

SUMMARY OF CONCOMITANT MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
PIRETANIDE	0 .	2 (0.4%)	2 (0.2%)
POLYMYXIN B SULFATE	2 (0.4%)	2 (0.4%)	4 (0.4%)
PROFLOX (NOS)	1 (0.2%)	2 (0.4%)	3 (0.3%)
PSEUDOEPHEDRINE	2 (0.4%)	2 (0.4%)	4 (0.4%)
QUININE SULPHATE	0 .	2 (0.4%)	2 (0.2%)
RUTOSIDE	2 (0.4%)	2 (0.4%)	4 (0.4%)
SALICYLIC ACID	0 .	2 (0.4%)	2 (0.2%)
SENEGA	1 (0.2%)	2 (0.4%)	3 (0.3%)
SENNA	2 (0.4%)	2 (0.4%)	4 (0.4%)
SODIUM CITRATE	3 (0.7%)	2 (0.4%)	5 (0.6%)
STOPAYNE (NOS)	0 .	2 (0.4%)	2 (0.2%)
SULPIRIDE	0 .	2 (0.4%)	2 (0.2%)
TERAZOSIN	0 .	2 (0.4%)	2 (0.2%)
TERBUTALINE	1 (0.2%)	2 (0.4%)	3 (0.3%)
TETRACYCLINE	3 (0.7%)	2 (0.4%)	5 (0.6%)
THIAMINE	1 (0.2%)	2 (0.4%)	3 (0.3%)
THIAMINE HYDROCHLORIDE	3 (0.7%)	2 (0.4%)	5 (0.6%)
THIAMPHENICOL	0 .	2 (0.4%)	2 (0.2%)
THIOCTIC ACID	0 .	2 (0.4%)	2 (0.2%)
TRAMADOL HYDROCHLORIDE	1 (0.2%)	2 (0.4%)	3 (0.3%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMIZATION AND MEDICATIONS INITIATED POST-RANDOMIZATION
4. TABLE INCLUDES CONCOMITANT MEDICATIONS USED FOR COPD EXACERBATIONS
5. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15B

SUMMARY OF CONCOMITANT MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
TRIAMCINOLONE ACETONIDE	1 (0.2%)	2 (0.4%)	3 (0.3%)
TRIMETAZIDINE HYDROCHLORIDE	1 (0.2%)	2 (0.4%)	3 (0.3%)
VENLAFAXINE HYDROCHLORIDE	2 (0.4%)	2 (0.4%)	4 (0.4%)
WARFARIN SODIUM	2 (0.4%)	2 (0.4%)	4 (0.4%)
ZOLPIDEM TARTRATE	1 (0.2%)	2 (0.4%)	3 (0.3%)
ACCUPRIN (NOS)	0 .	1 (0.2%)	1 (0.1%)
ACEDIUR (NOS)	0 .	1 (0.2%)	1 (0.1%)
ACETAZOLAMIDE	0 .	1 (0.2%)	1 (0.1%)
ACYCLOVIR	4 (0.9%)	1 (0.2%)	5 (0.6%)
ALDIOXA	1 (0.2%)	1 (0.2%)	2 (0.2%)
ALMITRINE DIMESILATE	0 .	1 (0.2%)	1 (0.1%)
ALPRAZOLAM	2 (0.4%)	1 (0.2%)	3 (0.3%)
ALTEPLASE	0 .	1 (0.2%)	1 (0.1%)
ALTHAEA OFFICINALIS	1 (0.2%)	1 (0.2%)	2 (0.2%)
ALUMINIUM HYDROXIDE	3 (0.7%)	1 (0.2%)	4 (0.4%)
AMBUPHYLLINE	0 .	1 (0.2%)	1 (0.1%)
AMCINONIDE	0 .	1 (0.2%)	1 (0.1%)
AMILORIDE	1 (0.2%)	1 (0.2%)	2 (0.2%)
AMINOMAL (NOS)	0 .	1 (0.2%)	1 (0.1%)
AMINOPHENAZONE	1 (0.2%)	1 (0.2%)	2 (0.2%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMIZATION AND MEDICATIONS INITIATED POST-RANDOMIZATION
4. TABLE INCLUDES CONCOMITANT MEDICATIONS USED FOR COPD EXACERBATIONS
5. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15B

SUMMARY OF CONCOMITANT MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
AMIODARONE	0 .	1 (0.2%)	1 (0.1%)
AMMONIUM BICARBONATE	1 (0.2%)	1 (0.2%)	2 (0.2%)
AMMONIUM CHLORIDE	5 (1.1%)	1 (0.2%)	6 (0.7%)
ANDROGRAPHIS PANICULATA	0 .	1 (0.2%)	1 (0.1%)
ARCTOSTAPHYLOS UVA-URSI	0 .	1 (0.2%)	1 (0.1%)
ARMENIACA VULGARIS	1 (0.2%)	1 (0.2%)	2 (0.2%)
ASPARAGINE	0 .	1 (0.2%)	1 (0.1%)
AZAPENTACENE POLYSULFONATE SODIUM	0 .	1 (0.2%)	1 (0.1%)
AZELASTINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
BACAMPICILLIN HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
BARNIDIPINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
BEE VENOM, STANDARD	0 .	1 (0.2%)	1 (0.1%)
BENSERAZIDE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
BENTONITE	0 .	1 (0.2%)	1 (0.1%)
BENZBROMARONE	0 .	1 (0.2%)	1 (0.1%)
BENZONATATE	1 (0.2%)	1 (0.2%)	2 (0.2%)
BEPANTHEN (NOS)	1 (0.2%)	1 (0.2%)	2 (0.2%)
BIMATOPROST	0 .	1 (0.2%)	1 (0.1%)
BISACODYL	0 .	1 (0.2%)	1 (0.1%)
BLEOMYCIN	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMIZATION AND MEDICATIONS INITIATED POST-RANDOMIZATION
4. TABLE INCLUDES CONCOMITANT MEDICATIONS USED FOR COPD EXACERBATIONS
5. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15B

SUMMARY OF CONCOMITANT MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
BRIMONIDINE	0 .	1 (0.2%)	1 (0.1%)
BUFLOMEDIL HYDROCHLORIDE	1 (0.2%)	1 (0.2%)	2 (0.2%)
BUPHENINE HYDROCHLORIDE	1 (0.2%)	1 (0.2%)	2 (0.2%)
BUTAMIRATE CITRATE	0 .	1 (0.2%)	1 (0.1%)
CALAMINE	0 .	1 (0.2%)	1 (0.1%)
CALCITRIOL	0 .	1 (0.2%)	1 (0.1%)
CALCIUM DOBESILATE	0 .	1 (0.2%)	1 (0.1%)
CALCIUM INOSITOL HEXAPHOSPHATE	0 .	1 (0.2%)	1 (0.1%)
CALCIUM PHOSPHATE	0 .	1 (0.2%)	1 (0.1%)
CANDESARTAN	0 .	1 (0.2%)	1 (0.1%)
CAPSAICIN	0 .	1 (0.2%)	1 (0.1%)
CARBASALATE CALCIUM	2 (0.4%)	1 (0.2%)	3 (0.3%)
CARBIDOPA	0 .	1 (0.2%)	1 (0.1%)
CARBOMER	0 .	1 (0.2%)	1 (0.1%)
CARISOPRODOL	0 .	1 (0.2%)	1 (0.1%)
CARMELLOSE SODIUM	0 .	1 (0.2%)	1 (0.1%)
CARVEDILOL	2 (0.4%)	1 (0.2%)	3 (0.3%)
CASSIA ANGUSTIFOLIA	0 .	1 (0.2%)	1 (0.1%)
CEFAZOLIN SODIUM	0 .	1 (0.2%)	1 (0.1%)
CEFODIZIME DISODIUM	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMIZATION AND MEDICATIONS INITIATED POST-RANDOMIZATION
4. TABLE INCLUDES CONCOMITANT MEDICATIONS USED FOR COPD EXACERBATIONS
5. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15B

SUMMARY OF CONCOMITANT MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
CEFPROZIL	3 (0.7%)	1 (0.2%)	4 (0.4%)
CEFTAZIDIME	0 .	1 (0.2%)	1 (0.1%)
CEFTIBUTEN	0 .	1 (0.2%)	1 (0.1%)
CEFTRIAXONE	0 .	1 (0.2%)	1 (0.1%)
CERIVASTATIN SODIUM	0 .	1 (0.2%)	1 (0.1%)
CHLORHEXIDINE	1 (0.2%)	1 (0.2%)	2 (0.2%)
CHLORHEXIDINE GLUCONATE	0 .	1 (0.2%)	1 (0.1%)
CHOLINE THEOPHYLLINATE	0 .	1 (0.2%)	1 (0.1%)
CIBENZOLINE	0 .	1 (0.2%)	1 (0.1%)
CILASTATIN	0 .	1 (0.2%)	1 (0.1%)
CIMICIFUGA RACEMOSA	0 .	1 (0.2%)	1 (0.1%)
CINCHOCAINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
CINNAMIC ESTER	0 .	1 (0.2%)	1 (0.1%)
CINNAMOMUM VERUM	0 .	1 (0.2%)	1 (0.1%)
CIPROFLOXACIN HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
CLEBOPRIDE	0 .	1 (0.2%)	1 (0.1%)
CLEBOPRIDE HYDROGEN MALEATE	0 .	1 (0.2%)	1 (0.1%)
CLENBUTEROL HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
CLINDAMYCIN	0 .	1 (0.2%)	1 (0.1%)
CLINDAMYCIN HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMIZATION AND MEDICATIONS INITIATED POST-RANDOMIZATION
4. TABLE INCLUDES CONCOMITANT MEDICATIONS USED FOR COPD EXACERBATIONS
5. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15B

SUMMARY OF CONCOMITANT MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
CLOBETASOL PROPIONATE	1 (0.2%)	1 (0.2%)	2 (0.2%)
CLOBUTINOL HYDROCHLORIDE	1 (0.2%)	1 (0.2%)	2 (0.2%)
CLONAZEPAM	0 .	1 (0.2%)	1 (0.1%)
CLOPERASTINE FENDIZOATE	0 .	1 (0.2%)	1 (0.1%)
CLOPIDOGREL	4 (0.9%)	1 (0.2%)	5 (0.6%)
CLOPREDNOL	0 .	1 (0.2%)	1 (0.1%)
CLOTIAZEPAM	0 .	1 (0.2%)	1 (0.1%)
CLOXACILLIN SODIUM	1 (0.2%)	1 (0.2%)	2 (0.2%)
COD-LIVER OIL	3 (0.7%)	1 (0.2%)	4 (0.4%)
CODEINE	2 (0.4%)	1 (0.2%)	3 (0.3%)
CODEINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
CODEINE PHOSPHATE HEMIHYDRATE	0 .	1 (0.2%)	1 (0.1%)
COLISTIN	0 .	1 (0.2%)	1 (0.1%)
CORTISONE	0 .	1 (0.2%)	1 (0.1%)
CORVASAL NOS	0 .	1 (0.2%)	1 (0.1%)
CYPROHEPTADINE	2 (0.4%)	1 (0.2%)	3 (0.3%)
DALTEPARIN SODIUM	0 .	1 (0.2%)	1 (0.1%)
DECONGESTANT NOS	0 .	1 (0.2%)	1 (0.1%)
DEFLAZACORT	2 (0.4%)	1 (0.2%)	3 (0.3%)
DELAPRIL	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMIZATION AND MEDICATIONS INITIATED POST-RANDOMIZATION
4. TABLE INCLUDES CONCOMITANT MEDICATIONS USED FOR COPD EXACERBATIONS
5. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15B

SUMMARY OF CONCOMITANT MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
DESIPRAMINE HYDROCHLORIDE	2 (0.4%)	1 (0.2%)	3 (0.3%)
DESOXIMETASONE	0 .	1 (0.2%)	1 (0.1%)
DEXAMETHASONE ISONICOTINATE	0 .	1 (0.2%)	1 (0.1%)
DEXAMETHASONE PALMITATE	0 .	1 (0.2%)	1 (0.1%)
DEXCHLORPHENIRAMINE	1 (0.2%)	1 (0.2%)	2 (0.2%)
DEXCHLORPHENIRAMINE MALEATE	1 (0.2%)	1 (0.2%)	2 (0.2%)
DEXIBUPROFEN	0 .	1 (0.2%)	1 (0.1%)
DEXTROMETHORPHAN	1 (0.2%)	1 (0.2%)	2 (0.2%)
DEXTROPROPOXYPHENE	1 (0.2%)	1 (0.2%)	2 (0.2%)
DEXTROPROPOXYPHENE NAPSILATE	2 (0.4%)	1 (0.2%)	3 (0.3%)
DIBENZOYLMETHANE	0 .	1 (0.2%)	1 (0.1%)
DICLOFENAC RESINATE	0 .	1 (0.2%)	1 (0.1%)
DIFENIDOL HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
DIGESTIVE ENZYMES	0 .	1 (0.2%)	1 (0.1%)
DIGITOXIN	1 (0.2%)	1 (0.2%)	2 (0.2%)
DIMENHYDRINATE	0 .	1 (0.2%)	1 (0.1%)
DIPOTASSIUM CLORAZEPATE	2 (0.4%)	1 (0.2%)	3 (0.3%)
DOCUSATE SODIUM	1 (0.2%)	1 (0.2%)	2 (0.2%)
DOMPERIDONE	0 .	1 (0.2%)	1 (0.1%)
DONEPEZIL	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMIZATION AND MEDICATIONS INITIATED POST-RANDOMIZATION
4. TABLE INCLUDES CONCOMITANT MEDICATIONS USED FOR COPD EXACERBATIONS
5. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15B

SUMMARY OF CONCOMITANT MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
DOSULEPIN	0 .	1 (0.2%)	1 (0.1%)
DOXAZOSIN	1 (0.2%)	1 (0.2%)	2 (0.2%)
DOXEPIN HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
E45 (NOS)	0 .	1 (0.2%)	1 (0.1%)
EBASTINE	1 (0.2%)	1 (0.2%)	2 (0.2%)
ECONAZOLE NITRATE	0 .	1 (0.2%)	1 (0.1%)
ELECTROLYTES NOS	0 .	1 (0.2%)	1 (0.1%)
EMETINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
EMOLLIENTS AND PROTECTIVES	0 .	1 (0.2%)	1 (0.1%)
ENOXAPARIN	2 (0.4%)	1 (0.2%)	3 (0.3%)
ESCHERICHIA COLI	0 .	1 (0.2%)	1 (0.1%)
ESTRADIOL VALERATE	0 .	1 (0.2%)	1 (0.1%)
ESTRIOL	0 .	1 (0.2%)	1 (0.1%)
ESTROGENS CONJUGATED	8 (1.8%)	1 (0.2%)	9 (1.0%)
ETAFEDRINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
ETHINYLOESTRADIOL	2 (0.4%)	1 (0.2%)	3 (0.3%)
ETOFYLLINE	2 (0.4%)	1 (0.2%)	3 (0.3%)
EUCALYPTUS GLOBULUS OIL	2 (0.4%)	1 (0.2%)	3 (0.3%)
EXPIGEN (NOS)	0 .	1 (0.2%)	1 (0.1%)
FENIPENTOL	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMIZATION AND MEDICATIONS INITIATED POST-RANDOMIZATION
4. TABLE INCLUDES CONCOMITANT MEDICATIONS USED FOR COPD EXACERBATIONS
5. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15B

SUMMARY OF CONCOMITANT MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
FLECAINIDE	0 .	1 (0.2%)	1 (0.1%)
FLUCLOXACILLIN SODIUM	0 .	1 (0.2%)	1 (0.1%)
FLUCONAZOLE	1 (0.2%)	1 (0.2%)	2 (0.2%)
FLUDROCORTISONE ACETATE	0 .	1 (0.2%)	1 (0.1%)
FLUNARIZINE	0 .	1 (0.2%)	1 (0.1%)
FLUOROURACIL	0 .	1 (0.2%)	1 (0.1%)
FLUTICASONE	1 (0.2%)	1 (0.2%)	2 (0.2%)
FORMOTEROL	1 (0.2%)	1 (0.2%)	2 (0.2%)
FOSFOMYCIN CALCIUM	1 (0.2%)	1 (0.2%)	2 (0.2%)
FOSINOPRIL SODIUM	0 .	1 (0.2%)	1 (0.1%)
FUSAFUNGINE	0 .	1 (0.2%)	1 (0.1%)
FUSIDATE SODIUM	0 .	1 (0.2%)	1 (0.1%)
FYTIC ACID	0 .	1 (0.2%)	1 (0.1%)
GATIFLOXACIN	2 (0.4%)	1 (0.2%)	3 (0.3%)
GELUSIL NOS	0 .	1 (0.2%)	1 (0.1%)
GEMFIBROZIL	2 (0.4%)	1 (0.2%)	3 (0.3%)
GENTAMICIN	0 .	1 (0.2%)	1 (0.1%)
GINKGO TREE LEAVES EXTRACT	0 .	1 (0.2%)	1 (0.1%)
GINSENG	0 .	1 (0.2%)	1 (0.1%)
GLUTATHIONE	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMIZATION AND MEDICATIONS INITIATED POST-RANDOMIZATION
4. TABLE INCLUDES CONCOMITANT MEDICATIONS USED FOR COPD EXACERBATIONS
5. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 13.15B

SUMMARY OF CONCOMITANT MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
GLYCEROL	0 .	1 (0.2%)	1 (0.1%)
HAEMOGLOBIN	0 .	1 (0.2%)	1 (0.1%)
HEPARINOID	0 .	1 (0.2%)	1 (0.1%)
HESPERIDIN METHYL CHALCONE	0 .	1 (0.2%)	1 (0.1%)
HOMEOPATHIC MEDICATION (NOS)	1 (0.2%)	1 (0.2%)	2 (0.2%)
HONEY	1 (0.2%)	1 (0.2%)	2 (0.2%)
HYALURONATE SODIUM	0 .	1 (0.2%)	1 (0.1%)
HYDROXYCARBAMIDE	0 .	1 (0.2%)	1 (0.1%)
HYDROXYCHLOROQUINE SULFATE	0 .	1 (0.2%)	1 (0.1%)
HYDROXYZINE EMBONATE	0 .	1 (0.2%)	1 (0.1%)
HYMECROMONE	0 .	1 (0.2%)	1 (0.1%)
IBUPROFEN ARGININE	1 (0.2%)	1 (0.2%)	2 (0.2%)
IMIPENEM	0 .	1 (0.2%)	1 (0.1%)
IMMUNOGLOBULIN HUMAN NORMAL	0 .	1 (0.2%)	1 (0.1%)
IRON	1 (0.2%)	1 (0.2%)	2 (0.2%)
ISONIAZID	0 .	1 (0.2%)	1 (0.1%)
ISOPHANE INSULIN	2 (0.4%)	1 (0.2%)	3 (0.3%)
KETOPROFEN	4 (0.9%)	1 (0.2%)	5 (0.6%)
KETOROLAC TROMETAMOL	0 .	1 (0.2%)	1 (0.1%)
KOREAN RED GINSENG EXTRACT	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMIZATION AND MEDICATIONS INITIATED POST-RANDOMIZATION
4. TABLE INCLUDES CONCOMITANT MEDICATIONS USED FOR COPD EXACERBATIONS
5. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15B

SUMMARY OF CONCOMITANT MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
LAMIVUDINE	0 .	1 (0.2%)	1 (0.1%)
LATANOPROST	6 (1.3%)	1 (0.2%)	7 (0.8%)
LAVENDER OIL	0 .	1 (0.2%)	1 (0.1%)
LECITHIN	0 .	1 (0.2%)	1 (0.1%)
LEVOCETIRIZINE	0 .	1 (0.2%)	1 (0.1%)
LINUM USITATISSIMUM OIL	0 .	1 (0.2%)	1 (0.1%)
LIOTHYRONINE	0 .	1 (0.2%)	1 (0.1%)
LOBELIA INFLATA	0 .	1 (0.2%)	1 (0.1%)
LOPRAZOLAM	0 .	1 (0.2%)	1 (0.1%)
LORACARBEF	1 (0.2%)	1 (0.2%)	2 (0.2%)
LOSARTAN	1 (0.2%)	1 (0.2%)	2 (0.2%)
LOVASTATIN	1 (0.2%)	1 (0.2%)	2 (0.2%)
LYMECYCLINE	1 (0.2%)	1 (0.2%)	2 (0.2%)
MACROGOL	1 (0.2%)	1 (0.2%)	2 (0.2%)
MAGALDRATE	0 .	1 (0.2%)	1 (0.1%)
MAGNESIUM SULFATE	2 (0.4%)	1 (0.2%)	3 (0.3%)
MANNITOL	0 .	1 (0.2%)	1 (0.1%)
MEBEVERINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
MEDICATION UNKNOWN	4 (0.9%)	1 (0.2%)	5 (0.6%)
MEFENAMIC ACID	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMIZATION AND MEDICATIONS INITIATED POST-RANDOMIZATION
4. TABLE INCLUDES CONCOMITANT MEDICATIONS USED FOR COPD EXACERBATIONS
5. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15B

SUMMARY OF CONCOMITANT MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
MEPROBAMATE	0 .	1 (0.2%)	1 (0.1%)
MEQUITAZINE	0 .	1 (0.2%)	1 (0.1%)
METFORMIN	3 (0.7%)	1 (0.2%)	4 (0.4%)
METHYL SALICYLATE	2 (0.4%)	1 (0.2%)	3 (0.3%)
METHYLDOPA	0 .	1 (0.2%)	1 (0.1%)
METHYLEPHEDRINE HYDROCHLORIDE-DL	0 .	1 (0.2%)	1 (0.1%)
METHYLPREDNISOLONE ACETATE	0 .	1 (0.2%)	1 (0.1%)
METHYLTESTOSTERONE	0 .	1 (0.2%)	1 (0.1%)
METOPROLOL	3 (0.7%)	1 (0.2%)	4 (0.4%)
METRONIDAZOLE	2 (0.4%)	1 (0.2%)	3 (0.3%)
MIDAZOLAM MALEATE	1 (0.2%)	1 (0.2%)	2 (0.2%)
MIDODRINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
MIRTAZAPINE	1 (0.2%)	1 (0.2%)	2 (0.2%)
MIZOLASTINE	0 .	1 (0.2%)	1 (0.1%)
MOROXYDINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
MORPHINE	0 .	1 (0.2%)	1 (0.1%)
MOXONIDINE	1 (0.2%)	1 (0.2%)	2 (0.2%)
MUCOPOLYSACCHARIDE POLYSULFATE	0 .	1 (0.2%)	1 (0.1%)
MUPIROCIN	1 (0.2%)	1 (0.2%)	2 (0.2%)
MYRISTICA FRAGANS EXTRACT	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMIZATION AND MEDICATIONS INITIATED POST-RANDOMIZATION
4. TABLE INCLUDES CONCOMITANT MEDICATIONS USED FOR COPD EXACERBATIONS
5. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 13.15B

SUMMARY OF CONCOMITANT MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
NAPHAZOLINE HYDROCHLORIDE	1 (0.2%)	1 (0.2%)	2 (0.2%)
NAPHAZOLINE NITRATE	1 (0.2%)	1 (0.2%)	2 (0.2%)
NAPROXEN SODIUM	1 (0.2%)	1 (0.2%)	2 (0.2%)
NEBIVOLOL HYDROCHLORIDE	1 (0.2%)	1 (0.2%)	2 (0.2%)
NEFAZODONE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
NICOTINIC ACID	1 (0.2%)	1 (0.2%)	2 (0.2%)
NIFUROXAZIDE	0 .	1 (0.2%)	1 (0.1%)
NITROFURAZONE	0 .	1 (0.2%)	1 (0.1%)
NORETHISTERONE	4 (0.9%)	1 (0.2%)	5 (0.6%)
NORETHISTERONE ACETATE	3 (0.7%)	1 (0.2%)	4 (0.4%)
NOSCAPINE HYDROCHLORIDE	1 (0.2%)	1 (0.2%)	2 (0.2%)
NOSCAPINE RESIN	0 .	1 (0.2%)	1 (0.1%)
OLEUM TEREBINTHINAE	1 (0.2%)	1 (0.2%)	2 (0.2%)
OMEGA-3 TRIGLYCERIDES	0 .	1 (0.2%)	1 (0.1%)
ORLISTAT	0 .	1 (0.2%)	1 (0.1%)
ORPHENADRINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
OXATOMIDE	0 .	1 (0.2%)	1 (0.1%)
OXYBUTYNIN HYDROCHLORIDE	2 (0.4%)	1 (0.2%)	3 (0.3%)
PARAFFIN, LIQUID	1 (0.2%)	1 (0.2%)	2 (0.2%)
PAROXETINE	2 (0.4%)	1 (0.2%)	3 (0.3%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMIZATION AND MEDICATIONS INITIATED POST-RANDOMIZATION
4. TABLE INCLUDES CONCOMITANT MEDICATIONS USED FOR COPD EXACERBATIONS
5. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15B

SUMMARY OF CONCOMITANT MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
PHENOL, LIQUEFIED	0 .	1 (0.2%)	1 (0.1%)
PHENPROCOUMON	2 (0.4%)	1 (0.2%)	3 (0.3%)
PILOCARPINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
PIRACETAM	1 (0.2%)	1 (0.2%)	2 (0.2%)
PIROXICAM	2 (0.4%)	1 (0.2%)	3 (0.3%)
PIZOTIFEN MALATE	0 .	1 (0.2%)	1 (0.1%)
POTASSIUM ASCORBATE	0 .	1 (0.2%)	1 (0.1%)
POTASSIUM CANRENOATE	0 .	1 (0.2%)	1 (0.1%)
POVIDONE-IODINE	0 .	1 (0.2%)	1 (0.1%)
PRAMIPEXOLE	0 .	1 (0.2%)	1 (0.1%)
PRAZOSIN HYDROCHLORIDE	3 (0.7%)	1 (0.2%)	4 (0.4%)
PREDNISOLONE CAPROATE	0 .	1 (0.2%)	1 (0.1%)
PROCHLORPERAZINE MALEATE	0 .	1 (0.2%)	1 (0.1%)
PROPACETAMOL	0 .	1 (0.2%)	1 (0.1%)
PROPACETAMOL HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
PROPAFENONE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
PROPIOMAZINE MALEATE	0 .	1 (0.2%)	1 (0.1%)
PROPRANOLOL	1 (0.2%)	1 (0.2%)	2 (0.2%)
PTEROCARPUS SANTALINUS	0 .	1 (0.2%)	1 (0.1%)
QUININE	1 (0.2%)	1 (0.2%)	2 (0.2%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMIZATION AND MEDICATIONS INITIATED POST-RANDOMIZATION
4. TABLE INCLUDES CONCOMITANT MEDICATIONS USED FOR COPD EXACERBATIONS
5. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15B

SUMMARY OF CONCOMITANT MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
REPAGLINIDE	0 .	1 (0.2%)	1 (0.1%)
RETINOL	1 (0.2%)	1 (0.2%)	2 (0.2%)
RETINOL PALMITATE	0 .	1 (0.2%)	1 (0.1%)
RIBOFLAVIN	0 .	1 (0.2%)	1 (0.1%)
RIFAXIMIN	0 .	1 (0.2%)	1 (0.1%)
ROBINIA PSEUDACACIA	0 .	1 (0.2%)	1 (0.1%)
ROSEMARY OIL	0 .	1 (0.2%)	1 (0.1%)
RUSCUS ACULEATUS	0 .	1 (0.2%)	1 (0.1%)
SACCHAROMYCES BOULARDII	0 .	1 (0.2%)	1 (0.1%)
SALMETEROL	0 .	1 (0.2%)	1 (0.1%)
SENNOSIDE A+B CALCIUM	0 .	1 (0.2%)	1 (0.1%)
SERENOA REPENS	2 (0.4%)	1 (0.2%)	3 (0.3%)
SILDENAFIL CITRATE	1 (0.2%)	1 (0.2%)	2 (0.2%)
SITOSTEROL	1 (0.2%)	1 (0.2%)	2 (0.2%)
SODIUM ACID CITRATE	0 .	1 (0.2%)	1 (0.1%)
SODIUM ADENOSINE TRIPHOSPHATE	0 .	1 (0.2%)	1 (0.1%)
SODIUM BROMIDE	1 (0.2%)	1 (0.2%)	2 (0.2%)
SODIUM CAMPHOSULFONATE	0 .	1 (0.2%)	1 (0.1%)
SOTALOL	1 (0.2%)	1 (0.2%)	2 (0.2%)
SOTALOL HYDROCHLORIDE	1 (0.2%)	1 (0.2%)	2 (0.2%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMIZATION AND MEDICATIONS INITIATED POST-RANDOMIZATION
4. TABLE INCLUDES CONCOMITANT MEDICATIONS USED FOR COPD EXACERBATIONS
5. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15B

SUMMARY OF CONCOMITANT MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
SPASMONAL (NOS)	0 .	1 (0.2%)	1 (0.1%)
SPIRULINA	0 .	1 (0.2%)	1 (0.1%)
STARCEF (NOS)	0 .	1 (0.2%)	1 (0.1%)
STAVUDINE	0 .	1 (0.2%)	1 (0.1%)
STERCULIA	1 (0.2%)	1 (0.2%)	2 (0.2%)
STERILE WATER	0 .	1 (0.2%)	1 (0.1%)
STREPTODORNASE	0 .	1 (0.2%)	1 (0.1%)
STREPTOKINASE	0 .	1 (0.2%)	1 (0.1%)
SULFADIMIDINE	0 .	1 (0.2%)	1 (0.1%)
SYNDOL (NOS)	0 .	1 (0.2%)	1 (0.1%)
TABACUM	0 .	1 (0.2%)	1 (0.1%)
TAMOXIFEN CITRATE	0 .	1 (0.2%)	1 (0.1%)
TAMSULOSIN	0 .	1 (0.2%)	1 (0.1%)
TETANUS TOXOID	1 (0.2%)	1 (0.2%)	2 (0.2%)
TETRACAINE	0 .	1 (0.2%)	1 (0.1%)
TETRAZEPAM	0 .	1 (0.2%)	1 (0.1%)
THEBACON HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
THIAMAZOLE	1 (0.2%)	1 (0.2%)	2 (0.2%)
TIAPROFENIC ACID	0 .	1 (0.2%)	1 (0.1%)
TICLOPIDINE	1 (0.2%)	1 (0.2%)	2 (0.2%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMIZATION AND MEDICATIONS INITIATED POST-RANDOMIZATION
4. TABLE INCLUDES CONCOMITANT MEDICATIONS USED FOR COPD EXACERBATIONS
5. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15B

SUMMARY OF CONCOMITANT MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
TILIDINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
TITANIUM DIOXIDE	0 .	1 (0.2%)	1 (0.1%)
TOCOPHEROL	2 (0.4%)	1 (0.2%)	3 (0.3%)
TOLNAFTATE	1 (0.2%)	1 (0.2%)	2 (0.2%)
TOLTERODINE L-TARTRATE	0 .	1 (0.2%)	1 (0.1%)
TRADITIONAL CHINESE MEDICINE NOS	0 .	1 (0.2%)	1 (0.1%)
TRAMAZOLINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
TRIPROLIDINE HYDROCHLORIDE	1 (0.2%)	1 (0.2%)	2 (0.2%)
TROPICAMIDE	0 .	1 (0.2%)	1 (0.1%)
URAPIDIL	0 .	1 (0.2%)	1 (0.1%)
VALACICLOVIR HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
VIBROCIL (NOS)	0 .	1 (0.2%)	1 (0.1%)
VINPOCETINE	1 (0.2%)	1 (0.2%)	2 (0.2%)
VITAMIN (NOS)	0 .	1 (0.2%)	1 (0.1%)
WHITE SOFT PARAFFIN	0 .	1 (0.2%)	1 (0.1%)
WOOL FAT	1 (0.2%)	1 (0.2%)	2 (0.2%)
XYLOPROCT (NOS)	0 .	1 (0.2%)	1 (0.1%)
ZINC	0 .	1 (0.2%)	1 (0.1%)
ZINC OXIDE	1 (0.2%)	1 (0.2%)	2 (0.2%)
ZUCLOPENTHIXOL	1 (0.2%)	1 (0.2%)	2 (0.2%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMIZATION AND MEDICATIONS INITIATED POST-RANDOMIZATION
4. TABLE INCLUDES CONCOMITANT MEDICATIONS USED FOR COPD EXACERBATIONS
5. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15B

SUMMARY OF CONCOMITANT MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
3-BENZHYDRYLOXY-8-ISOPROPYLNORTROPANE MESILATE	1 (0.2%)	0 .	1 (0.1%)
ACECLOFENAC	1 (0.2%)	0 .	1 (0.1%)
ACEPROMAZINE	1 (0.2%)	0 .	1 (0.1%)
ACEPROMETAZINE	1 (0.2%)	0 .	1 (0.1%)
ACETIC ACID	1 (0.2%)	0 .	1 (0.1%)
ACONITE	1 (0.2%)	0 .	1 (0.1%)
ACONITUM NAPELLUS	1 (0.2%)	0 .	1 (0.1%)
ACRIVASTINE	1 (0.2%)	0 .	1 (0.1%)
ALANINE	2 (0.4%)	0 .	2 (0.2%)
ALGIFEN (NOS)	1 (0.2%)	0 .	1 (0.1%)
ALIMEMAZINE TARTRATE	1 (0.2%)	0 .	1 (0.1%)
ALLANTOIN	1 (0.2%)	0 .	1 (0.1%)
ALPROSTADIL	1 (0.2%)	0 .	1 (0.1%)
ALTIZIDE	2 (0.4%)	0 .	2 (0.2%)
ALUMINIUM HYDROXIDE GEL	2 (0.4%)	0 .	2 (0.2%)
AMBROXOL	4 (0.9%)	0 .	4 (0.4%)
AMINOACETIC ACID	2 (0.4%)	0 .	2 (0.2%)
AMITRIPTYLINE HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
AMPHOTERICIN B	2 (0.4%)	0 .	2 (0.2%)
AMYLASE	1 (0.2%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMIZATION AND MEDICATIONS INITIATED POST-RANDOMIZATION
4. TABLE INCLUDES CONCOMITANT MEDICATIONS USED FOR COPD EXACERBATIONS
5. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15B

SUMMARY OF CONCOMITANT MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
ANADIN (NOS)	1 (0.2%)	0 .	1 (0.1%)
ANASTROZOLE	1 (0.2%)	0 .	1 (0.1%)
ANTAZOLINE	1 (0.2%)	0 .	1 (0.1%)
ASPARTATE POTASSIUM	1 (0.2%)	0 .	1 (0.1%)
ATORVASTATIN	4 (0.9%)	0 .	4 (0.4%)
ATTAPULGITE	1 (0.2%)	0 .	1 (0.1%)
BACTERIAL VACCINES	1 (0.2%)	0 .	1 (0.1%)
BEECHAMS FLU PLUS (NOS)	1 (0.2%)	0 .	1 (0.1%)
BENAZEPRIL HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
BENTAZEPAM	1 (0.2%)	0 .	1 (0.1%)
BENYLIN (NOS)	1 (0.2%)	0 .	1 (0.1%)
BENZOCAINE	1 (0.2%)	0 .	1 (0.1%)
BENZYLPENICILLIN	5 (1.1%)	0 .	5 (0.6%)
BETAINE ASCORBATE	1 (0.2%)	0 .	1 (0.1%)
BETAXOLOL	1 (0.2%)	0 .	1 (0.1%)
BETAXOLOL HYDROCHLORIDE	2 (0.4%)	0 .	2 (0.2%)
BIPERIDEN HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
BISMUTH SUBCARBONATE	1 (0.2%)	0 .	1 (0.1%)
BISULEPIN HYDROCHLORIDE	2 (0.4%)	0 .	2 (0.2%)
BRIMONIDINE TARTRATE	1 (0.2%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMIZATION AND MEDICATIONS INITIATED POST-RANDOMIZATION
4. TABLE INCLUDES CONCOMITANT MEDICATIONS USED FOR COPD EXACERBATIONS
5. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 13.15B

SUMMARY OF CONCOMITANT MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
BRINZOLAMIDE	1 (0.2%)	0 .	1 (0.1%)
BROMAZEPAM	1 (0.2%)	0 .	1 (0.1%)
BROTIZOLAM	1 (0.2%)	0 .	1 (0.1%)
BRYONIA ALBA EXTRACT	1 (0.2%)	0 .	1 (0.1%)
CALCIPOTRIOL	1 (0.2%)	0 .	1 (0.1%)
CALCITONIN, SALMON	1 (0.2%)	0 .	1 (0.1%)
CALCIUM CHLORIDE	2 (0.4%)	0 .	2 (0.2%)
CANRENONE	3 (0.7%)	0 .	3 (0.3%)
CARBIMAZOLE	1 (0.2%)	0 .	1 (0.1%)
CARBINOXAMINE MALEATE	1 (0.2%)	0 .	1 (0.1%)
CARBOCISTEINE LYSINE	1 (0.2%)	0 .	1 (0.1%)
CARNITINE HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
CEFADROXIL	1 (0.2%)	0 .	1 (0.1%)
CEFALEXIN	6 (1.3%)	0 .	6 (0.7%)
CEFALOTIN SODIUM	1 (0.2%)	0 .	1 (0.1%)
CEFONICID SODIUM	1 (0.2%)	0 .	1 (0.1%)
CEFOTIAM HEXETIL HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
CELIPROLOL HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
CEPACOL LOZENGES NOS	1 (0.2%)	0 .	1 (0.1%)
CETALKONIUM CHLORIDE	1 (0.2%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMIZATION AND MEDICATIONS INITIATED POST-RANDOMIZATION
4. TABLE INCLUDES CONCOMITANT MEDICATIONS USED FOR COPD EXACERBATIONS
5. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15B

SUMMARY OF CONCOMITANT MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
CETYLPYRIDINIUM CHLORIDE	2 (0.4%)	0 .	2 (0.2%)
CHLORHEXIDINE HYDROCHLORIDE	2 (0.4%)	0 .	2 (0.2%)
CHLORPHENAMINE	1 (0.2%)	0 .	1 (0.1%)
CHLORPROTHIXENE HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
CHLORTALIDONE	1 (0.2%)	0 .	1 (0.1%)
CHOLINE SALICYLATE	1 (0.2%)	0 .	1 (0.1%)
CHONDROITIN SULFATE SODIUM	1 (0.2%)	0 .	1 (0.1%)
CINEOLE	1 (0.2%)	0 .	1 (0.1%)
CINNARIZINE	2 (0.4%)	0 .	2 (0.2%)
CISAPRIDE	2 (0.4%)	0 .	2 (0.2%)
CITRUS AURANTIUM	1 (0.2%)	0 .	1 (0.1%)
CLIOQUINOL	1 (0.2%)	0 .	1 (0.1%)
CLOMIPRAMINE	1 (0.2%)	0 .	1 (0.1%)
CLONIDINE	1 (0.2%)	0 .	1 (0.1%)
CLONIDINE HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
CLOPAMIDE	1 (0.2%)	0 .	1 (0.1%)
CLOTIAPINE	1 (0.2%)	0 .	1 (0.1%)
COAL TAR	1 (0.2%)	0 .	1 (0.1%)
COLCHIMAX (NOS)	2 (0.4%)	0 .	2 (0.2%)
CYCLOPENTHIAZIDE	1 (0.2%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMIZATION AND MEDICATIONS INITIATED POST-RANDOMIZATION
4. TABLE INCLUDES CONCOMITANT MEDICATIONS USED FOR COPD EXACERBATIONS
5. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15B

SUMMARY OF CONCOMITANT MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
DEHYDROCHOLIC ACID	1 (0.2%)	0 .	1 (0.1%)
DEQUALINIUM CHLORIDE	1 (0.2%)	0 .	1 (0.1%)
DESOGESTREL	1 (0.2%)	0 .	1 (0.1%)
DICLOFENAC POTASSIUM	1 (0.2%)	0 .	1 (0.1%)
DICYCLOVERINE HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
DIFLUCORTOLONE	1 (0.2%)	0 .	1 (0.1%)
DIHYDROERGOCRISTINE MESILATE	2 (0.4%)	0 .	2 (0.2%)
DIHYDROERGOTAMINE MESILATE	2 (0.4%)	0 .	2 (0.2%)
DIHYDROERGOTOXINE MESILATE	1 (0.2%)	0 .	1 (0.1%)
DIMEVAMIDE	1 (0.2%)	0 .	1 (0.1%)
DIOSMIN	1 (0.2%)	0 .	1 (0.1%)
DIPHENHYDRAMINE	2 (0.4%)	0 .	2 (0.2%)
DIPHENHYDRAMINE HYDROCHLORIDE	4 (0.9%)	0 .	4 (0.4%)
DIPHTHERIA TOXOID	1 (0.2%)	0 .	1 (0.1%)
DIPROPHYLLINE	1 (0.2%)	0 .	1 (0.1%)
DIXYRAZINE	1 (0.2%)	0 .	1 (0.1%)
DL-LACTIC ACID	1 (0.2%)	0 .	1 (0.1%)
DL-LACTIC ACID SODIUM SALT	1 (0.2%)	0 .	1 (0.1%)
DOXYCYCLINE HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
DROSPIRENONE	1 (0.2%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMIZATION AND MEDICATIONS INITIATED POST-RANDOMIZATION
4. TABLE INCLUDES CONCOMITANT MEDICATIONS USED FOR COPD EXACERBATIONS
5. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15B

SUMMARY OF CONCOMITANT MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
ECHINACEA	1 (0.2%)	0 .	1 (0.1%)
ENOXACIN	1 (0.2%)	0 .	1 (0.1%)
ENOXOLONE	1 (0.2%)	0 .	1 (0.1%)
EPHEDRINE SULFATE	1 (0.2%)	0 .	1 (0.1%)
ERDOSTEINE	4 (0.9%)	0 .	4 (0.4%)
ERGOTAMINE TARTRATE	1 (0.2%)	0 .	1 (0.1%)
ERYTHROMYCIN ESTOLATE	2 (0.4%)	0 .	2 (0.2%)
ERYTHROMYCIN ETHYLSUCCINATE	1 (0.2%)	0 .	1 (0.1%)
ERYTHROMYCIN STEARATE	1 (0.2%)	0 .	1 (0.1%)
ESTAZOLAM	1 (0.2%)	0 .	1 (0.1%)
ESTRAMUSTINE	1 (0.2%)	0 .	1 (0.1%)
EUCALYPTUS GLOBULUS	1 (0.2%)	0 .	1 (0.1%)
FENSPIRIDE HYDROCHLORIDE	2 (0.4%)	0 .	2 (0.2%)
FENTANYL	2 (0.4%)	0 .	2 (0.2%)
FERROUS PHOSPHATE	1 (0.2%)	0 .	1 (0.1%)
FIBER	1 (0.2%)	0 .	1 (0.1%)
FISH OIL	1 (0.2%)	0 .	1 (0.1%)
FLECAINIDE ACETATE	1 (0.2%)	0 .	1 (0.1%)
FLUINDIONE	1 (0.2%)	0 .	1 (0.1%)
FLUMETASONE PIVALATE	1 (0.2%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMIZATION AND MEDICATIONS INITIATED POST-RANDOMIZATION
4. TABLE INCLUDES CONCOMITANT MEDICATIONS USED FOR COPD EXACERBATIONS
5. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15B

SUMMARY OF CONCOMITANT MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
FLUOROMETHOLONE	2 (0.4%)	0 .	2 (0.2%)
FLUPENTIXOL	1 (0.2%)	0 .	1 (0.1%)
FLURBIPROFEN	1 (0.2%)	0 .	1 (0.1%)
FLURBIPROFEN SODIUM	1 (0.2%)	0 .	1 (0.1%)
FLUTAMIDE	1 (0.2%)	0 .	1 (0.1%)
GENTAMICIN SULFATE	2 (0.4%)	0 .	2 (0.2%)
GENTIANA LUTEA EXTRACT	1 (0.2%)	0 .	1 (0.1%)
GLIMEPIRIDE	10 (2.2%)	0 .	10 (1.1%)
GLUCOSAMINE SULFATE	2 (0.4%)	0 .	2 (0.2%)
GLUTAMIC ACID	2 (0.4%)	0 .	2 (0.2%)
GLYCOL SALICYLATE	1 (0.2%)	0 .	1 (0.1%)
GRISEOFULVIN	1 (0.2%)	0 .	1 (0.1%)
HEPATITIS A VACCINE	1 (0.2%)	0 .	1 (0.1%)
HEXETIDINE	1 (0.2%)	0 .	1 (0.1%)
HYDROCORTISONE ACETATE	1 (0.2%)	0 .	1 (0.1%)
HYDROXYAPATITE	1 (0.2%)	0 .	1 (0.1%)
HYPROMELLOSE	2 (0.4%)	0 .	2 (0.2%)
ICHTHAMMOL	1 (0.2%)	0 .	1 (0.1%)
IMIPRAMINE	1 (0.2%)	0 .	1 (0.1%)
INSULIN ASPART	1 (0.2%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMIZATION AND MEDICATIONS INITIATED POST-RANDOMIZATION
4. TABLE INCLUDES CONCOMITANT MEDICATIONS USED FOR COPD EXACERBATIONS
5. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15B

SUMMARY OF CONCOMITANT MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
INSULIN GLARGINE	1 (0.2%)	0 .	1 (0.1%)
INSULIN NOS	1 (0.2%)	0 .	1 (0.1%)
ISOPROPYL ALCOHOL	1 (0.2%)	0 .	1 (0.1%)
KANAMYCIN SULFATE	1 (0.2%)	0 .	1 (0.1%)
LACTIC ACID	1 (0.2%)	0 .	1 (0.1%)
LAXATIVES, NOS	1 (0.2%)	0 .	1 (0.1%)
LEMON JUICE	1 (0.2%)	0 .	1 (0.1%)
LERCANIDIPINE HYDROCHLORIDE	3 (0.7%)	0 .	3 (0.3%)
LEVOBUNOLOL HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
LEVOCABASTINE	1 (0.2%)	0 .	1 (0.1%)
LEVOMEPROMAZINE	1 (0.2%)	0 .	1 (0.1%)
LINCOMYCIN	1 (0.2%)	0 .	1 (0.1%)
LIPEX (NOS)	1 (0.2%)	0 .	1 (0.1%)
LIVER EXTRACT	1 (0.2%)	0 .	1 (0.1%)
LYSATE OF HAEMOPHILUS INFLUENZAE	1 (0.2%)	0 .	1 (0.1%)
LYSATE OF KLEBSIELLA OZAENAE	1 (0.2%)	0 .	1 (0.1%)
LYSATE OF KLEBSIELLA PNEUMONIAE	1 (0.2%)	0 .	1 (0.1%)
LYSATE OF MORAXELLA CATARRHALIS	1 (0.2%)	0 .	1 (0.1%)
LYSATE OF STREPTOCOCCUS	1 (0.2%)	0 .	1 (0.1%)
MAGNESIUM CHLORIDE	1 (0.2%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMIZATION AND MEDICATIONS INITIATED POST-RANDOMIZATION
4. TABLE INCLUDES CONCOMITANT MEDICATIONS USED FOR COPD EXACERBATIONS
5. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 13.15B

SUMMARY OF CONCOMITANT MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
MAGNESIUM PYRIDOXAL PHOSPHATE GLUTAMINATE	1 (0.2%)	0 .	1 (0.1%)
MAGNESIUM TRISILICATE	1 (0.2%)	0 .	1 (0.1%)
MANIDIPINE HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
MEBEVERINE	1 (0.2%)	0 .	1 (0.1%)
MEDRYSONE	1 (0.2%)	0 .	1 (0.1%)
MELITRACEN	1 (0.2%)	0 .	1 (0.1%)
MENTHA PIPERITA	1 (0.2%)	0 .	1 (0.1%)
MEPTAZINOL HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
MEPYRAMINE THEOPHYLLINE ACETATE	2 (0.4%)	0 .	2 (0.2%)
METHADONE HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
METHYL HYDROXYBENZOATE	1 (0.2%)	0 .	1 (0.1%)
METHYLPREDNISOLONE ACEPONATE	1 (0.2%)	0 .	1 (0.1%)
METILDIGOXIN	2 (0.4%)	0 .	2 (0.2%)
MIDAZOLAM	1 (0.2%)	0 .	1 (0.1%)
MORPHINE SULFATE	2 (0.4%)	0 .	2 (0.2%)
MYRTOL	3 (0.7%)	0 .	3 (0.3%)
NAFTIDROFURYL OXALATE	1 (0.2%)	0 .	1 (0.1%)
NAPHAZOLINE	1 (0.2%)	0 .	1 (0.1%)
NATEGLINIDE	1 (0.2%)	0 .	1 (0.1%)
NICARDIPINE HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMIZATION AND MEDICATIONS INITIATED POST-RANDOMIZATION
4. TABLE INCLUDES CONCOMITANT MEDICATIONS USED FOR COPD EXACERBATIONS
5. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15B

SUMMARY OF CONCOMITANT MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
NORFLOXACIN	1 (0.2%)	0 .	1 (0.1%)
OLANZAPINE	1 (0.2%)	0 .	1 (0.1%)
OLEANDOMYCIN PHOSPHATE	1 (0.2%)	0 .	1 (0.1%)
OMEPRAZOLE MAGNESIUM	1 (0.2%)	0 .	1 (0.1%)
OPIPRAMOL HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
ORTHOSIPHON STAMINEUS	1 (0.2%)	0 .	1 (0.1%)
OXANTEL	1 (0.2%)	0 .	1 (0.1%)
OXETACAINE	1 (0.2%)	0 .	1 (0.1%)
PANCREATIN	2 (0.4%)	0 .	2 (0.2%)
PARACODINE (NOS)	1 (0.2%)	0 .	1 (0.1%)
PAROXETINE HYDROCHLORIDE	3 (0.7%)	0 .	3 (0.3%)
PECTIN	1 (0.2%)	0 .	1 (0.1%)
PENTOXYVERINE CITRATE	1 (0.2%)	0 .	1 (0.1%)
PERINDOPRIL ERBUMINE	1 (0.2%)	0 .	1 (0.1%)
PETHIDINE	1 (0.2%)	0 .	1 (0.1%)
PHENAZONE	1 (0.2%)	0 .	1 (0.1%)
PHENFORMIN HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
PHENIRAMINE MALEATE	1 (0.2%)	0 .	1 (0.1%)
PHENOBARBITAL	1 (0.2%)	0 .	1 (0.1%)
PHENOXYMETHYLPENICILLIN	2 (0.4%)	0 .	2 (0.2%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMIZATION AND MEDICATIONS INITIATED POST-RANDOMIZATION
4. TABLE INCLUDES CONCOMITANT MEDICATIONS USED FOR COPD EXACERBATIONS
5. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 13.15B

SUMMARY OF CONCOMITANT MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
PHOLCODINE	1 (0.2%)	0 .	1 (0.1%)
PHOSPHORIC ACID, SODIUM SALT	1 (0.2%)	0 .	1 (0.1%)
PHOSPHORUS	1 (0.2%)	0 .	1 (0.1%)
PILOCARPINE	1 (0.2%)	0 .	1 (0.1%)
PINDOLOL	1 (0.2%)	0 .	1 (0.1%)
PIPERACILLIN SODIUM	1 (0.2%)	0 .	1 (0.1%)
PIPRADROL HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
PLATYCODON GRANDIFLORUM	2 (0.4%)	0 .	2 (0.2%)
POLIOMYELITIS VACCINE	1 (0.2%)	0 .	1 (0.1%)
POTASSIUM HYDROXYQUINOLINE SULFATE	1 (0.2%)	0 .	1 (0.1%)
PREDNISOLONE ACETATE	2 (0.4%)	0 .	2 (0.2%)
PREDNISOLONE SODIUM SUCCINATE	1 (0.2%)	0 .	1 (0.1%)
PRISTINAMYCIN	2 (0.4%)	0 .	2 (0.2%)
PROCTOSEDYL NOS	1 (0.2%)	0 .	1 (0.1%)
PROPYL PARABEN	1 (0.2%)	0 .	1 (0.1%)
PROPYPHENAZONE	1 (0.2%)	0 .	1 (0.1%)
PYGEUM AFRICANUM	3 (0.7%)	0 .	3 (0.3%)
PYRETHRINS	1 (0.2%)	0 .	1 (0.1%)
QUINAPRIL HYDROCHLORIDE	3 (0.7%)	0 .	3 (0.3%)
QUININE HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMIZATION AND MEDICATIONS INITIATED POST-RANDOMIZATION
4. TABLE INCLUDES CONCOMITANT MEDICATIONS USED FOR COPD EXACERBATIONS
5. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15B

SUMMARY OF CONCOMITANT MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
RABEPRAZOLE	1 (0.2%)	0 .	1 (0.1%)
RABEPRAZOLE SODIUM	1 (0.2%)	0 .	1 (0.1%)
RESERPINE	1 (0.2%)	0 .	1 (0.1%)
RHINATHIOL (NOS)	1 (0.2%)	0 .	1 (0.1%)
ROBITUSSIN (NOS)	1 (0.2%)	0 .	1 (0.1%)
ROFECOXIB	6 (1.3%)	0 .	6 (0.7%)
ROSIGLITAZONE MALEATE	1 (0.2%)	0 .	1 (0.1%)
SAPONARIA OFFICINALIS EXTRACT	1 (0.2%)	0 .	1 (0.1%)
SELEGILINE HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
SENNOSIDE A+B	1 (0.2%)	0 .	1 (0.1%)
SERTRALINE	1 (0.2%)	0 .	1 (0.1%)
SIBUTRAMINE	1 (0.2%)	0 .	1 (0.1%)
SILICON DIOXIDE	1 (0.2%)	0 .	1 (0.1%)
SINUTAB (NOS)	2 (0.4%)	0 .	2 (0.2%)
SODIUM ACETATE	1 (0.2%)	0 .	1 (0.1%)
SULFASALAZINE	1 (0.2%)	0 .	1 (0.1%)
TAMOXIFEN	1 (0.2%)	0 .	1 (0.1%)
TAZOBACTAM SODIUM	1 (0.2%)	0 .	1 (0.1%)
TENOXICAM	1 (0.2%)	0 .	1 (0.1%)
TERBINAFINE	2 (0.4%)	0 .	2 (0.2%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMIZATION AND MEDICATIONS INITIATED POST-RANDOMIZATION
4. TABLE INCLUDES CONCOMITANT MEDICATIONS USED FOR COPD EXACERBATIONS
5. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 13.15B

SUMMARY OF CONCOMITANT MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
TERFENADINE	1 (0.2%)	0 .	1 (0.1%)
TETRACYCLINE HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
THIETHYLPERAZINE	1 (0.2%)	0 .	1 (0.1%)
THYME	1 (0.2%)	0 .	1 (0.1%)
THYMUS VULGARIS	1 (0.2%)	0 .	1 (0.1%)
TIBOLONE	1 (0.2%)	0 .	1 (0.1%)
TICARCILLIN DISODIUM	1 (0.2%)	0 .	1 (0.1%)
TIOTROPIUM	1 (0.2%)	0 .	1 (0.1%)
TOBRAMYCIN	2 (0.4%)	0 .	2 (0.2%)
TORASEMIDE SODIUM	1 (0.2%)	0 .	1 (0.1%)
TRANDOLAPRIL	1 (0.2%)	0 .	1 (0.1%)
TRANEXAMIC ACID	1 (0.2%)	0 .	1 (0.1%)
TRIAMCINOLONE	1 (0.2%)	0 .	1 (0.1%)
TRIAZOLAM	1 (0.2%)	0 .	1 (0.1%)
TRIFLUOPERAZINE HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
TRIMIPRAMINE	1 (0.2%)	0 .	1 (0.1%)
TRINOVIN (NOS)	1 (0.2%)	0 .	1 (0.1%)
TROXERUTIN	1 (0.2%)	0 .	1 (0.1%)
TYPHOID VACCINE	1 (0.2%)	0 .	1 (0.1%)
TYROTHRICIN	2 (0.4%)	0 .	2 (0.2%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMIZATION AND MEDICATIONS INITIATED POST-RANDOMIZATION
4. TABLE INCLUDES CONCOMITANT MEDICATIONS USED FOR COPD EXACERBATIONS
5. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15B

SUMMARY OF CONCOMITANT MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
UNASYN (NOS)	1 (0.2%)	0 .	1 (0.1%)
UNOPROST (NOS)	1 (0.2%)	0 .	1 (0.1%)
UREA	1 (0.2%)	0 .	1 (0.1%)
URTICA DIOICA	1 (0.2%)	0 .	1 (0.1%)
VALPROATE SODIUM	3 (0.7%)	0 .	3 (0.3%)
VITAMIN B NOS	2 (0.4%)	0 .	2 (0.2%)
WHITE PETROLEUM	1 (0.2%)	0 .	1 (0.1%)
ZOPICLONE	5 (1.1%)	0 .	5 (0.6%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMIZATION AND MEDICATIONS INITIATED POST-RANDOMIZATION
4. TABLE INCLUDES CONCOMITANT MEDICATIONS USED FOR COPD EXACERBATIONS
5. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 13.15C

SUMMARY OF POST-THERAPY MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
TOTAL	170 (37.6%)	165 (36.3%)	335 (36.9%)
FLUTICASONE PROPIONATE	50 (11.1%)	58 (12.7%)	108 (11.9%)
SALMETEROL XINAFOATE	45 (10.0%)	58 (12.7%)	103 (11.4%)
SALBUTAMOL	50 (11.1%)	50 (11.0%)	100 (11.0%)
TIOTROPIUM BROMIDE	22 (4.9%)	26 (5.7%)	48 (5.3%)
IPRATROPIUM BROMIDE	24 (5.3%)	24 (5.3%)	48 (5.3%)
BUDESONIDE	18 (4.0%)	19 (4.2%)	37 (4.1%)
THEOPHYLLINE	13 (2.9%)	13 (2.9%)	26 (2.9%)
PREDNISOLONE	12 (2.7%)	12 (2.6%)	24 (2.6%)
PREDNISONE	8 (1.8%)	12 (2.6%)	20 (2.2%)
CLAVULANATE POTASSIUM	7 (1.5%)	11 (2.4%)	18 (2.0%)
AMOXICILLIN TRIHYDRATE	7 (1.5%)	10 (2.2%)	17 (1.9%)
BECLOMETASONE DIPROPIONATE	7 (1.5%)	8 (1.8%)	15 (1.7%)
DOXYCYCLINE	3 (0.7%)	8 (1.8%)	11 (1.2%)
EFORMOTEROL FUMARATE	16 (3.5%)	8 (1.8%)	24 (2.6%)
FENOTEROL HYDROBROMIDE	5 (1.1%)	8 (1.8%)	13 (1.4%)
ACETYLCYSTEINE	5 (1.1%)	6 (1.3%)	11 (1.2%)
ACETYLSALICYLIC ACID	6 (1.3%)	5 (1.1%)	11 (1.2%)
AMINOPHYLLINE	5 (1.1%)	5 (1.1%)	10 (1.1%)
AMOXICILLIN	8 (1.8%)	5 (1.1%)	13 (1.4%)
CIPROFLOXACIN	4 (0.9%)	5 (1.1%)	9 (1.0%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING POST-THERAPY MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR POST-THERAPY MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS INITIATED ON OR AFTER DATE OF LAST DOSE OF DOUBLE-BLIND TREATMENT
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15C

SUMMARY OF POST-THERAPY MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
FUROSEMIDE	5 (1.1%)	5 (1.1%)	10 (1.1%)
DICLOFENAC SODIUM	1 (0.2%)	4 (0.9%)	5 (0.6%)
FORMOTEROL	6 (1.3%)	4 (0.9%)	10 (1.1%)
OMEPRAZOLE	3 (0.7%)	4 (0.9%)	7 (0.8%)
TERBUTALINE	1 (0.2%)	4 (0.9%)	5 (0.6%)
CEFTRIAXONE SODIUM	0 .	3 (0.7%)	3 (0.3%)
CLARITHROMYCIN	2 (0.4%)	3 (0.7%)	5 (0.6%)
METHYLPREDNISOLONE	1 (0.2%)	3 (0.7%)	4 (0.4%)
MOXIFLOXACIN HYDROCHLORIDE	1 (0.2%)	3 (0.7%)	4 (0.4%)
PARACETAMOL	8 (1.8%)	3 (0.7%)	11 (1.2%)
ROXITHROMYCIN	1 (0.2%)	3 (0.7%)	4 (0.4%)
SALBUTAMOL SULFATE	5 (1.1%)	3 (0.7%)	8 (0.9%)
SALMETEROL	2 (0.4%)	3 (0.7%)	5 (0.6%)
SODIUM CHLORIDE	3 (0.7%)	3 (0.7%)	6 (0.7%)
AZITHROMYCIN	2 (0.4%)	2 (0.4%)	4 (0.4%)
BENDROFLUMETHIAZIDE	1 (0.2%)	2 (0.4%)	3 (0.3%)
BISOPROLOL FUMARATE	1 (0.2%)	2 (0.4%)	3 (0.3%)
DIGOXIN	0 .	2 (0.4%)	2 (0.2%)
ENALAPRIL	1 (0.2%)	2 (0.4%)	3 (0.3%)
ETOFYLLINE	0 .	2 (0.4%)	2 (0.2%)
IBUPROFEN	1 (0.2%)	2 (0.4%)	3 (0.3%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING POST-THERAPY MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR POST-THERAPY MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS INITIATED ON OR AFTER DATE OF LAST DOSE OF DOUBLE-BLIND TREATMENT
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15C

SUMMARY OF POST-THERAPY MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
INFLUENZA VACCINE	0 .	2 (0.4%)	2 (0.2%)
LACTULOSE	1 (0.2%)	2 (0.4%)	3 (0.3%)
LEVOFLOXACIN	2 (0.4%)	2 (0.4%)	4 (0.4%)
LORATADINE	2 (0.4%)	2 (0.4%)	4 (0.4%)
MEPYRAMINE THEOPHYLLINE ACETATE	1 (0.2%)	2 (0.4%)	3 (0.3%)
NICOTINE	3 (0.7%)	2 (0.4%)	5 (0.6%)
POTASSIUM CHLORIDE	2 (0.4%)	2 (0.4%)	4 (0.4%)
RANITIDINE	0 .	2 (0.4%)	2 (0.2%)
RANITIDINE HYDROCHLORIDE	1 (0.2%)	2 (0.4%)	3 (0.3%)
ROFECOXIB	0 .	2 (0.4%)	2 (0.2%)
SODIUM CITRATE	0 .	2 (0.4%)	2 (0.2%)
VITAMINS NOS	3 (0.7%)	2 (0.4%)	5 (0.6%)
ZOPICLONE	1 (0.2%)	2 (0.4%)	3 (0.3%)
ACYCLOVIR	0 .	1 (0.2%)	1 (0.1%)
ALFUZOSIN HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
AMBROXOL HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
AMILORIDE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
AMINOMAL (NOS)	0 .	1 (0.2%)	1 (0.1%)
AMITRIPTYLINE	0 .	1 (0.2%)	1 (0.1%)
AMLODIPINE BESILATE	0 .	1 (0.2%)	1 (0.1%)
AMMONIUM CHLORIDE	1 (0.2%)	1 (0.2%)	2 (0.2%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING POST-THERAPY MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR POST-THERAPY MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS INITIATED ON OR AFTER DATE OF LAST DOSE OF DOUBLE-BLIND TREATMENT
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15C

SUMMARY OF POST-THERAPY MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
AMPICILLIN	1 (0.2%)	1 (0.2%)	2 (0.2%)
ANTIBIOTICS NOS	0 .	1 (0.2%)	1 (0.1%)
ASCORBIC ACID	1 (0.2%)	1 (0.2%)	2 (0.2%)
ATORVASTATIN CALCIUM	1 (0.2%)	1 (0.2%)	2 (0.2%)
BACILLUS SUBTILIS	0 .	1 (0.2%)	1 (0.1%)
BAMBUTEROL	0 .	1 (0.2%)	1 (0.1%)
BAMBUTEROL HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
BETAMETHASONE SODIUM PHOSPHATE	0 .	1 (0.2%)	1 (0.1%)
BUPROPION HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
CANDESARTAN CILEXETIL	1 (0.2%)	1 (0.2%)	2 (0.2%)
CEFADROXIL MONOHYDRATE	0 .	1 (0.2%)	1 (0.1%)
CEFALEXIN	0 .	1 (0.2%)	1 (0.1%)
CEFIXIME	0 .	1 (0.2%)	1 (0.1%)
CEFPODOXIME PROXETIL	0 .	1 (0.2%)	1 (0.1%)
CEFPROZIL	0 .	1 (0.2%)	1 (0.1%)
CEFUROXIME	1 (0.2%)	1 (0.2%)	2 (0.2%)
CELECOXIB	0 .	1 (0.2%)	1 (0.1%)
CETIRIZINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
CHLOROQUINE SULFATE	0 .	1 (0.2%)	1 (0.1%)
CHLORPHENAMINE MALEATE	0 .	1 (0.2%)	1 (0.1%)
CITALOPRAM	1 (0.2%)	1 (0.2%)	2 (0.2%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING POST-THERAPY MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR POST-THERAPY MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS INITIATED ON OR AFTER DATE OF LAST DOSE OF DOUBLE-BLIND TREATMENT
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15C

SUMMARY OF POST-THERAPY MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
CLOPIDOGREL SULFATE	1 (0.2%)	1 (0.2%)	2 (0.2%)
CODEINE	0 .	1 (0.2%)	1 (0.1%)
CODEINE PHOSPHATE	3 (0.7%)	1 (0.2%)	4 (0.4%)
CYANOCOBALAMIN	0 .	1 (0.2%)	1 (0.1%)
DEPRAX (NOS)	0 .	1 (0.2%)	1 (0.1%)
DEXAMETHASONE	0 .	1 (0.2%)	1 (0.1%)
DEXTROMETHORPHAN HYDROBROMIDE	0 .	1 (0.2%)	1 (0.1%)
DICLOFENAC	0 .	1 (0.2%)	1 (0.1%)
DIPHENYLPYRALINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
DIPHTHERIA TOXOID	0 .	1 (0.2%)	1 (0.1%)
DIPYRIDAMOLE	0 .	1 (0.2%)	1 (0.1%)
DOPAMINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
DOXYCYCLINE HYCLATE	0 .	1 (0.2%)	1 (0.1%)
ECHINACEA PURPUREA	0 .	1 (0.2%)	1 (0.1%)
ELECTROLYTES NOS	0 .	1 (0.2%)	1 (0.1%)
ENOXAPARIN	2 (0.4%)	1 (0.2%)	3 (0.3%)
ENOXAPARIN SODIUM	0 .	1 (0.2%)	1 (0.1%)
ESOMEPRAZOLE MAGNESIUM	1 (0.2%)	1 (0.2%)	2 (0.2%)
ETHENZAMIDE	2 (0.4%)	1 (0.2%)	3 (0.3%)
FELODIPINE	0 .	1 (0.2%)	1 (0.1%)
FLUDIAZEPAM	1 (0.2%)	1 (0.2%)	2 (0.2%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING POST-THERAPY MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR POST-THERAPY MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS INITIATED ON OR AFTER DATE OF LAST DOSE OF DOUBLE-BLIND TREATMENT
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15C

SUMMARY OF POST-THERAPY MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
FOLIC ACID	1 (0.2%)	1 (0.2%)	2 (0.2%)
FRAMYCETIN SULFATE	0 .	1 (0.2%)	1 (0.1%)
GASTROGEL (NOS)	0 .	1 (0.2%)	1 (0.1%)
GENTAMICIN	1 (0.2%)	1 (0.2%)	2 (0.2%)
GLIBENCLAMIDE	0 .	1 (0.2%)	1 (0.1%)
GRAMICIDIN	0 .	1 (0.2%)	1 (0.1%)
GUAIFENESIN	0 .	1 (0.2%)	1 (0.1%)
HEPARIN CALCIUM	0 .	1 (0.2%)	1 (0.1%)
HESPERIDIN	2 (0.4%)	1 (0.2%)	3 (0.3%)
HYDROCHLOROTHIAZIDE	0 .	1 (0.2%)	1 (0.1%)
HYDROCORTISONE	0 .	1 (0.2%)	1 (0.1%)
HYDROCORTISONE SODIUM SUCCINATE	1 (0.2%)	1 (0.2%)	2 (0.2%)
INFLUENZA VIRUS VACCINE INACTIVATED	1 (0.2%)	1 (0.2%)	2 (0.2%)
INSULIN HUMAN	0 .	1 (0.2%)	1 (0.1%)
ISOSORBIDE MONONITRATE	2 (0.4%)	1 (0.2%)	3 (0.3%)
KETOCONAZOLE	0 .	1 (0.2%)	1 (0.1%)
LACTOBACILLUS ACIDOPHILUS	0 .	1 (0.2%)	1 (0.1%)
LEVOTHYROXINE SODIUM	0 .	1 (0.2%)	1 (0.1%)
LISINOPRIL	0 .	1 (0.2%)	1 (0.1%)
LOSARTAN POTASSIUM	1 (0.2%)	1 (0.2%)	2 (0.2%)
MACROGOL	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING POST-THERAPY MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR POST-THERAPY MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS INITIATED ON OR AFTER DATE OF LAST DOSE OF DOUBLE-BLIND TREATMENT
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15C

SUMMARY OF POST-THERAPY MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
METAMIZOLE SODIUM	2 (0.4%)	1 (0.2%)	3 (0.3%)
METHYLEPHEDRINE HYDROCHLORIDE	2 (0.4%)	1 (0.2%)	3 (0.3%)
METHYLEPHEDRINE HYDROCHLORIDE-DL	0 .	1 (0.2%)	1 (0.1%)
METHYLPREDNISOLONE SODIUM SUCCINATE	2 (0.4%)	1 (0.2%)	3 (0.3%)
METOCLOPRAMIDE	0 .	1 (0.2%)	1 (0.1%)
METOCLOPRAMIDE HYDROCHLORIDE	3 (0.7%)	1 (0.2%)	4 (0.4%)
METRONIDAZOLE	0 .	1 (0.2%)	1 (0.1%)
MINERALS NOS	1 (0.2%)	1 (0.2%)	2 (0.2%)
MISOPROSTOL	0 .	1 (0.2%)	1 (0.1%)
MONTELUKAST SODIUM	1 (0.2%)	1 (0.2%)	2 (0.2%)
MOXONIDINE	0 .	1 (0.2%)	1 (0.1%)
NAPROXEN	0 .	1 (0.2%)	1 (0.1%)
NICOMORPHINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
NICOUMALONE	0 .	1 (0.2%)	1 (0.1%)
NIFEDIPINE	0 .	1 (0.2%)	1 (0.1%)
NIMODIPINE	0 .	1 (0.2%)	1 (0.1%)
NUTRITIONAL SUPPLEMENT NOS	0 .	1 (0.2%)	1 (0.1%)
NYSTATIN	0 .	1 (0.2%)	1 (0.1%)
OFLOXACIN	0 .	1 (0.2%)	1 (0.1%)
OTALGAN (NOS)	0 .	1 (0.2%)	1 (0.1%)
OXAZEPAM	2 (0.4%)	1 (0.2%)	3 (0.3%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING POST-THERAPY MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR POST-THERAPY MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS INITIATED ON OR AFTER DATE OF LAST DOSE OF DOUBLE-BLIND TREATMENT
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15C

SUMMARY OF POST-THERAPY MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
OXITROPIUM BROMIDE	2 (0.4%)	1 (0.2%)	3 (0.3%)
OXYGEN	3 (0.7%)	1 (0.2%)	4 (0.4%)
PANTOPRAZOLE	0 .	1 (0.2%)	1 (0.1%)
PANTOPRAZOLE SODIUM	0 .	1 (0.2%)	1 (0.1%)
PERINDOPRIL	2 (0.4%)	1 (0.2%)	3 (0.3%)
PHENACETIN	2 (0.4%)	1 (0.2%)	3 (0.3%)
PIPERACILLIN SODIUM	0 .	1 (0.2%)	1 (0.1%)
PRAVASTATIN SODIUM	0 .	1 (0.2%)	1 (0.1%)
PROPOFOL	0 .	1 (0.2%)	1 (0.1%)
RILMENIDINE	0 .	1 (0.2%)	1 (0.1%)
ROBITUSSIN (NOS)	0 .	1 (0.2%)	1 (0.1%)
SODIUM BICARBONATE	0 .	1 (0.2%)	1 (0.1%)
SOTALOL	1 (0.2%)	1 (0.2%)	2 (0.2%)
SOTALOL HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
STREPTOCOCCUS FAECALIS	0 .	1 (0.2%)	1 (0.1%)
SULFAMETHIZOLE	0 .	1 (0.2%)	1 (0.1%)
TAZOBACTAM SODIUM	0 .	1 (0.2%)	1 (0.1%)
TELITHROMYCIN	1 (0.2%)	1 (0.2%)	2 (0.2%)
TELMISARTAN	0 .	1 (0.2%)	1 (0.1%)
TEMAZEPAM	0 .	1 (0.2%)	1 (0.1%)
TETANUS TOXOID	1 (0.2%)	1 (0.2%)	2 (0.2%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING POST-THERAPY MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR POST-THERAPY MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS INITIATED ON OR AFTER DATE OF LAST DOSE OF DOUBLE-BLIND TREATMENT
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15C

SUMMARY OF POST-THERAPY MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
THIAZINAMIUM METILSULFATE	0 .	1 (0.2%)	1 (0.1%)
TINZAPARIN SODIUM	0 .	1 (0.2%)	1 (0.1%)
TIOTROPIUM	1 (0.2%)	1 (0.2%)	2 (0.2%)
TRIAMCINOLONE	0 .	1 (0.2%)	1 (0.1%)
TRIPELENNAMINE	2 (0.4%)	1 (0.2%)	3 (0.3%)
VERAPAMIL HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
VITAMIN B SUBSTANCES NOS	0 .	1 (0.2%)	1 (0.1%)
WARFARIN	1 (0.2%)	1 (0.2%)	2 (0.2%)
XYLOMETAZOLINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
AMIODARONE HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
BLOOD CELLS, PACKED HUMAN	1 (0.2%)	0 .	1 (0.1%)
BROMHEXINE	1 (0.2%)	0 .	1 (0.1%)
BUSPIRONE HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
CEFACLOR	1 (0.2%)	0 .	1 (0.1%)
CEFAZOLIN	1 (0.2%)	0 .	1 (0.1%)
CLAVULANIC ACID	1 (0.2%)	0 .	1 (0.1%)
CLONAZEPAM	1 (0.2%)	0 .	1 (0.1%)
CLOPIDOGREL	2 (0.4%)	0 .	2 (0.2%)
DIAZEPAM	1 (0.2%)	0 .	1 (0.1%)
DICLOXACILLIN SODIUM MONOHYDRATE	1 (0.2%)	0 .	1 (0.1%)
DIHYDROCODEINE	1 (0.2%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING POST-THERAPY MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR POST-THERAPY MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS INITIATED ON OR AFTER DATE OF LAST DOSE OF DOUBLE-BLIND TREATMENT
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 13.15C

SUMMARY OF POST-THERAPY MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
DILTIAZEM	1 (0.2%)	0 .	1 (0.1%)
DOCUSATE SODIUM	2 (0.4%)	0 .	2 (0.2%)
DOXAZOSIN	1 (0.2%)	0 .	1 (0.1%)
ENALAPRIL MALEATE	3 (0.7%)	0 .	3 (0.3%)
ERDOSTEINE	2 (0.4%)	0 .	2 (0.2%)
FERROUS SULPHATE	2 (0.4%)	0 .	2 (0.2%)
FLUNISOLIDE	1 (0.2%)	0 .	1 (0.1%)
GELUSIL NOS	1 (0.2%)	0 .	1 (0.1%)
GLYCERYL TRINITRATE	1 (0.2%)	0 .	1 (0.1%)
GOSERELIN	1 (0.2%)	0 .	1 (0.1%)
HEPARIN	1 (0.2%)	0 .	1 (0.1%)
ISOSORBIDE DINITRATE	1 (0.2%)	0 .	1 (0.1%)
ITOPRIDE HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
MENTHA PIPERITA OIL	1 (0.2%)	0 .	1 (0.1%)
METOPROLOL SUCCINATE	1 (0.2%)	0 .	1 (0.1%)
MITOXANTRONE	1 (0.2%)	0 .	1 (0.1%)
MORPHINE	1 (0.2%)	0 .	1 (0.1%)
NEOMYCIN	1 (0.2%)	0 .	1 (0.1%)
OLANZAPINE	1 (0.2%)	0 .	1 (0.1%)
OXACILLIN SODIUM	1 (0.2%)	0 .	1 (0.1%)
PHENYLEPHRINE HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING POST-THERAPY MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR POST-THERAPY MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS INITIATED ON OR AFTER DATE OF LAST DOSE OF DOUBLE-BLIND TREATMENT
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15C

SUMMARY OF POST-THERAPY MEDICATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
PNEUMOCOCCAL VACCINE	1 (0.2%)	0 .	1 (0.1%)
PRAZOSIN HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
PREDNISOLONE ACETATE	1 (0.2%)	0 .	1 (0.1%)
PROPAFENONE HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
RAMIPRIL	4 (0.9%)	0 .	4 (0.4%)
SENNA	3 (0.7%)	0 .	3 (0.3%)
SIMVASTATIN	1 (0.2%)	0 .	1 (0.1%)
SORBITOL	1 (0.2%)	0 .	1 (0.1%)
SPIRONOLACTONE	1 (0.2%)	0 .	1 (0.1%)
THIAMINE	1 (0.2%)	0 .	1 (0.1%)
TRANDOLAPRIL	1 (0.2%)	0 .	1 (0.1%)
TRIMETHOPRIM	1 (0.2%)	0 .	1 (0.1%)
ZINC	1 (0.2%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING POST-THERAPY MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR POST-THERAPY MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS INITIATED ON OR AFTER DATE OF LAST DOSE OF DOUBLE-BLIND TREATMENT
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15D

SUMMARY OF MEDICATIONS GIVEN FOR COPD EXACERBATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
TOTAL	179 (39.6%)	175 (38.5%)	354 (39.0%)
PREDNISONE	32 (7.1%)	45 (9.9%)	77 (8.5%)
AMOXICILLIN	25 (5.5%)	37 (8.1%)	62 (6.8%)
PREDNISOLONE	46 (10.2%)	37 (8.1%)	83 (9.2%)
IPRATROPIUM BROMIDE	34 (7.5%)	29 (6.4%)	63 (6.9%)
CLAVULANATE POTASSIUM	17 (3.8%)	28 (6.2%)	45 (5.0%)
AMOXICILLIN TRIHYDRATE	20 (4.4%)	25 (5.5%)	45 (5.0%)
SALBUTAMOL	20 (4.4%)	22 (4.8%)	42 (4.6%)
ACETYLCYSTEINE	17 (3.8%)	16 (3.5%)	33 (3.6%)
CLARITHROMYCIN	14 (3.1%)	14 (3.1%)	28 (3.1%)
LEVOFLOXACIN	12 (2.7%)	11 (2.4%)	23 (2.5%)
SALBUTAMOL SULFATE	8 (1.8%)	11 (2.4%)	19 (2.1%)
AZITHROMYCIN	7 (1.5%)	10 (2.2%)	17 (1.9%)
CIPROFLOXACIN	11 (2.4%)	9 (2.0%)	20 (2.2%)
DOXYCYCLINE	13 (2.9%)	9 (2.0%)	22 (2.4%)
PARACETAMOL	8 (1.8%)	9 (2.0%)	17 (1.9%)
TELITHROMYCIN	3 (0.7%)	9 (2.0%)	12 (1.3%)
METHYLPREDNISOLONE	13 (2.9%)	8 (1.8%)	21 (2.3%)
MOXIFLOXACIN HYDROCHLORIDE	12 (2.7%)	8 (1.8%)	20 (2.2%)
AMBROXOL HYDROCHLORIDE	4 (0.9%)	7 (1.5%)	11 (1.2%)
CEFUROXIME	4 (0.9%)	7 (1.5%)	11 (1.2%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING COPD EXACERBATIONS MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR COPD EXACERBATIONS MEDICATION USE DURING THE 52 WEEK DOUBLE BLIND PERIOD
3. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15D

SUMMARY OF MEDICATIONS GIVEN FOR COPD EXACERBATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
THEOPHYLLINE	7 (1.5%)	7 (1.5%)	14 (1.5%)
TIOTROPIUM BROMIDE	4 (0.9%)	7 (1.5%)	11 (1.2%)
BUDESONIDE	10 (2.2%)	5 (1.1%)	15 (1.7%)
GUAIFENESIN	3 (0.7%)	5 (1.1%)	8 (0.9%)
CEFACLOR	4 (0.9%)	4 (0.9%)	8 (0.9%)
CEFIXIME	5 (1.1%)	4 (0.9%)	9 (1.0%)
CLAVULANIC ACID	4 (0.9%)	4 (0.9%)	8 (0.9%)
CODEINE PHOSPHATE	4 (0.9%)	4 (0.9%)	8 (0.9%)
FLUTICASONE PROPIONATE	5 (1.1%)	4 (0.9%)	9 (1.0%)
OXYGEN	1 (0.2%)	4 (0.9%)	5 (0.6%)
ROXITHROMYCIN	11 (2.4%)	4 (0.9%)	15 (1.7%)
AMINOPHYLLINE	5 (1.1%)	3 (0.7%)	8 (0.9%)
AMPICILLIN	4 (0.9%)	3 (0.7%)	7 (0.8%)
BETAMETHASONE SODIUM PHOSPHATE	5 (1.1%)	3 (0.7%)	8 (0.9%)
CARBOCISTEINE	4 (0.9%)	3 (0.7%)	7 (0.8%)
CEFTRIAXONE SODIUM	2 (0.4%)	3 (0.7%)	5 (0.6%)
CLOPERASTINE	1 (0.2%)	3 (0.7%)	4 (0.4%)
DEXTROMETHORPHAN HYDROBROMIDE	0 .	3 (0.7%)	3 (0.3%)
DIPHENYLPYRALINE HYDROCHLORIDE	0 .	3 (0.7%)	3 (0.3%)
EFORMOTEROL FUMARATE	2 (0.4%)	3 (0.7%)	5 (0.6%)
FUROSEMIDE	1 (0.2%)	3 (0.7%)	4 (0.4%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING COPD EXACERBATIONS MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR COPD EXACERBATIONS MEDICATION USE DURING THE 52 WEEK DOUBLE BLIND PERIOD
3. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15D

SUMMARY OF MEDICATIONS GIVEN FOR COPD EXACERBATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
HYDROCORTISONE	2 (0.4%)	3 (0.7%)	5 (0.6%)
METHYLEPHEDRINE HYDROCHLORIDE	3 (0.7%)	3 (0.7%)	6 (0.7%)
METHYLPREDNISOLONE SODIUM SUCCINATE	6 (1.3%)	3 (0.7%)	9 (1.0%)
MOXIFLOXACIN	6 (1.3%)	3 (0.7%)	9 (1.0%)
OMEPRAZOLE	0 .	3 (0.7%)	3 (0.3%)
SALMETEROL XINAFOATE	6 (1.3%)	3 (0.7%)	9 (1.0%)
SODIUM CHLORIDE	0 .	3 (0.7%)	3 (0.3%)
VITAMINS NOS	2 (0.4%)	3 (0.7%)	5 (0.6%)
BECLOMETASONE DIPROPIONATE	5 (1.1%)	2 (0.4%)	7 (0.8%)
BROMHEXINE HYDROCHLORIDE	1 (0.2%)	2 (0.4%)	3 (0.3%)
CHLORPHENAMINE MALEATE	2 (0.4%)	2 (0.4%)	4 (0.4%)
DIMEMORFAN PHOSPHATE	2 (0.4%)	2 (0.4%)	4 (0.4%)
EPHEDRINE HYDROCHLORIDE	2 (0.4%)	2 (0.4%)	4 (0.4%)
ETHENZAMIDE	2 (0.4%)	2 (0.4%)	4 (0.4%)
FENOTEROL HYDROBROMIDE	3 (0.7%)	2 (0.4%)	5 (0.6%)
FLUNISOLIDE	1 (0.2%)	2 (0.4%)	3 (0.3%)
HERBALS NOS	1 (0.2%)	2 (0.4%)	3 (0.3%)
HESPERIDIN	2 (0.4%)	2 (0.4%)	4 (0.4%)
HYDROCORTISONE SODIUM SUCCINATE	0 .	2 (0.4%)	2 (0.2%)
LEVODROPROPIZINE	0 .	2 (0.4%)	2 (0.2%)
METAMIZOLE SODIUM	2 (0.4%)	2 (0.4%)	4 (0.4%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING COPD EXACERBATIONS MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR COPD EXACERBATIONS MEDICATION USE DURING THE 52 WEEK DOUBLE BLIND PERIOD
3. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15D

SUMMARY OF MEDICATIONS GIVEN FOR COPD EXACERBATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
NIMODIPINE	0 .	2 (0.4%)	2 (0.2%)
OXITROPIUM BROMIDE	3 (0.7%)	2 (0.4%)	5 (0.6%)
PHENACETIN	2 (0.4%)	2 (0.4%)	4 (0.4%)
PROFLOX (NOS)	0 .	2 (0.4%)	2 (0.2%)
RANITIDINE HYDROCHLORIDE	0 .	2 (0.4%)	2 (0.2%)
TERBUTALINE	1 (0.2%)	2 (0.4%)	3 (0.3%)
THIAMPHENICOL	0 .	2 (0.4%)	2 (0.2%)
TRIMETHOPRIM	1 (0.2%)	2 (0.4%)	3 (0.3%)
TRIPELENNAMINE	2 (0.4%)	2 (0.4%)	4 (0.4%)
ACETYLSALICYLIC ACID	0 .	1 (0.2%)	1 (0.1%)
AMINOMAL (NOS)	0 .	1 (0.2%)	1 (0.1%)
AMINOPHENAZONE	0 .	1 (0.2%)	1 (0.1%)
AMMONIUM CHLORIDE	3 (0.7%)	1 (0.2%)	4 (0.4%)
ANTIMONY POTASSIUM TARTRATE	0 .	1 (0.2%)	1 (0.1%)
BENZOIC ACID	0 .	1 (0.2%)	1 (0.1%)
BETAMETHASONE	2 (0.4%)	1 (0.2%)	3 (0.3%)
BUPHENINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
CAMPHOR	0 .	1 (0.2%)	1 (0.1%)
CASSIA ANGUSTIFOLIA	0 .	1 (0.2%)	1 (0.1%)
CEFALEXIN MONOHYDRATE	0 .	1 (0.2%)	1 (0.1%)
CEFAZOLIN	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING COPD EXACERBATIONS MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR COPD EXACERBATIONS MEDICATION USE DURING THE 52 WEEK DOUBLE BLIND PERIOD
3. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15D

SUMMARY OF MEDICATIONS GIVEN FOR COPD EXACERBATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
CEFAZOLIN SODIUM	0 .	1 (0.2%)	1 (0.1%)
CEFTAZIDIME	0 .	1 (0.2%)	1 (0.1%)
CEFTIBUTEN	0 .	1 (0.2%)	1 (0.1%)
CEFTRIAXONE	0 .	1 (0.2%)	1 (0.1%)
CHOLINE THEOPHYLLINATE	0 .	1 (0.2%)	1 (0.1%)
CILASTATIN	0 .	1 (0.2%)	1 (0.1%)
CITRIC ACID	1 (0.2%)	1 (0.2%)	2 (0.2%)
CLENBUTEROL HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
CLINDAMYCIN HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
CRESOLSULFONIC ACID	0 .	1 (0.2%)	1 (0.1%)
CYPROHEPTADINE	1 (0.2%)	1 (0.2%)	2 (0.2%)
CYPROHEPTADINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
DEFLAZACORT	2 (0.4%)	1 (0.2%)	3 (0.3%)
DEXTROMETHORPHAN	0 .	1 (0.2%)	1 (0.1%)
DIAZEPAM	0 .	1 (0.2%)	1 (0.1%)
DIMENHYDRINATE	0 .	1 (0.2%)	1 (0.1%)
DOXYCYCLINE HYCLATE	0 .	1 (0.2%)	1 (0.1%)
DOXYLAMINE SUCCINATE	0 .	1 (0.2%)	1 (0.1%)
EPRAZINONE	2 (0.4%)	1 (0.2%)	3 (0.3%)
ERYTHROMYCIN	6 (1.3%)	1 (0.2%)	7 (0.8%)
ETHANOL	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING COPD EXACERBATIONS MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR COPD EXACERBATIONS MEDICATION USE DURING THE 52 WEEK DOUBLE BLIND PERIOD
3. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15D

SUMMARY OF MEDICATIONS GIVEN FOR COPD EXACERBATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
ETHYLMORPHINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
ETOFYLLINE	0 .	1 (0.2%)	1 (0.1%)
FORMOTEROL	1 (0.2%)	1 (0.2%)	2 (0.2%)
GENTAMICIN	0 .	1 (0.2%)	1 (0.1%)
IMIPENEM	0 .	1 (0.2%)	1 (0.1%)
LIQUORICE LIQUID EXTRACT	0 .	1 (0.2%)	1 (0.1%)
LOPERAMIDE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
LYSOZYME HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
MENTHOL	1 (0.2%)	1 (0.2%)	2 (0.2%)
METHYLEPHEDRINE HYDROCHLORIDE-DL	0 .	1 (0.2%)	1 (0.1%)
METOCLOPRAMIDE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
NADROPARIN CALCIUM	0 .	1 (0.2%)	1 (0.1%)
NAPROXEN SODIUM	0 .	1 (0.2%)	1 (0.1%)
ORCIPRENALINE SULFATE	0 .	1 (0.2%)	1 (0.1%)
PAPAVER SOMNIFERUM	0 .	1 (0.2%)	1 (0.1%)
PHENYLEPHRINE	0 .	1 (0.2%)	1 (0.1%)
PIMPINELLA ANISUM	0 .	1 (0.2%)	1 (0.1%)
POTASSIUM CHLORIDE	0 .	1 (0.2%)	1 (0.1%)
PROPACETAMOL	0 .	1 (0.2%)	1 (0.1%)
SALMETEROL	0 .	1 (0.2%)	1 (0.1%)
SODIUM BROMIDE	1 (0.2%)	1 (0.2%)	2 (0.2%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING COPD EXACERBATIONS MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR COPD EXACERBATIONS MEDICATION USE DURING THE 52 WEEK DOUBLE BLIND PERIOD
3. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15D

SUMMARY OF MEDICATIONS GIVEN FOR COPD EXACERBATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
SODIUM CAMPHOSULFONATE	0 .	1 (0.2%)	1 (0.1%)
SODIUM CITRATE	0 .	1 (0.2%)	1 (0.1%)
SULFAMETHOXAZOLE	0 .	1 (0.2%)	1 (0.1%)
THEBACON HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
TIAPROFENIC ACID	0 .	1 (0.2%)	1 (0.1%)
VITAMIN B SUBSTANCES NOS	0 .	1 (0.2%)	1 (0.1%)
ACONITE	1 (0.2%)	0 .	1 (0.1%)
ACONITUM NAPELLUS	1 (0.2%)	0 .	1 (0.1%)
ALTHAEA OFFICINALIS	1 (0.2%)	0 .	1 (0.1%)
AMBROXOL	3 (0.7%)	0 .	3 (0.3%)
AMYLASE	1 (0.2%)	0 .	1 (0.1%)
ASPARTATE POTASSIUM	1 (0.2%)	0 .	1 (0.1%)
BENZYLPENICILLIN	1 (0.2%)	0 .	1 (0.1%)
BETAINE ASCORBATE	1 (0.2%)	0 .	1 (0.1%)
BISULEPIN HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
BROMHEXINE	1 (0.2%)	0 .	1 (0.1%)
BRYONIA ALBA EXTRACT	1 (0.2%)	0 .	1 (0.1%)
CARBINOXAMINE MALEATE	1 (0.2%)	0 .	1 (0.1%)
CARBOCISTEINE LYSINE	1 (0.2%)	0 .	1 (0.1%)
CARNITINE HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
CEFALEXIN	1 (0.2%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING COPD EXACERBATIONS MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR COPD EXACERBATIONS MEDICATION USE DURING THE 52 WEEK DOUBLE BLIND PERIOD
3. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15D

SUMMARY OF MEDICATIONS GIVEN FOR COPD EXACERBATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
CEFONICID SODIUM	1 (0.2%)	0 .	1 (0.1%)
CEFPODOXIME PROXETIL	1 (0.2%)	0 .	1 (0.1%)
CEFPROZIL	3 (0.7%)	0 .	3 (0.3%)
CETIRIZINE	1 (0.2%)	0 .	1 (0.1%)
CETIRIZINE HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
CITRUS AURANTIUM	1 (0.2%)	0 .	1 (0.1%)
CLOBUTINOL HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
COCILLANA	3 (0.7%)	0 .	3 (0.3%)
DICLOFENAC	1 (0.2%)	0 .	1 (0.1%)
DIPHENHYDRAMINE HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
DIPROPHYLLINE	1 (0.2%)	0 .	1 (0.1%)
DL-LACTIC ACID	1 (0.2%)	0 .	1 (0.1%)
DOXYCYCLINE HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
ERDOSTEINE	2 (0.4%)	0 .	2 (0.2%)
ERYTHROMYCIN ETHYLSUCCINATE	1 (0.2%)	0 .	1 (0.1%)
FERROUS PHOSPHATE	1 (0.2%)	0 .	1 (0.1%)
FEXOFENADINE HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
FRAMYCETIN SULFATE	1 (0.2%)	0 .	1 (0.1%)
GENTAMICIN SULFATE	1 (0.2%)	0 .	1 (0.1%)
GENTIANA LUTEA EXTRACT	1 (0.2%)	0 .	1 (0.1%)
HYDROXYZINE	2 (0.4%)	0 .	2 (0.2%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING COPD EXACERBATIONS MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR COPD EXACERBATIONS MEDICATION USE DURING THE 52 WEEK DOUBLE BLIND PERIOD
3. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15D

SUMMARY OF MEDICATIONS GIVEN FOR COPD EXACERBATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
IBUPROFEN	1 (0.2%)	0 .	1 (0.1%)
IPRATROPIUM	1 (0.2%)	0 .	1 (0.1%)
LINCOMYCIN	1 (0.2%)	0 .	1 (0.1%)
LORACARBEF	1 (0.2%)	0 .	1 (0.1%)
LORATADINE	3 (0.7%)	0 .	3 (0.3%)
LYMECYCLINE	1 (0.2%)	0 .	1 (0.1%)
MEPYRAMINE THEOPHYLLINE ACETATE	1 (0.2%)	0 .	1 (0.1%)
METAMIZOLE MAGNESIUM	1 (0.2%)	0 .	1 (0.1%)
METRONIDAZOLE	1 (0.2%)	0 .	1 (0.1%)
MOMETASONE FUROATE	1 (0.2%)	0 .	1 (0.1%)
MYRTOL	1 (0.2%)	0 .	1 (0.1%)
NAPHAZOLINE NITRATE	1 (0.2%)	0 .	1 (0.1%)
NIMESULIDE	1 (0.2%)	0 .	1 (0.1%)
NUTRITIONAL SUPPLEMENT NOS	1 (0.2%)	0 .	1 (0.1%)
OFLOXACIN	1 (0.2%)	0 .	1 (0.1%)
PARACODINE (NOS)	1 (0.2%)	0 .	1 (0.1%)
PENTOXYVERINE CITRATE	1 (0.2%)	0 .	1 (0.1%)
PHENOXYMETHYLPENICILLIN POTASSIUM	1 (0.2%)	0 .	1 (0.1%)
PHENYLEPHRINE HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
PIPERACILLIN SODIUM	1 (0.2%)	0 .	1 (0.1%)
PLATYCODON GRANDIFLORUM	1 (0.2%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING COPD EXACERBATIONS MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR COPD EXACERBATIONS MEDICATION USE DURING THE 52 WEEK DOUBLE BLIND PERIOD
3. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.15D

SUMMARY OF MEDICATIONS GIVEN FOR COPD EXACERBATIONS
BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENERIC TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
PREDNISOLONE ACETATE	1 (0.2%)	0 .	1 (0.1%)
PREDNISOLONE SODIUM SUCCINATE	1 (0.2%)	0 .	1 (0.1%)
PRISTINAMYCIN	1 (0.2%)	0 .	1 (0.1%)
PSEUDOEPHEDRINE HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
PYRIDOXINE HYDROCHLORIDE	1 (0.2%)	0 .	1 (0.1%)
QUINAPRIL	1 (0.2%)	0 .	1 (0.1%)
ROFECOXIB	1 (0.2%)	0 .	1 (0.1%)
SAPONARIA OFFICINALIS EXTRACT	1 (0.2%)	0 .	1 (0.1%)
SIMVASTATIN	1 (0.2%)	0 .	1 (0.1%)
TAZOBACTAM SODIUM	1 (0.2%)	0 .	1 (0.1%)
THYME	1 (0.2%)	0 .	1 (0.1%)
THYMUS VULGARIS	1 (0.2%)	0 .	1 (0.1%)
TIOTROPIUM	1 (0.2%)	0 .	1 (0.1%)
TRIAMCINOLONE	1 (0.2%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING COPD EXACERBATIONS MEDICATION
2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMIZED PATIENTS ASSESSED FOR COPD EXACERBATIONS MEDICATION USE DURING THE 52 WEEK DOUBLE BLIND PERIOD
3. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.16A

SUMMARY OF STUDY MEDICATION COMPLIANCE (%) BY TREATMENT GROUP AND VISIT/WEEK

PROTOCOL 157

VISIT/WEEK	COMPLIANCE	TREATMENT GROUP PLACEBO	SB 207499
SINGLE BLIND RUN-IN	< 80%	13 (2.9%)	11 (2.4%)
	80-120%	428 (95.1%)	432 (94.9%)
	> 120%	9 (2.0%)	12 (2.6%)
	NUMBER EVALUATED	450	455
VISIT 2/RUN-IN	< 80%	16 (3.7%)	24 (5.4%)
	80-120%	418 (96.1%)	416 (93.3%)
	> 120%	1 (0.2%)	6 (1.3%)
	NUMBER EVALUATED	435	446
VISIT 3/BASELINE	< 80%	9 (2.0%)	12 (2.7%)
	80-120%	427 (95.3%)	430 (95.1%)
	> 120%	12 (2.7%)	10 (2.2%)
	NUMBER EVALUATED	448	452
VISIT 4/WEEK 2	< 80%	18 (4.1%)	28 (6.4%)
	80-120%	416 (95.6%)	409 (93.4%)
	> 120%	1 (0.2%)	1 (0.2%)
	NUMBER EVALUATED	435	438
VISIT 5/WEEK 4	< 80%	19 (4.4%)	27 (6.5%)
	80-120%	405 (94.6%)	379 (91.8%)
	> 120%	4 (0.9%)	7 (1.7%)
	NUMBER EVALUATED	428	413
VISIT 6/WEEK 8	< 80%	13 (3.1%)	22 (5.5%)
	80-120%	407 (96.9%)	376 (94.2%)
	> 120%	0 .	1 (0.3%)
	NUMBER EVALUATED	420	399
VISIT 7/WEEK 12	< 80%	11 (2.7%)	24 (6.4%)
	80-120%	393 (97.0%)	351 (93.4%)
	> 120%	1 (0.2%)	1 (0.3%)
	NUMBER EVALUATED	405	376
VISIT 8/WEEK 20	< 80%	11 (2.8%)	16 (4.6%)
	80-120%	375 (96.9%)	332 (95.1%)
	> 120%	1 (0.3%)	1 (0.3%)
	NUMBER EVALUATED	387	349
VISIT 9/WEEK 28	< 80%	13 (3.4%)	15 (4.6%)
	80-120%	367 (96.3%)	312 (94.8%)
	> 120%	1 (0.3%)	2 (0.6%)

1. SINGLE-BLIND RUN-IN REPRESENTS COMPLIANCE DURING THE PLACEBO RUN-IN PERIOD
2. OVERALL REPRESENTS COMPLIANCE OVER 52 WEEK DOUBLE-BLIND PERIOD
3. TABLE INCLUDES RANDOMIZED PATIENTS WITH NON-MISSING COMPLIANCE DATA

CONFIDENTIAL

SB 207499

TABLE 13.16A

SUMMARY OF STUDY MEDICATION COMPLIANCE (%) BY TREATMENT GROUP AND VISIT/WEEK

PROTOCOL 157

VISIT/WEEK	COMPLIANCE	TREATMENT GROUP PLACEBO		TREATMENT GROUP SB 207499	
VISIT 9/WEEK 28	NUMBER EVALUATED	381		329	
VISIT 10/WEEK 36	< 80%	10	(2.8%)	10	(3.2%)
	80-120%	347	(96.1%)	301	(96.5%)
	> 120%	4	(1.1%)	1	(0.3%)
	NUMBER EVALUATED	361		312	
VISIT 11/WEEK 44	< 80%	11	(3.2%)	12	(4.0%)
	80-120%	330	(95.9%)	284	(95.6%)
	> 120%	3	(0.9%)	1	(0.3%)
	NUMBER EVALUATED	344		297	
VISIT 12/WEEK 52	< 80%	13	(3.9%)	11	(3.9%)
	80-120%	316	(95.2%)	273	(95.8%)
	> 120%	3	(0.9%)	1	(0.4%)
	NUMBER EVALUATED	332		285	
OVERALL	< 80%	26	(5.8%)	49	(10.9%)
	80-120%	419	(93.3%)	400	(88.9%)
	> 120%	4	(0.9%)	1	(0.2%)
	NUMBER EVALUATED	449		450	

1. SINGLE-BLIND RUN-IN REPRESENTS COMPLIANCE DURING THE PLACEBO RUN-IN PERIOD
2. OVERALL REPRESENTS COMPLIANCE OVER 52 WEEK DOUBLE-BLIND PERIOD
3. TABLE INCLUDES RANDOMIZED PATIENTS WITH NON-MISSING COMPLIANCE DATA

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 13.16B

DESCRIPTIVE STATISTICS FOR STUDY MEDICATION COMPLIANCE (%) BY TREATMENT GROUP AND VISIT/WEEK

PROTOCOL 157

VISIT/WEEK	Statistic	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
SINGLE BLIND RUN-IN	N	450	455
	MEAN	97.68	98.06
	STD	14.40	15.90
	MEDIAN	96.67	97.22
	MIN	50.00	48.21
	MAX	242.86	254.55
VISIT 2/RUN-IN	N	435	446
	MEAN	96.10	96.61
	STD	8.75	12.28
	MEDIAN	100.00	98.69
	MIN	46.43	46.43
	MAX	127.27	250.00
VISIT 3/BASELINE	N	448	452
	MEAN	98.00	98.00
	STD	16.02	14.98
	MEDIAN	96.43	96.88
	MIN	31.25	50.00
	MAX	242.86	254.55
VISIT 4/WEEK 2	N	435	438
	MEAN	96.31	94.82
	STD	9.33	12.73
	MEDIAN	100.00	100.00
	MIN	31.25	20.83
	MAX	170.00	130.00
VISIT 5/WEEK 4	N	428	413
	MEAN	96.54	95.41
	STD	12.03	15.31
	MEDIAN	100.00	96.88
	MIN	3.57	14.29
	MAX	203.33	200.00
VISIT 6/WEEK 8	N	420	399
	MEAN	96.28	95.04
	STD	9.28	10.89
	MEDIAN	98.28	98.21
	MIN	16.07	0.00
	MAX	114.29	125.00
VISIT 7/WEEK 12	N	405	376

1. SINGLE-BLIND RUN-IN REPRESENTS COMPLIANCE DURING THE PLACEBO RUN-IN PERIOD
2. OVERALL REPRESENTS COMPLIANCE OVER 52 WEEK DOUBLE-BLIND PERIOD
3. TABLE INCLUDES RANDOMIZED PATIENTS WITH NON-MISSING COMPLIANCE DATA

CONFIDENTIAL

SB 207499

TABLE 13.16B

DESCRIPTIVE STATISTICS FOR STUDY MEDICATION COMPLIANCE (%) BY TREATMENT GROUP AND VISIT/WEEK

PROTOCOL 157

VISIT/WEEK	Statistic	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
VISIT 7/WEEK 12	MEAN	96.55	94.60
	STD	8.36	14.02
	MEDIAN	98.28	98.21
	MIN	17.86	0.00
	MAX	126.19	136.36
VISIT 8/WEEK 20	N	387	349
	MEAN	97.22	96.38
	STD	7.36	9.30
	MEDIAN	99.09	99.04
	MIN	42.24	25.00
	MAX	125.00	142.22
VISIT 9/WEEK 28	N	381	329
	MEAN	96.83	96.60
	STD	8.45	10.09
	MEDIAN	99.02	98.36
	MIN	42.31	0.00
	MAX	132.08	130.95
VISIT 10/WEEK 36	N	361	312
	MEAN	96.91	96.64
	STD	10.32	9.68
	MEDIAN	98.33	98.93
	MIN	0.00	5.84
	MAX	160.00	134.00
VISIT 11/WEEK 44	N	344	297
	MEAN	96.77	97.41
	STD	9.10	8.21
	MEDIAN	98.23	99.11
	MIN	0.00	32.43
	MAX	127.08	122.45
VISIT 12/WEEK 52	N	332	285
	MEAN	96.80	96.84
	STD	10.36	8.79
	MEDIAN	99.11	99.11
	MIN	3.92	28.57
	MAX	140.00	125.00
OVERALL	N	449	450
	MEAN	95.21	92.24

1. SINGLE-BLIND RUN-IN REPRESENTS COMPLIANCE DURING THE PLACEBO RUN-IN PERIOD
2. OVERALL REPRESENTS COMPLIANCE OVER 52 WEEK DOUBLE-BLIND PERIOD
3. TABLE INCLUDES RANDOMIZED PATIENTS WITH NON-MISSING COMPLIANCE DATA

CONFIDENTIAL

SB 207499

TABLE 13.16B

DESCRIPTIVE STATISTICS FOR STUDY MEDICATION COMPLIANCE (%) BY TREATMENT GROUP AND VISIT/WEEK

PROTOCOL 157

VISIT/WEEK	Statistic	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
OVERALL	STD	10.34	14.20
	MEDIAN	97.93	97.26
	MIN	28.26	20.65
	MAX	170.00	121.43

1. SINGLE-BLIND RUN-IN REPRESENTS COMPLIANCE DURING THE PLACEBO RUN-IN PERIOD
2. OVERALL REPRESENTS COMPLIANCE OVER 52 WEEK DOUBLE-BLIND PERIOD
3. TABLE INCLUDES RANDOMIZED PATIENTS WITH NON-MISSING COMPLIANCE DATA

CONFIDENTIAL

SB 207499

TABLE 13.17

SUMMARY OF PATIENT SMOKING STATUS BY BASELINE STATUS, TREATMENT GROUP AND VISIT/WEEK
PROTOCOL 157

VISIT	TREATMENT GROUP	BASELINE	VISIT STATUS: SMOKING		VISIT STATUS: NOT-SMOKING		TOTAL
VISIT 4/WEEK 2	PLACEBO	SMOKING	178	(96.2%)	7	(3.8%)	185
		NOT-SMOKING	6	(2.3%)	250	(97.7%)	256
		MISSING	0		0		0
		TOTAL	184	(41.7%)	257	(58.3%)	441
	SB 207499	SMOKING	179	(96.8%)	6	(3.2%)	185
		NOT-SMOKING	5	(2.0%)	241	(98.0%)	246
		MISSING	0		0		0
		TOTAL	184	(42.7%)	247	(57.3%)	431
VISIT 5/WEEK 4	PLACEBO	SMOKING	177	(97.8%)	4	(2.2%)	181
		NOT-SMOKING	9	(3.6%)	242	(96.4%)	251
		MISSING	0		0		0
		TOTAL	186	(43.1%)	246	(56.9%)	432
	SB 207499	SMOKING	173	(96.6%)	6	(3.4%)	179
		NOT-SMOKING	6	(2.6%)	223	(97.4%)	229
		MISSING	0		0		0
		TOTAL	179	(43.9%)	229	(56.1%)	408
VISIT 6/WEEK 8	PLACEBO	SMOKING	169	(96.0%)	7	(4.0%)	176
		NOT-SMOKING	14	(5.8%)	226	(94.2%)	240
		MISSING	0		0		0
		TOTAL	183	(44.0%)	233	(56.0%)	416
	SB 207499	SMOKING	166	(95.4%)	8	(4.6%)	174
		NOT-SMOKING	4	(1.8%)	219	(98.2%)	223
		MISSING	0		0		0
		TOTAL	170	(42.8%)	227	(57.2%)	397
VISIT 7/WEEK 12	PLACEBO	SMOKING	163	(94.2%)	10	(5.8%)	173
		NOT-SMOKING	12	(5.2%)	221	(94.8%)	233
		MISSING	0		0		0
		TOTAL	175	(43.1%)	231	(56.9%)	406
	SB 207499	SMOKING	161	(96.4%)	6	(3.6%)	167
		NOT-SMOKING	4	(2.0%)	200	(98.0%)	204
		MISSING	0		0		0
		TOTAL	165	(44.5%)	206	(55.5%)	371
VISIT 8/WEEK 20	PLACEBO	SMOKING	154	(92.8%)	12	(7.2%)	166
		NOT-SMOKING	10	(4.4%)	217	(95.6%)	227

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ASSESSED AT BASELINE AND VISIT
2. SUMMARY IS FOR RANDOMIZED PATIENTS

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 13.17

SUMMARY OF PATIENT SMOKING STATUS BY BASELINE STATUS, TREATMENT GROUP AND VISIT/WEEK
PROTOCOL 157

VISIT	TREATMENT GROUP	BASELINE	VISIT STATUS: SMOKING		VISIT STATUS: NOT-SMOKING		TOTAL
VISIT 8/WEEK 20	PLACEBO	MISSING	0		0		0
		TOTAL	164	(41.7%)	229	(58.3%)	393
	SB 207499	SMOKING	146	(93.6%)	10	(6.4%)	156
		NOT-SMOKING	6	(3.1%)	186	(96.9%)	192
		MISSING	0		0		0
		TOTAL	152	(43.7%)	196	(56.3%)	348
VISIT 9/WEEK 28	PLACEBO	SMOKING	145	(90.6%)	15	(9.4%)	160
		NOT-SMOKING	11	(5.0%)	210	(95.0%)	221
		MISSING	0		0		0
		TOTAL	156	(40.9%)	225	(59.1%)	381
	SB 207499	SMOKING	139	(93.3%)	10	(6.7%)	149
		NOT-SMOKING	3	(1.6%)	179	(98.4%)	182
		MISSING	0		0		0
		TOTAL	142	(42.9%)	189	(57.1%)	331
VISIT 10/WEEK 36	PLACEBO	SMOKING	143	(92.3%)	12	(7.7%)	155
		NOT-SMOKING	8	(3.9%)	199	(96.1%)	207
		MISSING	0		0		0
		TOTAL	151	(41.7%)	211	(58.3%)	362
	SB 207499	SMOKING	133	(94.3%)	8	(5.7%)	141
		NOT-SMOKING	3	(1.7%)	170	(98.3%)	173
		MISSING	0		0		0
		TOTAL	136	(43.3%)	178	(56.7%)	314
VISIT 11/WEEK 44	PLACEBO	SMOKING	139	(92.1%)	12	(7.9%)	151
		NOT-SMOKING	7	(3.6%)	187	(96.4%)	194
		MISSING	0		0		0
		TOTAL	146	(42.3%)	199	(57.7%)	345
	SB 207499	SMOKING	128	(94.1%)	8	(5.9%)	136
		NOT-SMOKING	4	(2.4%)	161	(97.6%)	165
		MISSING	0		0		0
		TOTAL	132	(43.9%)	169	(56.1%)	301
VISIT 12/WEEK 52	PLACEBO	SMOKING	131	(90.3%)	14	(9.7%)	145
		NOT-SMOKING	7	(3.7%)	182	(96.3%)	189
		MISSING	0		0		0
		TOTAL	138	(41.3%)	196	(58.7%)	334

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ASSESSED AT BASELINE AND VISIT
2. SUMMARY IS FOR RANDOMIZED PATIENTS

CONFIDENTIAL

SB 207499

TABLE 13.17

SUMMARY OF PATIENT SMOKING STATUS BY BASELINE STATUS, TREATMENT GROUP AND VISIT/WEEK
PROTOCOL 157

VISIT	TREATMENT GROUP	BASELINE	VISIT STATUS: SMOKING		VISIT STATUS: NOT-SMOKING		TOTAL
VISIT 12/WEEK 52	SB 207499	SMOKING	122	(91.7%)	11	(8.3%)	133
		NOT-SMOKING	2	(1.3%)	151	(98.7%)	153
		MISSING	0		0		0
		TOTAL	124	(43.4%)	162	(56.6%)	286

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ASSESSED AT BASELINE AND VISIT
2. SUMMARY IS FOR RANDOMIZED PATIENTS

CONFIDENTIAL

14. Efficacy Data Source Tables

Page

TABLE 14A.1A SUMMARY OF AVERAGE CHANGE FROM BASELINE OVER 52 WEEKS (REPEATED MEASURES ANALYSIS) IN PRE-BD TROUGH FEV1 (L) BY SMOKING STATUS-PP 334

TABLE 14A.1B SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN PRE-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP - PP 335

TABLE 14A.1BS SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN PRE-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP - PP BASELINE SMOKERS 336

TABLE 14A.1BT SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN PRE-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP - PP BASELINE NON-SMOKERS 337

TABLE 14A.1BU SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN PRE-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP - PP BASELINE/ON THEPAPY SMOKING STATUS: S/S 338

TABLE 14A.1BV SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN PRE-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP - PP BASELINE/ON THEPAPY NON-SMOKING STATUS: N/N 339

TABLE 14A.1BW SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN PRE-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP - PP BASELINE/ON THEPAPY SMOKING STATUS: N/S OR S/N 340

TABLE 14A.1C DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN PRE-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP - PP BASELINE SMOKERS 341

TABLE 14A.1CS DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN PRE-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP - PP BASELINE SMOKERS 342

TABLE 14A.1CT DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN PRE-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP - PP BASELINE NON-SMOKERS 343

TABLE 14A.1CU DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN PRE-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP - PP BASELINE/ON THERAPY SMOKING STATUS: S/S 344

TABLE 14A.1CV DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN PRE-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP - PP BASELINE/ON THERAPY SMOKING STATUS: N/N 345

TABLE 14A.1CW DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN PRE-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP 346

TABLE 14A.7A SUMMARY OF LEVEL II / III COPD EXACERBATION RATES PER PATIENT YEAR BY TREATMENT GROUP - PP 347

TABLE 14A.7B SUMMARY OF COPD EXACERBATION RATES PER PATIENT YEAR BY TREATMENT GROUP - PP 348

TABLE 14A.7C SUMMARY OF LEVEL II / III EXACERBATION-FREE SURVIVAL BY SMOKING STATUS AND TREATMENT GROUP - PP 349

TABLE 14A.7D SUMMARY OF EXACERBATION-FREE SURVIVAL BY SMOKING STATUS AND TREATMENT GROUP - PP 350

TABLE 14A.7E SUMMARY OF POISSON REGRESSION ON PROGNOSTIC FACTORS FOR TIME TO FIRST LEVEL II / III EXACERBATION - PP 351

TABLE 14A.7F SUMMARY OF POISSON REGRESSION ON PROGNOSTIC FACTORS FOR TIME TO FIRST EXACERBATION - PP 352

TABLE 14.1A SUMMARY OF AVERAGE CHANGE FROM BASELINE OVER 52 WEEKS (REPEATED MEASURES ANALYSIS) IN PRE-BD TROUGH FEV1 (L) BY SMOKING STATUS - ITT 353

TABLE 14.1AX SUMMARY OF AVERAGE CHANGE FROM BASELINE OVER 52 WEEKS (REPEATED MEASURES ANALYSIS) IN PRE-BD TROUGH FEV1 (L) BY REVERSIBILITY - ITT 354

TABLE 14.1B SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN PRE-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP - ITT 355

TABLE 14.1BS SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN PRE-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP - ITT BASELINE SMOKERS 356

TABLE 14.1BT SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN PRE-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP - ITT BASELINE NON-SMOKERS 357

TABLE 14.1BU SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN PRE-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP - ITT BASELINE/ON THERAPY SMOKING STATUS: S/S 358

TABLE 14.1BV SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN PRE-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP - ITT BASELINE/ON THERAPY SMOKING STATUS: N/N 359

TABLE 14.1BW SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN PRE-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP - ITT BASELINE/ON THERAPY SMOKING STATUS: N/S OR S/N 360

TABLE 14.1BX SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN TROUGH FEV1 BY WEEK AND TREATMENT GROUP - ITT NON-REVERSIBLE PATIENTS 361

TABLE 14.1BY SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN TROUGH FEV1 BY WEEK AND TREATMENT GROUP - ITT REVERSIBLE PATIENTS 362

TABLE 14.1C DESCRIPTIVE STATISTICS FOR PRE-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP - ITT 363

TABLE 14.1CS DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN PRE-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP - ITT BASELINE SMOKERS 364

TABLE 14.1CT DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN PRE-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP - ITT BASELINE NON-SMOKERS 365

TABLE 14.1CU DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN PRE-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP - ITT BASELINE/ON THERAPY SMOKING STATUS: S/S 366

TABLE 14.1CV DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN PRE-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP - ITT BASELINE/ON THERAPY SMOKING STATUS: N/N 367

TABLE 14.1CW DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN PRE-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP - ITT BASELINE/ON THERAPY SMOKING STATUS: N/S OR S/N 368

TABLE 14.1I DESCRIPTIVE STATISTICS FOR PRE-BD TROUGH FEV1 (L) AT ENDPOINT BY COUNTRY AND TREATMENT GROUP - ITT 369

TABLE 14.1J DESCRIPTIVE STATISTICS FOR PRE-BD TROUGH FEV1 (L) AT ENDPOINT BY GENDER AND TREATMENT GROUP - ITT 371

TABLE 14.1K DESCRIPTIVE STATISTICS FOR PRE-BD TROUGH FEV1 (L) AT ENDPOINT BY ATS SEVERITY AND TREATMENT GROUP - ITT 372

TABLE 14.1M DESCRIPTIVE STATISTICS FOR PRE-BD TROUGH FEV1 (L) AT ENDPOINT BY REVERSIBILITY AND TREATMENT GROUP - ITT ITT 373

TABLE 14.1N SUMMARY OF TESTS OF SIGNIFICANCE FOR INTERACTION TERMS FOR CHANGE FROM BASELINE IN PRE-BD TROUGH FEV1 (L) - ITT 374

TABLE 14.2A SUMMARY OF AVERAGE CHANGE FROM BASELINE OVER 52 WEEKS (REPEATED MEASURES ANALYSIS) IN TOTAL SCORE OF THE SGRQ - ITT 375

TABLE 14.2AX SUMMARY OF AVERAGE CHANGE FROM BASELINE OVER 52 WEEKS (REPEATED MEASURES ANALYSIS) IN TOTAL SCORE OF THE SGRQ BY REVERSIBILITY - ITT 376

TABLE 14.2B SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN TOTAL SCORE OF THE SGRQ BY WEEK AND TREATMENT GROUP - ITT . 377

TABLE 14.2BS SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN TOTAL SCORE OF THE SGRQ BY WEEK AND TREATMENT GROUP - ITT BASELINE SMOKERS 378

TABLE 14.2BT SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN TOTAL SCORE OF THE SGRQ BY WEEK AND TREATMENT GROUP - ITT BASELINE NON-SMOKERS 379

TABLE 14.2BU SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN TOTAL SCORE OF THE SGRQ BY WEEK AND TREATMENT GROUP - ITT BASELINE/ON-THERAPY SMOKING STATUS: S/S 380

TABLE 14.2BV SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN TOTAL SCORE OF THE SGRQ BY WEEK AND TREATMENT GROUP - ITT BASELINE/ON-THERAPY SMOKING STATUS: N/N 381

TABLE 14.2BW SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN TOTAL SCORE OF THE SGRQ BY WEEK AND TREATMENT GROUP - ITT BASELINE/ON-THERAPY SMOKING STATUS: N/S OR S/N 382

TABLE 14.2BX SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN TOTAL SCORE OF THE SGRQ BY WEEK AND TREATMENT GROUP - ITT NON-REVERSIBLE PATIENTS 383

TABLE 14.2BY SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN TOTAL SCORE OF THE SGRQ BY WEEK AND TREATMENT GROUP - ITT REVERSIBLE PATIENTS 384

TABLE 14.2C DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN TOTAL SCORE OF THE SGRQ BY WEEK AND TREATMENT GROUP - ITT . 385

TABLE 14.2CS DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN TOTAL SCORE OF THE SGRQ BY WEEK AND TREATMENT GROUP - ITT BASELINE SMOKERS 386

TABLE 14.2CT DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN TOTAL SCORE OF THE SGRQ BY WEEK AND TREATMENT GROUP - ITT BASELINE NON-SMOKERS 387

TABLE 14.2CU DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN TOTAL SCORE OF THE SGRQ BY WEEK AND TREATMENT GROUP - ITT BASELINE/ON-THERAPY SMOKING STATUS: S/S 388

TABLE 14.2CV DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN TOTAL SCORE OF THE SGRQ BY WEEK AND TREATMENT GROUP - ITT BASELINE/ON-THERAPY SMOKING STATUS: N/N 389

TABLE 14.2CW DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN TOTAL SCORE OF THE SGRQ BY WEEK AND TREATMENT GROUP - ITT BASELINE/ON-THERAPY SMOKING STATUS: S/N OR N/S 390

TABLE 14.2I DESCRIPTIVE STATISTICS FOR TOTAL SCORE OF THE SGRQ AT ENDPOINT BY COUNTRY AND TREATMENT GROUP - ITT 391

TABLE 14.3A SUMMARY OF AVERAGE CHANGE FROM BASELINE OVER 52 WEEKS (REPEATED MEASURES ANALYSIS) IN POST-BD TROUGH FEV1 (L) BY SMOKING STATUS AND TREATMENT GROUP - ITT 393

TABLE 14.3B SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN POST-BD TROUGH FEV1(L) BY WEEK AND TREATMENT GROUP - ITT . . . 394

TABLE 14.3BS SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN POST-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP - ITT BASELINE SMOKERS 395

TABLE 14.3BT SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN POST-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP - ITT BASELINE NON-SMOKERS 396

TABLE 14.3BU SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN POST-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP - ITT BASELINE/ON THERAPY SMOKING STATUS: S/S 397

TABLE 14.3BV SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN POST-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP - ITT BASELINE/ON THERAPY SMOKING STATUS: N/N 398

TABLE 14.3BW SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN POST-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP - ITT BASELINE/ON THERAPY SMOKING STATUS: N/S OR S/N 399

TABLE 14.3C DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN IN POST-BD TROUGH FEV1(L) BY WEEK AND TREATMENT GROUP - ITT . 400

TABLE 14.3CS DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN POST-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP - ITT BASELINE SMOKERS 401

TABLE 14.3CT DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN POST-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP - ITT BASELINE NON-SMOKERS 402

TABLE 14.3CU DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN POST-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP - ITT BASELINE/ON THERAPY SMOKING STATUS: S/S 403

TABLE 14.3CV DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN POST-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP - ITT BASELINE/ON THERAPY SMOKING STATUS: N/N 404

TABLE 14.3CW DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN POST-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP - ITT BASELINE/ON THERAPY SMOKING STATUS: N/S OR S/N 405

TABLE 14.4A SUMMARY OF AVERAGE CHANGE FROM BASELINE OVER 52 WEEKS (REPEATED MEASURES ANALYSIS) IN SUMMARY SYMPTOM SCORE ITT 406

TABLE 14.4B SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN SUMMARY SYMPTOM SCORE BY WEEK AND TREATMENT GROUP - ITT . 407

TABLE 14.4C DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN IN SUMMARY SYMPTOM SCORE BY WEEK AND TREATMENT GROUP - ITT 408

TABLE 14.5A SUMMARY OF AVERAGE CHANGE FROM BASELINE OVER 52 WEEKS (REPEATED MEASURES ANALYSIS) IN TROUGH FVC (L) ITT 409

TABLE 14.5B SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN TROUGH FVC (L) BY WEEK AND TREATMENT GROUP - ITT 410

TABLE 14.5C DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN TROUGH FVC(L) BY WEEK AND TREATMENT GROUP - ITT 411

TABLE 14.6A SUMMARY OF AVERAGE CHANGE FROM BASELINE OVER 52 WEEKS (REPEATED MEASURES ANALYSIS) OF PERCENT OF DAYS SYMPTOM FREE - ITT 412

TABLE 14.6B SUMMARY STATISTICS FOR PERCENT OF DAYS SYMPTOM FREE BY WEEK AND TREATMENT GROUP - ITT 413

TABLE 14.6C DESCRIPTIVE STATISTICS FOR PERCENT OF DAYS SYMPTOM FREE BY WEEK AND TREATMENT GROUP - ITT 414

TABLE 14.7A SUMMARY OF LEVEL II / III COPD EXACERBATION RATES PER PATIENT YEAR BY TREATMENT GOUP - ALL RANDOMIZED PATIENTS . . 415

TABLE 14.7B SUMMARY OF COPD EXACERBATION RATES PER PATIENT YEAR BY TREATMENT GROUP - ALL RANDOMIZED PATIENTS 416

TABLE 14.7C SUMMARY OF LEVEL II / III EXACERBATION-FREE SURVIVAL BY SMOKING STATUS AND TREATMENT - ALL RANDOMIZED PATIENTS . 417

TABLE 14.7D SUMMARY OF EXACERBATION-FREE SURVIVAL BY SMOKING STATUS AND TREATMENT - ALL RANDOMIZED PATIENTS 418

TABLE 14.7E SUMMARY OF POISSON REGRESSION ON PROGNOSTIC FACTORS FOR LEVEL II / III EXACERBATIONS - ALL RANDOMIZED PATIENTS 419

TABLE 14.7F SUMMARY OF POISSON REGRESSION ON PROGNOSTIC FACTORS FOR EXACERBATIONS - ALL RANDOMIZED PATIENTS 420

TABLE 14.7H FREQUENCY AND RATE OF COPD EXACERBATIONS BY LEVEL, BASELINE/ON-THERAPY SMOKING STATUS AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS 421

TABLE 14.7I SUMMARY OF COPD EXACERBATION RATES PER PATIENT YEAR BY COUNTRY AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS 423

TABLE 14.7J SUMMARY OF COPD EXACERBATION RATES PER PATIENT YEAR BY GENDER AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS 426

TABLE 14.7K SUMMARY OF COPD EXACERBATION RATES PER PATIENT YEAR BY ATS SEVERITY AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS 427

TABLE 14.7N SUMMARY OF LEVEL II/III COPD EXACERBATION RATES PER PATIENT YEAR BY REVERSIBILITY AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS 428

TABLE 14.7O SUMMARY OF COPD EXACERBATION RATES PER PATIENT YEAR BY REVERSIBILITY AND TREATMENT GROUP - ALL RANDOMIZED PATIENTS 431

TABLE 14.7R SUMMARY OF MARGINAL REGRESSION ANALYSIS OF TIME TO MULTIPLE EXACERBATION - ALL RANDOMIZED PATIENTS 434

TABLE 14.7S DURATION (DAYS) OF EXACERBATION BY TREATMENT GROUP - ALL RANDOMIZED PATIENTS 435

TABLE 14.7T SUMMARY OF LEVEL II / III COPD EXACERBATION RATES PER PATIENT YEAR BY SMOKING STATUS AND TREATMENT GOUP - ALL RANDOMIZED PATIENTS 436

TABLE 14.7U SUMMARY OF EXACERBATION RATES PER PATIENT YEAR BY SMOKING STATUS AND TREATMENT GOUP - ALL RANDOMIZED PATIENTS 437

TABLE 14.7X SUMMARY OF LEVEL II / III EXACERBATION-FREE SURVIVAL BY REVERSIBILITY AND TREATMENT - ALL RANDOMIZED PATIENTS 438

TABLE 14.7Y SUMMARY OF EXACERBATION-FREE SURVIVAL BY REVERSIBILITY AND TREATMENT - ALL RANDOMIZED PATIENTS 439

TABLE 14.8A SUMMARY OF AVERAGE CHANGE FROM BASELINE OVER 52 WEEKS (REPEATED MEASURES ANALYSIS) IN BRONCHODILATOR EFFECT - ITT 440

TABLE 14.8B SUMMARY STATISTICS FOR BRONCHODILATOR EFFECT BY WEEK AND TREATMENT GROUP - ITT 441

TABLE 14.8C DESCRIPTIVE STATISTICS FOR BRONCHODILATOR EFFECT BY WEEK AND TREATMENT GROUP - ITT 442

TABLE 14.9A SUMMARY OF AVERAGE CHANGE FROM BASELINE OVER 52 WEEKS (REPEATED MEASURES ANALYSIS) IN TROUGH PEF(L/MIN) - ITT 443

TABLE 14.9B SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN TROUGH PEF (L/MIN) BY WEEK AND TREATMENT GROUP - ITT 444

TABLE 14.9C DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN TROUGH PEF(L/MIN) BY WEEK AND TREATMENT GROUP - ITT 445

TABLE 14.1O SUMMARY OF TESTS OF SIGNIFICANCE FOR PROGNOSTIC FACTORS EFFECTING CHANGE FROM BASELINE IN TROUGH FEV1 (L) - ITT 446

TABLE 14.10A SUMMARY OF AVERAGE CHANGE FROM BASELINE OVER 52 WEEKS (REPEATED MEASURES ANALYSIS) IN DOMICILIARY PEF(L/MIN) BY SMOKING STATUS - ITT 447

TABLE 14.10B SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN DOMICILIARY PEF (L/MIN) BY WEEK AND TREATMENT GROUP - ITT 448

TABLE 14.10C DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN DOMICILIARY PEF(L/MIN) BY WEEK AND TREATMENT GROUP - ITT 449

TABLE 14.11B SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN EQ-5D TARRIF HEALTH STATE BY WEEK AND TREATMENT GROUP - ITT 450

TABLE 14.11C DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN EQ-5D TARRIF HEALTH STATE BY WEEK AND TREATMENT GROUP - ITT 451

TABLE 14.12B SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN EQ-5D THERMOMETER HEALTH SCALE BY WEEK AND TREATMENT GROUP - ITT 452

TABLE 14.12C DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN EQ-5D THERMOMETER HEALTH SCALE BY WEEK AND TREATMENT GROUP - ITT 453

TABLE 14.14B SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN CD4+/CD8+ RATIO BY WEEK AND TREATMENT GROUP - ITT 454

TABLE 14.14C DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN CD4+/CD8+ RATIO BY WEEK AND TREATMENT GROUP - ITT 455

TABLE 14.15B SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN RESIDUAL VOLUME BY WEEK AND TREATMENT GROUP - ITT 456

TABLE 14.15C DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN RESIDUAL VOLUME BY WEEK AND TREATMENT GROUP - ITT 457

TABLE 14.16B SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN SERUM C REACTIVE PROTEIN (MG) BY WEEK AND TREATMENT GROUP - ITT 458

TABLE 14.16C DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN SERUM C REACTIVE PROTEIN (MG) BY WEEK AND TREATMENT GROUP - ITT 459

TABLE 14.21A SUMMARY OF AVERAGE CHANGE FROM BASELINE OVER 52 WEEKS (REPEATED MEASURES ANALYSIS) IN ACTIVITY SCORE OF THE SGRQ - ITT 460

TABLE 14.21B SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN ACTIVITY SCORE OF THE SGRQ BY WEEK AND TREATMENT GROUP - ITT 461

TABLE 14.21C DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN ACTIVITY SCORE OF THE SGRQ BY WEEK AND TREATMENT GROUP - ITT 462

TABLE 14.22A SUMMARY OF AVERAGE CHANGE FROM BASELINE OVER 52 WEEKS (REPEATED MEASURES ANALYSIS) IN IMPACT SCORE OF THE SGRQ - ITT. 463

TABLE 14.22B SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN IMPACT SCORE OF THE SGRQ BY WEEK AND TREATMENT GROUP - ITT 464

TABLE 14.22C DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN IMPACT SCORE OF THE SGRQ BY WEEK AND TREATMENT GROUP - ITT 465

TABLE 14.23A SUMMARY OF AVERAGE CHANGE FROM BASELINE OVER 52 WEEKS (REPEATED MEASURES ANALYSIS) IN SYMPTOMS SCORE OF THE SGRQ - ITT 466

TABLE 14.23B SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN SYMPTOMS SCORE OF THE SGRQ BY WEEK AND TREATMENT GROUP - ITT 467

TABLE 14.23C DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN SYMPTOMS SCORE OF THE SGRQ BY WEEK AND TREATMENT GROUP - ITT 468

TABLE 14.24A SUMMARY OF AVERAGE CHANGE FROM BASELINE OVER 52 WEEKS (REPEATED MEASURES ANALYSIS) IN TROUGH FEF25-75 (L/SEC) - ITT 469

TABLE 14.24B SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN TROUGH FEF25-75 (L/SEC) BY WEEK AND TREATMENT GROUP - ITT . . . 470

TABLE 14.24C DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN TROUGH FEF25-75 (L/SEC) BY WEEK AND TREATMENT GROUP - ITT . . . 471

TABLE 14.25A SUMMARY OF AVERAGE CHANGE FROM BASELINE OVER 52 WEEKS (REPEATED MEASURES ANALYSIS) IN DOMICILIARY COUGH - ITT 472

TABLE 14.25B SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN DOMICILIARY COUGH BY WEEK AND TREATMENT GROUP - ITT 473

TABLE 14.25C DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN DOMICILIARY COUGH BY WEEK AND TREATMENT GROUP - ITT 474

TABLE 14.26A SUMMARY OF AVERAGE CHANGE FROM BASELINE OVER 52 WEEKS (REPEATED MEASURES ANALYSIS) IN DOMICILIARY SPUTUM - ITT 475

TABLE 14.26B SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN DOMICILIARY SPUTUM BY WEEK AND TREATMENT GROUP - ITT 476

TABLE 14.26C DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN DOMICILIARY SPUTUM BY WEEK AND TREATMENT GROUP - ITT 477

TABLE 14.27A SUMMARY OF AVERAGE CHANGE FROM BASELINE OVER 52 WEEKS (REPEATED MEASURES ANALYSIS) IN DOMICILIARY BREATHLESSNESS - ITT 478

TABLE 14.27B SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN DOMICILIARY BREATHLESSNESS BY WEEK AND TREATMENT GROUP - ITT 479

TABLE 14.27C DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN DOMICILIARY BREATHLESSNESS BY WEEK AND TREATMENT GROUP - ITT 480

TABLE 14.30 AVERAGE DAILY INHALER USE BY TREATMENT GROUP - ITT . . 481

TABLE 14.31 PERCENT OF DAYS WHITOUT SALBUTAMOL BY TREATMENT GROUP - ITT 482

TABLE 14.32 AVERAGE NUMBER OF NIGHTTIME AWAKENINGS BY TREATMENT GROUP - ITT 483

TABLE 14.33 AVERAGE DAILY BREATHLESSNESS SCORE BY TREATMENT GROUP - ITT 484

TABLE 14.34 AVERAGE DAILY COUGHING SCORE BY TREATMENT GROUP - ITT 485

TABLE 14.35 AVERAGE DAILY SPUTUM QUANTITY BY TREATMENT GROUP - ITT 486

TABLE 14.36 AVERAGE DAILY SPUTUM COLOUR BY TREATMENT GROUP - ITT 487

TABLE 14.37 AVERAGE DAILY MISSED TIME FROM WORK OR USUAL ACTIVITIES BY TREATMENT GROUP - ITT 488

TABLE 14.38 AVERAGE DAILY CAREGIVER ASSISTANCE BY TREATMENT GROUP - ITT 489

TABLE 14.41 INVESTIGATOR GLOBAL ASSESSMENTS BY TREATMENT GROUP - ITT 490

TABLE 14.42 PATIENT GLOBAL ASSESSMENTS BY TREATMENT GROUP - ITT 491

TABLE 14.1O2 SUMMARY OF ANALYSES OF CONTINUOUS PROGNOSTIC FACTORS AFFECTING CHANGE FROM BASELINE IN TROUGH FEV1 (L) - ITT 492

TABLE 14.1O3 SUMMARY OF ANALYSES OF CATEGORICAL PROGNOSTIC FACTORS AFFECTING CHANGE FROM BASELINE IN TROUGH FEV1 (L) - ITT 493

SB 207499

TABLE 14A.1A

SUMMARY OF AVERAGE CHANGE FROM BASELINE OVER 52 WEEKS (REPEATED MEASURES ANALYSIS) IN PRE-BD TROUGH FEV1 (L) BY SMOKING STATUS-PP
PROTOCOL 157

			BASELINE		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
SMOKING STATUS BASELINE/ON-THERAPY	TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
S/-	PLACEBO	164	1.528	0.044	-0.051	0.015	-0.081	-0.021	.	.	.	
	SB 207499	157	1.412	0.043	-0.003	0.015	-0.032	0.026	0.048	0.013	0.083	0.007*
N/-	PLACEBO	194	1.361	0.035	-0.051	0.012	-0.074	-0.027	.	.	.	
	SB 207499	174	1.316	0.037	-0.012	0.013	-0.037	0.014	0.039	0.010	0.068	0.009*
S/S	PLACEBO	130	1.530	0.054	-0.059	0.018	-0.096	-0.023	.	.	.	
	SB 207499	129	1.397	0.054	-0.013	0.018	-0.049	0.024	0.046	0.007	0.086	0.023*
N/N	PLACEBO	179	1.348	0.035	-0.048	0.012	-0.072	-0.024	.	.	.	
	SB 207499	167	1.316	0.037	-0.008	0.013	-0.034	0.018	0.040	0.010	0.070	0.009*
S/N or N/S	PLACEBO	49	1.525	0.069	-0.050	0.024	-0.097	-0.002	.	.	.	
	SB 207499	35	1.437	0.076	-0.018	0.026	-0.069	0.033	0.031	-0.031	0.094	0.324
All Patients	PLACEBO	358	1.429	0.026	-0.046	0.009	-0.064	-0.028	.	.	.	
	SB 207499	331	1.354	0.027	-0.005	0.009	-0.023	0.014	0.041	0.019	0.064	0.000*

1.MEANS ARE ADJUSTED FOR BASELINE VALUE, COUNTRY AND WEEK
2. STATISTICS ARE REPORTED BASED ON THE MAXIMUM OF THREE REPORTED VALUES OF FEV1 (L)
3. * SIGNIFICANTLY DIFFERENT FROM PLACEBO
4. SMOKING STATUS: S= SMOKER ; N= NON-SMOKER ; - = EITHER

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14A.1B

SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN PRE-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP - PP
PROTOCOL 157

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	359	1.426	0.026	.	.	.	.	.	.	.	.
	SB 207499	337	1.349	0.026	.	.	.	.	.	.	.	.
WEEK 4	PLACEBO	339	1.340	0.011	-0.035	0.011	-0.057	-0.014	.	.	.	.
	SB 207499	309	1.383	0.011	0.008	0.011	-0.015	0.031	0.043	0.015	0.072	0.003
WEEK 8	PLACEBO	325	1.367	0.012	-0.017	0.012	-0.040	0.006	.	.	.	.
	SB 207499	297	1.384	0.012	0.001	0.012	-0.024	0.025	0.017	-0.013	0.047	0.258
WEEK 12	PLACEBO	313	1.358	0.012	-0.031	0.012	-0.055	-0.007	.	.	.	.
	SB 207499	279	1.404	0.013	0.015	0.013	-0.010	0.040	0.046	0.015	0.077	0.003
WEEK 20	PLACEBO	301	1.334	0.014	-0.057	0.014	-0.084	-0.029	.	.	.	.
	SB 207499	267	1.390	0.015	-0.000	0.015	-0.029	0.029	0.057	0.022	0.092	0.002
WEEK 28	PLACEBO	281	1.343	0.014	-0.057	0.014	-0.084	-0.030	.	.	.	.
	SB 207499	250	1.395	0.015	-0.005	0.015	-0.034	0.024	0.052	0.016	0.087	0.004
WEEK 36	PLACEBO	267	1.351	0.016	-0.049	0.016	-0.079	-0.018	.	.	.	.
	SB 207499	247	1.373	0.016	-0.027	0.016	-0.058	0.005	0.022	-0.017	0.061	0.267
WEEK 44	PLACEBO	258	1.329	0.015	-0.069	0.015	-0.099	-0.039	.	.	.	.
	SB 207499	234	1.383	0.016	-0.015	0.016	-0.046	0.017	0.054	0.016	0.093	0.006
WEEK 52	PLACEBO	249	1.345	0.015	-0.054	0.015	-0.084	-0.024	.	.	.	.
	SB 207499	225	1.390	0.016	-0.009	0.016	-0.040	0.022	0.045	0.007	0.082	0.019
ENDPOINT	PLACEBO	359	1.310	0.012	-0.064	0.012	-0.087	-0.041	.	.	.	.
	SB 207499	337	1.357	0.012	-0.017	0.012	-0.040	0.007	0.047	0.017	0.077	0.002

1. MEANS ARE ADJUSTED FOR BASELINE VALUE AND COUNTRY
2. BASELINE = VISIT 3; WEEK 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 5, 6, 7, 8, 9, 10, 11, 12; ENDPOINT = LOCF
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14A.1BS

SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN PRE-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP
- PP BASELINE SMOKERS
PROTOCOL 157

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	165	1.525	0.044	.	.	.	.	.	.	.	.
	SB 207499	160	1.412	0.042	.	.	.	.	.	.	.	.
WEEK 4	PLACEBO	153	1.397	0.018	-0.062	0.018	-0.097	-0.027	.	.	.	.
	SB 207499	144	1.460	0.017	0.001	0.017	-0.033	0.035	0.063	0.020	0.105	0.004
WEEK 8	PLACEBO	146	1.440	0.020	-0.019	0.020	-0.058	0.020	.	.	.	.
	SB 207499	143	1.463	0.019	0.004	0.019	-0.034	0.042	0.023	-0.024	0.070	0.333
WEEK 12	PLACEBO	143	1.429	0.021	-0.026	0.021	-0.068	0.016	.	.	.	.
	SB 207499	134	1.467	0.021	0.013	0.021	-0.029	0.054	0.039	-0.011	0.088	0.129
WEEK 20	PLACEBO	140	1.389	0.024	-0.064	0.024	-0.112	-0.017	.	.	.	.
	SB 207499	131	1.453	0.024	0.000	0.024	-0.047	0.047	0.064	0.007	0.122	0.027
WEEK 28	PLACEBO	127	1.414	0.023	-0.058	0.023	-0.103	-0.013	.	.	.	.
	SB 207499	123	1.480	0.022	0.008	0.022	-0.036	0.051	0.066	0.011	0.120	0.019
WEEK 36	PLACEBO	124	1.391	0.027	-0.074	0.027	-0.128	-0.021	.	.	.	.
	SB 207499	123	1.439	0.026	-0.026	0.026	-0.077	0.024	0.048	-0.013	0.109	0.122
WEEK 44	PLACEBO	121	1.378	0.026	-0.080	0.026	-0.131	-0.028	.	.	.	.
	SB 207499	116	1.439	0.025	-0.019	0.025	-0.068	0.031	0.061	0.000	0.122	0.049
WEEK 52	PLACEBO	115	1.401	0.028	-0.066	0.028	-0.120	-0.011	.	.	.	.
	SB 207499	110	1.460	0.026	-0.006	0.026	-0.057	0.045	0.060	0.000	0.119	0.049
ENDPOINT	PLACEBO	165	1.381	0.020	-0.071	0.020	-0.110	-0.031	.	.	.	.
	SB 207499	160	1.430	0.019	-0.021	0.019	-0.060	0.017	0.049	0.002	0.097	0.043

1. MEANS ARE ADJUSTED FOR BASELINE VALUE AND COUNTRY
2. BASELINE = VISIT 3; WEEK 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 5, 6, 7, 8, 9, 10, 11, 12; ENDPOINT = LOCF
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14A.1BT

SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN PRE-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP
- PP BASELINE NON-SMOKERS
PROTOCOL 157

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	194	1.357	0.035	.	.	.	.	.	.	.	.
	SB 207499	177	1.306	0.037	.	.	.	.	.	.	.	.
WEEK 4	PLACEBO	186	1.283	0.016	-0.022	0.016	-0.052	0.009	.	.	.	.
	SB 207499	165	1.316	0.017	0.011	0.017	-0.022	0.044	0.032	-0.006	0.071	0.096
WEEK 8	PLACEBO	179	1.292	0.016	-0.026	0.016	-0.057	0.005	.	.	.	.
	SB 207499	154	1.306	0.017	-0.012	0.017	-0.046	0.023	0.015	-0.024	0.053	0.454
WEEK 12	PLACEBO	170	1.292	0.016	-0.038	0.016	-0.070	-0.006	.	.	.	.
	SB 207499	145	1.346	0.018	0.015	0.018	-0.020	0.050	0.053	0.014	0.092	0.007
WEEK 20	PLACEBO	161	1.265	0.018	-0.069	0.018	-0.104	-0.033	.	.	.	.
	SB 207499	136	1.316	0.020	-0.018	0.020	-0.057	0.022	0.051	0.007	0.095	0.022
WEEK 28	PLACEBO	154	1.276	0.019	-0.060	0.019	-0.098	-0.022	.	.	.	.
	SB 207499	127	1.314	0.022	-0.021	0.022	-0.064	0.021	0.039	-0.009	0.086	0.113
WEEK 36	PLACEBO	143	1.306	0.021	-0.033	0.021	-0.074	0.008	.	.	.	.
	SB 207499	124	1.312	0.023	-0.027	0.023	-0.071	0.018	0.006	-0.045	0.057	0.810
WEEK 44	PLACEBO	137	1.268	0.020	-0.074	0.020	-0.113	-0.034	.	.	.	.
	SB 207499	118	1.319	0.022	-0.023	0.022	-0.067	0.020	0.050	0.001	0.100	0.046
WEEK 52	PLACEBO	134	1.291	0.021	-0.047	0.021	-0.088	-0.006	.	.	.	.
	SB 207499	115	1.322	0.023	-0.016	0.023	-0.061	0.029	0.031	-0.017	0.080	0.207
ENDPOINT	PLACEBO	194	1.242	0.016	-0.064	0.016	-0.095	-0.034	.	.	.	.
	SB 207499	177	1.285	0.016	-0.021	0.016	-0.053	0.012	0.044	0.005	0.082	0.026

1. MEANS ARE ADJUSTED FOR BASELINE VALUE AND COUNTRY
2. BASELINE = VISIT 3; WEEK 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 5, 6, 7, 8, 9, 10, 11, 12; ENDPOINT = LOCF
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14A.1BU

SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN PRE-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP
- PP BASELINE/ON THEPAPY SMOKING STATUS: S/S
PROTOCOL 157

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	131	1.532	0.053	.	.	.	.	.	.	.	.
	SB 207499	132	1.407	0.052	.	.	.	.	.	.	.	.
WEEK 4	PLACEBO	123	1.396	0.021	-0.075	0.021	-0.117	-0.034	.	.	.	.
	SB 207499	119	1.459	0.021	-0.013	0.021	-0.055	0.029	0.062	0.015	0.110	0.010
WEEK 8	PLACEBO	118	1.452	0.026	-0.025	0.026	-0.075	0.026	.	.	.	.
	SB 207499	118	1.473	0.025	-0.004	0.025	-0.053	0.046	0.021	-0.032	0.075	0.435
WEEK 12	PLACEBO	116	1.451	0.026	-0.026	0.026	-0.078	0.026	.	.	.	.
	SB 207499	111	1.494	0.026	0.017	0.026	-0.035	0.069	0.043	-0.016	0.101	0.150
WEEK 20	PLACEBO	110	1.410	0.030	-0.070	0.030	-0.129	-0.012	.	.	.	.
	SB 207499	106	1.489	0.030	0.009	0.030	-0.050	0.067	0.079	0.013	0.145	0.019
WEEK 28	PLACEBO	104	1.406	0.028	-0.087	0.028	-0.142	-0.032	.	.	.	.
	SB 207499	100	1.468	0.028	-0.025	0.028	-0.080	0.029	0.062	-0.001	0.125	0.054
WEEK 36	PLACEBO	102	1.397	0.032	-0.084	0.032	-0.147	-0.021	.	.	.	.
	SB 207499	100	1.442	0.032	-0.039	0.032	-0.102	0.024	0.045	-0.022	0.112	0.183
WEEK 44	PLACEBO	101	1.388	0.033	-0.090	0.033	-0.155	-0.026	.	.	.	.
	SB 207499	92	1.469	0.034	-0.010	0.034	-0.078	0.058	0.081	0.012	0.150	0.022
WEEK 52	PLACEBO	97	1.416	0.031	-0.065	0.031	-0.126	-0.003	.	.	.	.
	SB 207499	90	1.467	0.032	-0.015	0.032	-0.079	0.049	0.050	-0.016	0.116	0.135
ENDPOINT	PLACEBO	131	1.396	0.024	-0.076	0.024	-0.123	-0.029	.	.	.	.
	SB 207499	132	1.438	0.024	-0.034	0.024	-0.081	0.012	0.041	-0.012	0.095	0.126

1. MEANS ARE ADJUSTED FOR BASELINE VALUE AND COUNTRY
2. BASELINE = VISIT 3; WEEK 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 5, 6, 7, 8, 9, 10, 11, 12; ENDPOINT = LOCF
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14A.1BV

SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN PRE-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP
- PP BASELINE/ON THEPAPY NON-SMOKING STATUS: N/N
PROTOCOL 157

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	179	1.345	0.035	.	.	.	.	.	.	.	.
	SB 207499	170	1.307	0.037	.	.	.	.	.	.	.	.
WEEK 4	PLACEBO	172	1.275	0.016	-0.021	0.016	-0.053	0.010	.	.	.	.
	SB 207499	158	1.311	0.017	0.014	0.017	-0.019	0.048	0.035	-0.004	0.075	0.080
WEEK 8	PLACEBO	165	1.285	0.016	-0.024	0.016	-0.056	0.008	.	.	.	.
	SB 207499	148	1.297	0.018	-0.012	0.018	-0.047	0.023	0.012	-0.028	0.052	0.558
WEEK 12	PLACEBO	155	1.282	0.017	-0.036	0.017	-0.068	-0.003	.	.	.	.
	SB 207499	142	1.337	0.018	0.019	0.018	-0.015	0.054	0.055	0.015	0.095	0.007
WEEK 20	PLACEBO	149	1.253	0.018	-0.069	0.018	-0.106	-0.033	.	.	.	.
	SB 207499	131	1.311	0.020	-0.011	0.020	-0.051	0.029	0.058	0.014	0.103	0.011
WEEK 28	PLACEBO	140	1.268	0.019	-0.055	0.019	-0.092	-0.017	.	.	.	.
	SB 207499	125	1.305	0.021	-0.017	0.021	-0.059	0.024	0.037	-0.009	0.084	0.117
WEEK 36	PLACEBO	133	1.302	0.021	-0.026	0.021	-0.067	0.015	.	.	.	.
	SB 207499	123	1.301	0.022	-0.027	0.022	-0.071	0.017	-0.001	-0.051	0.050	0.983
WEEK 44	PLACEBO	126	1.266	0.020	-0.064	0.020	-0.105	-0.024	.	.	.	.
	SB 207499	116	1.305	0.022	-0.026	0.022	-0.069	0.017	0.039	-0.011	0.089	0.130
WEEK 52	PLACEBO	123	1.281	0.022	-0.046	0.022	-0.089	-0.004	.	.	.	.
	SB 207499	113	1.310	0.023	-0.018	0.023	-0.063	0.028	0.029	-0.022	0.079	0.263
ENDPOINT	PLACEBO	179	1.236	0.016	-0.060	0.016	-0.092	-0.029	.	.	.	.
	SB 207499	170	1.278	0.017	-0.019	0.017	-0.053	0.014	0.041	0.001	0.081	0.043

1. MEANS ARE ADJUSTED FOR BASELINE VALUE AND COUNTRY
2. BASELINE = VISIT 3; WEEK 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 5, 6, 7, 8, 9, 10, 11, 12; ENDPOINT = LOCF
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14A.1BW

SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN PRE-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP
- PP BASELINE/ON THEPAPY SMOKING STATUS: N/S OR S/N
PROTOCOL 157

		WEEKLY ASSESSMENT			CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	49	1.525	0.069	.	.	.	.	.	.	.	.
	SB 207499	35	1.437	0.076	.	.	.	.	.	.	.	.
WEEK 4	PLACEBO	44	1.374	0.033	-0.037	0.033	-0.104	0.030	.	.	.	.
	SB 207499	32	1.421	0.036	0.011	0.036	-0.061	0.082	0.048	-0.041	0.137	0.288
WEEK 8	PLACEBO	42	1.374	0.033	-0.026	0.033	-0.093	0.041	.	.	.	.
	SB 207499	31	1.422	0.037	0.021	0.037	-0.053	0.095	0.047	-0.048	0.142	0.324
WEEK 12	PLACEBO	42	1.364	0.034	-0.038	0.034	-0.107	0.030	.	.	.	.
	SB 207499	26	1.337	0.038	-0.065	0.038	-0.142	0.011	-0.027	-0.123	0.069	0.574
WEEK 20	PLACEBO	42	1.339	0.038	-0.049	0.038	-0.125	0.028	.	.	.	.
	SB 207499	30	1.297	0.043	-0.090	0.043	-0.175	-0.005	-0.042	-0.152	0.068	0.451
WEEK 28	PLACEBO	37	1.394	0.044	-0.030	0.044	-0.119	0.059	.	.	.	.
	SB 207499	25	1.420	0.047	-0.004	0.047	-0.100	0.091	0.026	-0.104	0.155	0.691
WEEK 36	PLACEBO	32	1.340	0.060	-0.095	0.060	-0.216	0.026	.	.	.	.
	SB 207499	24	1.380	0.061	-0.055	0.061	-0.179	0.068	0.040	-0.130	0.210	0.637
WEEK 44	PLACEBO	31	1.317	0.046	-0.091	0.046	-0.184	0.002	.	.	.	.
	SB 207499	26	1.357	0.047	-0.052	0.047	-0.146	0.043	0.040	-0.089	0.168	0.536
WEEK 52	PLACEBO	29	1.379	0.050	-0.049	0.050	-0.151	0.053	.	.	.	.
	SB 207499	22	1.444	0.055	0.016	0.055	-0.095	0.127	0.065	-0.078	0.209	0.363
ENDPOINT	PLACEBO	49	1.330	0.036	-0.056	0.036	-0.128	0.015	.	.	.	.
	SB 207499	35	1.381	0.038	-0.005	0.038	-0.081	0.072	0.052	-0.045	0.148	0.288

1. MEANS ARE ADJUSTED FOR BASELINE VALUE AND COUNTRY
2. BASELINE = VISIT 3; WEEK 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 5, 6, 7, 8, 9, 10, 11, 12; ENDPOINT = LOCF
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14A.1C

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN PRE-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP
- PP BASELINE SMOKERS
PROTOCOL 157

		BASELINE		WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	359	1.409	0.449	1.409	0.449	1.360	0.510	2.920	.	.	.	.	.
	SB 207499	337	1.336	0.446	1.336	0.446	1.280	0.490	2.800	.	.	.	.	.
WEEK 4	PLACEBO	339	1.409	0.449	1.378	0.459	1.320	0.510	2.840	-0.030	0.175	-0.030	-0.660	0.650
	SB 207499	309	1.338	0.447	1.352	0.470	1.280	0.480	3.180	0.014	0.192	0.000	-0.690	0.980
WEEK 8	PLACEBO	325	1.430	0.451	1.421	0.470	1.360	0.490	3.130	-0.010	0.189	-0.010	-0.510	0.740
	SB 207499	297	1.332	0.447	1.344	0.476	1.280	0.350	2.990	0.012	0.185	0.010	-0.760	0.820
WEEK 12	PLACEBO	313	1.433	0.454	1.405	0.476	1.360	0.480	3.340	-0.028	0.199	-0.030	-0.620	0.900
	SB 207499	279	1.339	0.454	1.359	0.484	1.260	0.520	2.930	0.020	0.179	0.000	-0.500	0.880
WEEK 20	PLACEBO	301	1.424	0.455	1.380	0.482	1.350	0.520	3.380	-0.044	0.224	-0.050	-0.730	1.000
	SB 207499	267	1.353	0.451	1.366	0.483	1.320	0.470	2.830	0.013	0.198	0.020	-0.690	0.800
WEEK 28	PLACEBO	281	1.432	0.459	1.389	0.503	1.360	0.510	3.810	-0.044	0.223	-0.050	-0.710	0.970
	SB 207499	250	1.364	0.452	1.374	0.481	1.345	0.450	3.160	0.010	0.187	0.005	-0.580	0.670
WEEK 36	PLACEBO	267	1.433	0.459	1.396	0.502	1.370	0.460	3.400	-0.037	0.245	-0.050	-0.890	0.820
	SB 207499	247	1.364	0.458	1.352	0.486	1.270	0.470	2.960	-0.012	0.200	-0.020	-0.580	0.700
WEEK 44	PLACEBO	258	1.443	0.457	1.397	0.496	1.335	0.570	3.180	-0.046	0.231	-0.050	-0.680	1.010
	SB 207499	234	1.348	0.448	1.360	0.477	1.310	0.490	2.920	0.013	0.210	0.010	-0.640	0.720
WEEK 52	PLACEBO	249	1.429	0.456	1.384	0.479	1.360	0.500	2.950	-0.045	0.210	-0.060	-0.600	0.590
	SB 207499	225	1.366	0.451	1.370	0.463	1.340	0.450	2.860	0.004	0.207	0.010	-0.660	0.790
ENDPOINT	PLACEBO	359	1.409	0.449	1.354	0.470	1.320	0.460	3.180	-0.055	0.210	-0.060	-0.800	0.590
	SB 207499	337	1.336	0.446	1.332	0.457	1.270	0.350	2.960	-0.004	0.201	0.000	-0.690	0.790

1. STATISITCS ARE REPORTED BASED ON THE VALUE CORRESPONDING TO THE MAXIMUM FEV1 (L)
2. MEAN VALUES ARE SAMPLE MEANS
3. BASELINE = VISIT 3; WEEK 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 5, 6, 7, 8, 9, 10, 11, 12; ENDPOINT = LOCF

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14A.1CS

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN PRE-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP
- PP BASELINE SMOKERS
PROTOCOL 157

			BASELINE		WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	165	1.512	0.448	1.512	0.448	1.500	0.620	2.920	.	.	.	.	.
	SB 207499	160	1.388	0.487	1.388	0.487	1.335	0.490	2.800	.	.	.	.	.
WEEK 4	PLACEBO	153	1.517	0.442	1.466	0.449	1.420	0.570	2.780	-0.051	0.176	-0.050	-0.660	0.460
	SB 207499	144	1.396	0.488	1.409	0.511	1.360	0.530	3.180	0.013	0.188	0.010	-0.690	0.560
WEEK 8	PLACEBO	146	1.547	0.444	1.535	0.464	1.530	0.500	3.130	-0.012	0.206	-0.020	-0.510	0.740
	SB 207499	143	1.369	0.486	1.389	0.517	1.340	0.490	2.990	0.019	0.187	0.020	-0.600	0.550
WEEK 12	PLACEBO	143	1.540	0.449	1.517	0.475	1.500	0.570	3.300	-0.023	0.227	-0.020	-0.620	0.900
	SB 207499	134	1.364	0.492	1.390	0.509	1.265	0.570	2.920	0.026	0.174	0.020	-0.470	0.490
WEEK 20	PLACEBO	140	1.521	0.457	1.489	0.491	1.445	0.600	3.210	-0.032	0.260	-0.030	-0.730	1.000
	SB 207499	131	1.381	0.489	1.415	0.524	1.320	0.580	2.830	0.034	0.202	0.030	-0.650	0.800
WEEK 28	PLACEBO	127	1.532	0.462	1.497	0.514	1.440	0.510	3.120	-0.035	0.234	-0.030	-0.710	0.920
	SB 207499	123	1.411	0.494	1.445	0.518	1.380	0.580	3.160	0.035	0.193	0.020	-0.560	0.670
WEEK 36	PLACEBO	124	1.533	0.458	1.495	0.508	1.470	0.510	3.400	-0.038	0.266	-0.060	-0.890	0.760
	SB 207499	123	1.397	0.504	1.406	0.529	1.280	0.470	2.960	0.009	0.203	-0.010	-0.470	0.700
WEEK 44	PLACEBO	121	1.532	0.454	1.487	0.494	1.440	0.570	3.180	-0.045	0.253	-0.060	-0.680	1.010
	SB 207499	116	1.379	0.484	1.403	0.509	1.310	0.540	2.920	0.024	0.220	0.025	-0.590	0.670
WEEK 52	PLACEBO	115	1.522	0.447	1.469	0.464	1.460	0.500	2.670	-0.053	0.236	-0.060	-0.600	0.530
	SB 207499	110	1.408	0.493	1.424	0.496	1.440	0.540	2.860	0.016	0.204	0.015	-0.660	0.500
ENDPOINT	PLACEBO	165	1.512	0.448	1.449	0.482	1.450	0.500	3.180	-0.063	0.229	-0.060	-0.700	0.530
	SB 207499	160	1.388	0.487	1.389	0.487	1.370	0.540	2.960	0.001	0.207	0.010	-0.690	0.500

1. STATISITCS ARE REPORTED BASED ON THE VALUE CORRESPONDING TO THE MAXIMUM FEV1 (L)
2. MEAN VALUES ARE SAMPLE MEANS
3. BASELINE = VISIT 3; WEEK 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 5, 6, 7, 8, 9, 10, 11, 12; ENDPOINT = LOCF

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14A.1CT

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN PRE-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP
- PP BASELINE NON-SMOKERS
PROTOCOL 157

		BASELINE		WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	194	1.322	0.433	1.322	0.433	1.235	0.510	2.840	.	.	.	.	.
	SB 207499	177	1.289	0.401	1.289	0.401	1.220	0.500	2.560	.	.	.	.	.
WEEK 4	PLACEBO	186	1.320	0.436	1.306	0.456	1.195	0.510	2.840	-0.014	0.173	-0.015	-0.440	0.650
	SB 207499	165	1.288	0.403	1.303	0.426	1.250	0.480	2.480	0.015	0.195	0.000	-0.570	0.980
WEEK 8	PLACEBO	179	1.336	0.435	1.328	0.456	1.230	0.490	2.950	-0.008	0.175	0.000	-0.430	0.550
	SB 207499	154	1.297	0.407	1.302	0.433	1.255	0.350	2.520	0.005	0.182	0.000	-0.760	0.820
WEEK 12	PLACEBO	170	1.343	0.439	1.310	0.458	1.225	0.480	3.340	-0.032	0.173	-0.030	-0.480	0.500
	SB 207499	145	1.317	0.416	1.331	0.458	1.260	0.520	2.930	0.014	0.184	-0.010	-0.500	0.880
WEEK 20	PLACEBO	161	1.340	0.437	1.285	0.455	1.190	0.520	3.380	-0.055	0.189	-0.070	-0.660	0.560
	SB 207499	136	1.326	0.410	1.319	0.437	1.310	0.470	2.380	-0.007	0.193	-0.015	-0.690	0.560
WEEK 28	PLACEBO	154	1.350	0.441	1.299	0.477	1.235	0.580	3.810	-0.051	0.214	-0.060	-0.570	0.970
	SB 207499	127	1.319	0.405	1.304	0.433	1.250	0.450	2.410	-0.014	0.179	-0.020	-0.580	0.420
WEEK 36	PLACEBO	143	1.345	0.444	1.310	0.483	1.260	0.460	3.240	-0.036	0.226	-0.040	-0.810	0.820
	SB 207499	124	1.332	0.408	1.299	0.435	1.245	0.470	2.490	-0.033	0.194	-0.040	-0.580	0.590
WEEK 44	PLACEBO	137	1.364	0.447	1.318	0.485	1.230	0.620	3.170	-0.046	0.210	-0.050	-0.660	0.530
	SB 207499	118	1.316	0.410	1.318	0.442	1.290	0.490	2.810	0.002	0.201	-0.010	-0.640	0.720
WEEK 52	PLACEBO	134	1.349	0.450	1.311	0.481	1.215	0.510	2.950	-0.037	0.185	-0.060	-0.450	0.590
	SB 207499	115	1.326	0.405	1.319	0.426	1.300	0.450	2.690	-0.007	0.210	-0.020	-0.470	0.790
ENDPOINT	PLACEBO	194	1.322	0.433	1.273	0.445	1.195	0.460	2.950	-0.049	0.193	-0.050	-0.800	0.590
	SB 207499	177	1.289	0.401	1.281	0.423	1.240	0.350	2.690	-0.007	0.196	-0.010	-0.560	0.790

1. STATISITCS ARE REPORTED BASED ON THE VALUE CORRESPONDING TO THE MAXIMUM FEV1 (L)
2. MEAN VALUES ARE SAMPLE MEANS
3. BASELINE = VISIT 3; WEEK 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 5, 6, 7, 8, 9, 10, 11, 12; ENDPOINT = LOCF

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14A.1CU

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN PRE-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP
- PP BASELINE/ON THERAPY SMOKING STATUS: S/S
PROTOCOL 157

		BASELINE			WEEKLY ASSESSMENT				CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	131	1.548	0.459	1.548	0.459	1.550	0.620	2.920	.	.	.	.	.
	SB 207499	132	1.396	0.492	1.396	0.492	1.335	0.490	2.800	.	.	.	.	.
WEEK 4	PLACEBO	123	1.543	0.455	1.487	0.459	1.430	0.570	2.780	-0.056	0.180	-0.050	-0.660	0.460
	SB 207499	119	1.397	0.494	1.403	0.522	1.330	0.530	3.180	0.006	0.188	0.010	-0.690	0.560
WEEK 8	PLACEBO	118	1.573	0.459	1.560	0.459	1.535	0.500	3.130	-0.013	0.201	-0.010	-0.510	0.740
	SB 207499	118	1.380	0.498	1.400	0.527	1.340	0.490	2.990	0.020	0.197	0.025	-0.600	0.550
WEEK 12	PLACEBO	116	1.570	0.461	1.546	0.483	1.540	0.610	3.300	-0.024	0.235	-0.025	-0.620	0.900
	SB 207499	111	1.381	0.503	1.408	0.522	1.300	0.570	2.920	0.028	0.183	0.020	-0.470	0.490
WEEK 20	PLACEBO	110	1.556	0.469	1.527	0.511	1.480	0.620	3.210	-0.029	0.266	-0.030	-0.730	1.000
	SB 207499	106	1.402	0.499	1.447	0.533	1.365	0.580	2.830	0.045	0.207	0.045	-0.650	0.800
WEEK 28	PLACEBO	104	1.564	0.483	1.525	0.532	1.450	0.510	3.120	-0.039	0.244	-0.035	-0.710	0.920
	SB 207499	100	1.421	0.510	1.450	0.538	1.395	0.610	3.160	0.029	0.199	0.015	-0.560	0.670
WEEK 36	PLACEBO	102	1.547	0.483	1.513	0.513	1.500	0.510	3.400	-0.034	0.249	-0.060	-0.600	0.760
	SB 207499	100	1.414	0.516	1.425	0.546	1.280	0.470	2.960	0.011	0.212	-0.015	-0.470	0.700
WEEK 44	PLACEBO	101	1.553	0.477	1.503	0.515	1.460	0.570	3.180	-0.050	0.252	-0.060	-0.680	1.010
	SB 207499	92	1.397	0.493	1.426	0.524	1.310	0.540	2.920	0.030	0.225	0.030	-0.590	0.670
WEEK 52	PLACEBO	97	1.544	0.459	1.485	0.469	1.510	0.500	2.670	-0.059	0.233	-0.060	-0.570	0.530
	SB 207499	90	1.413	0.504	1.413	0.501	1.370	0.540	2.860	0.000	0.204	0.010	-0.660	0.500
ENDPOINT	PLACEBO	131	1.548	0.459	1.483	0.485	1.510	0.500	3.180	-0.066	0.227	-0.060	-0.700	0.530
	SB 207499	132	1.396	0.492	1.388	0.485	1.360	0.540	2.960	-0.008	0.207	0.010	-0.690	0.500

1. STATISITCS ARE REPORTED BASED ON THE VALUE CORRESPONDING TO THE MAXIMUM FEV1 (L)
2. MEAN VALUES ARE SAMPLE MEANS
3. BASELINE = VISIT 3; WEEK 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 5, 6, 7, 8, 9, 10, 11, 12; ENDPOINT = LOCF

CONFIDENTIAL

SB 207499

TABLE 14A.1CV

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN PRE-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP
- PP BASELINE/ON THERAPY SMOKING STATUS: N/N
PROTOCOL 157

		BASELINE		WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	179	1.306	0.418	1.306	0.418	1.230	0.510	2.350	.	.	.	.	.
	SB 207499	170	1.288	0.403	1.288	0.403	1.230	0.500	2.560	.	.	.	.	.
WEEK 4	PLACEBO	172	1.305	0.421	1.292	0.436	1.195	0.510	2.740	-0.013	0.175	-0.010	-0.440	0.650
	SB 207499	158	1.287	0.406	1.304	0.430	1.255	0.480	2.480	0.017	0.197	0.000	-0.570	0.980
WEEK 8	PLACEBO	165	1.322	0.421	1.315	0.437	1.220	0.490	2.710	-0.007	0.179	0.000	-0.430	0.550
	SB 207499	148	1.295	0.409	1.298	0.436	1.255	0.350	2.520	0.003	0.182	0.000	-0.760	0.820
WEEK 12	PLACEBO	155	1.326	0.424	1.294	0.433	1.220	0.480	2.440	-0.031	0.172	-0.020	-0.480	0.470
	SB 207499	142	1.310	0.416	1.327	0.461	1.255	0.520	2.930	0.017	0.181	-0.005	-0.500	0.880
WEEK 20	PLACEBO	149	1.322	0.417	1.266	0.421	1.190	0.520	2.540	-0.056	0.188	-0.060	-0.660	0.560
	SB 207499	131	1.322	0.412	1.320	0.442	1.320	0.470	2.380	-0.002	0.192	0.000	-0.690	0.560
WEEK 28	PLACEBO	140	1.331	0.423	1.285	0.437	1.235	0.580	2.960	-0.046	0.201	-0.050	-0.570	0.610
	SB 207499	125	1.313	0.405	1.301	0.435	1.240	0.450	2.410	-0.012	0.180	-0.010	-0.580	0.420
WEEK 36	PLACEBO	133	1.328	0.426	1.299	0.462	1.260	0.460	3.170	-0.030	0.220	-0.040	-0.520	0.820
	SB 207499	123	1.327	0.406	1.294	0.434	1.240	0.470	2.490	-0.033	0.195	-0.040	-0.580	0.590
WEEK 44	PLACEBO	126	1.347	0.431	1.306	0.466	1.215	0.620	2.680	-0.041	0.207	-0.050	-0.660	0.530
	SB 207499	116	1.313	0.410	1.312	0.441	1.285	0.490	2.810	-0.001	0.201	-0.010	-0.640	0.720
WEEK 52	PLACEBO	123	1.332	0.431	1.296	0.465	1.210	0.510	2.940	-0.036	0.186	-0.060	-0.450	0.590
	SB 207499	113	1.323	0.404	1.314	0.426	1.300	0.450	2.690	-0.008	0.212	-0.020	-0.470	0.790
ENDPOINT	PLACEBO	179	1.306	0.418	1.259	0.431	1.180	0.460	2.940	-0.046	0.195	-0.050	-0.800	0.590
	SB 207499	170	1.288	0.403	1.280	0.426	1.240	0.350	2.690	-0.008	0.199	-0.005	-0.560	0.790

1. STATISITCS ARE REPORTED BASED ON THE VALUE CORRESPONDING TO THE MAXIMUM FEV1 (L)
2. MEAN VALUES ARE SAMPLE MEANS
3. BASELINE = VISIT 3; WEEK 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 5, 6, 7, 8, 9, 10, 11, 12; ENDPOINT = LOCF

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14A.1CW

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN PRE-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP

PROTOCOL 157

		BASELINE			WEEKLY ASSESSMENT				CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	49	1.416	0.442	1.416	0.442	1.300	0.690	2.840	.	.	.	.	.
	SB 207499	35	1.343	0.444	1.343	0.444	1.330	0.600	2.590	.	.	.	.	.
WEEK 4	PLACEBO	44	1.439	0.444	1.413	0.493	1.300	0.650	2.840	-0.026	0.152	-0.035	-0.380	0.280
	SB 207499	32	1.372	0.444	1.402	0.443	1.365	0.560	2.490	0.030	0.181	0.000	-0.280	0.520
WEEK 8	PLACEBO	42	1.455	0.442	1.445	0.530	1.295	0.530	2.950	-0.011	0.196	-0.060	-0.300	0.570
	SB 207499	31	1.326	0.414	1.347	0.447	1.340	0.540	2.580	0.022	0.147	0.020	-0.230	0.370
WEEK 12	PLACEBO	42	1.449	0.445	1.424	0.515	1.285	0.570	3.340	-0.025	0.191	-0.040	-0.290	0.540
	SB 207499	26	1.327	0.433	1.326	0.428	1.255	0.600	2.410	-0.001	0.149	0.010	-0.390	0.260
WEEK 20	PLACEBO	42	1.440	0.464	1.401	0.512	1.375	0.600	3.380	-0.039	0.228	-0.055	-0.710	0.540
	SB 207499	30	1.315	0.428	1.280	0.444	1.260	0.660	2.610	-0.035	0.177	-0.015	-0.380	0.480
WEEK 28	PLACEBO	37	1.445	0.436	1.400	0.570	1.360	0.630	3.810	-0.046	0.246	-0.110	-0.480	0.970
	SB 207499	25	1.392	0.417	1.432	0.416	1.380	0.580	2.680	0.040	0.171	0.010	-0.230	0.440
WEEK 36	PLACEBO	32	1.501	0.427	1.423	0.556	1.310	0.780	3.240	-0.077	0.326	-0.060	-0.890	0.500
	SB 207499	24	1.347	0.456	1.346	0.451	1.325	0.610	2.440	-0.001	0.162	-0.005	-0.290	0.330
WEEK 44	PLACEBO	31	1.476	0.420	1.424	0.490	1.330	0.790	3.170	-0.052	0.256	-0.010	-0.640	0.350
	SB 207499	26	1.328	0.448	1.342	0.445	1.360	0.570	2.330	0.013	0.199	0.030	-0.420	0.380
WEEK 52	PLACEBO	29	1.453	0.468	1.419	0.516	1.300	0.640	2.950	-0.034	0.231	0.020	-0.600	0.330
	SB 207499	22	1.395	0.446	1.480	0.465	1.510	0.640	2.620	0.085	0.188	0.085	-0.260	0.410
ENDPOINT	PLACEBO	49	1.416	0.442	1.356	0.493	1.280	0.600	2.950	-0.061	0.218	-0.060	-0.600	0.450
	SB 207499	35	1.343	0.444	1.380	0.475	1.340	0.620	2.620	0.037	0.194	0.000	-0.260	0.410

1. STATISITCS ARE REPORTED BASED ON THE VALUE CORRESPONDING TO THE MAXIMUM FEV1 (L)
2. MEAN VALUES ARE SAMPLE MEANS
3. BASELINE = VISIT 3; WEEK 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 5, 6, 7, 8, 9, 10, 11, 12; ENDPOINT = LOCF

CONFIDENTIAL

SB 207499

TABLE 14A.7A

SUMMARY OF LEVEL II / III COPD EXACERBATION RATES PER PATIENT YEAR BY TREATMENT
GROUP - PP
PROTOCOL 157

TREATMENT	N	RATE PER PATIENT YEAR	95% CI	INCIDENCE DENSITY RATIO	95% CI	P-VALUE
PLACEBO	414	0.430	(0.339, 0.545)	.		.
SB 207499	422	0.462	(0.362, 0.588)	1.0737	(0.815, 1.415)	0.6134

1. RATES ARE CALCULATED BY POISSON REGRESSION WITH TREATMENT DURATION AS AN OFFSET VARIABLE AND WITH TREATMENT AND COUNTRY AS THE ONLY COVARIATES.
2. INCIDENCE DENSITY RATIO IS SB207499 RELATIVE TO PLACEBO

CONFIDENTIAL

SB 207499

TABLE 14A.7B

SUMMARY OF COPD EXACERBATION RATES PER PATIENT YEAR BY TREATMENT GROUP - PP
PROTOCOL 157

TREATMENT	N	RATE PER PATIENT YEAR	95% CI	INCIDENCE DENSITY RATIO	95% CI	P-VALUE
PLACEBO	414	0.905	(0.739, 1.109)	.		.
SB 207499	422	0.859	(0.701, 1.052)	0.9487	(0.766, 1.176)	0.6305

1. RATES ARE CALCULATED BY POISSON REGRESSION WITH TREATMENT DURATION AS AN OFFSET VARIABLE AND WITH TREATMENT AND COUNTRY AS THE ONLY COVARIATES.
2. INCIDENCE DENSITY RATIO IS SB207499 RELATIVE TO PLACEBO

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14A.7C

SUMMARY OF LEVEL II / III EXACERBATION-FREE SURVIVAL BY SMOKING STATUS AND TREATMENT GROUP - PP
PROTOCOL 157

SMOKING STATUS BASELINE/ON-THERAPY	TREATMENT GROUP	NUMBER OF PATIENTS EXAC.-FREE	EXACERBATION-FREE SURVIVAL AT 52 WEEKS PERCENT EXAC.-FREE	95% CI	P-VALUE
S/-	PLACEBO	133	72.1%	(65.1%, 79.1%)	.
	SB 207499	139	68.7%	(61.4%, 76.1%)	0.566
N/-	PLACEBO	171	69.4%	(63.1%, 75.7%)	.
	SB 207499	177	70.0%	(63.4%, 76.6%)	0.909
S/S	PLACEBO	112	77.5%	(70.3%, 84.8%)	.
	SB 207499	111	68.8%	(60.7%, 76.9%)	0.137
N/N	PLACEBO	151	67.9%	(61.3%, 74.6%)	.
	SB 207499	161	70.5%	(63.7%, 77.2%)	0.747
S/N or N/S	PLACEBO	34	62.1%	(48.1%, 76.2%)	.
	SB 207499	29	67.4%	(52.0%, 82.8%)	0.618
All Patients	PLACEBO	304	70.6%	(65.9%, 75.3%)	.
	SB 207499	316	69.4%	(64.4%, 74.3%)	0.645

1. EXACERBATION-FREE SURVIVAL IS ESTIMATED USING KAPLAN-MEIER ESTIMATE OF TIME-TO-FIRST EXACERBATION
2. P-VALUE IS BASED ON LOG-RANK TEST
3. SMOKING STATUS: S= SMOKER ; N= NON-SMOKER ; - = EITHER

CONFIDENTIAL

SB 207499

TABLE 14A.7D

SUMMARY OF EXACERBATION-FREE SURVIVAL BY SMOKING STATUS AND TREATMENT GROUP - PP
PROTOCOL 157

SMOKING STATUS BASELINE/ON-THERAPY	TREATMENT GROUP	NUMBER OF PATIENTS EXAC.-FREE	EXACERBATION-FREE SURVIVAL AT 52 WEEKS PERCENT EXAC.-FREE	95% CI	P-VALUE
S/-	PLACEBO	97	50.9%	(43.2%, 58.6%)	.
	SB 207499	107	50.5%	(42.7%, 58.4%)	0.968
N/-	PLACEBO	132	52.2%	(45.4%, 59.0%)	.
	SB 207499	145	53.3%	(46.0%, 60.5%)	0.904
S/S	PLACEBO	81	54.8%	(46.3%, 63.4%)	.
	SB 207499	84	49.5%	(40.8%, 58.2%)	0.549
N/N	PLACEBO	114	50.1%	(43.0%, 57.2%)	.
	SB 207499	132	54.6%	(47.2%, 62.1%)	0.622
S/N or N/S	PLACEBO	28	50.2%	(35.9%, 64.6%)	.
	SB 207499	22	50.5%	(34.5%, 66.5%)	0.968
All Patients	PLACEBO	229	51.6%	(46.5%, 56.7%)	.
	SB 207499	252	52.0%	(46.6%, 57.3%)	0.945

1. EXACERBATION-FREE SURVIVAL IS ESTIMATED USING KAPLAN-MEIER ESTIMATE OF TIME-TO-FIRST EXACERBATION
2. P-VALUE IS BASED ON LOG-RANK TEST
3. SMOKING STATUS: S= SMOKER ; N= NON-SMOKER ; - = EITHER

CONFIDENTIAL

SB 207499

TABLE 14A.7E

SUMMARY OF POISSON REGRESSION ON PROGNOSTIC FACTORS FOR TIME TO FIRST LEVEL II / III EXACERBATION - PP
PROTOCOL 157

FACTOR	INCIDENCE DENSITY RATIO	95% CI	P-VALUE
% PREDICTED FEV1	0.9769	(0.96, 0.99)	0.0010
AGE	1.0272	(1.01, 1.05)	0.0073
GENDER	1.4501	(1.01, 2.08)	0.0424
SMOKING STATUS	1.0567	(0.76, 1.48)	0.7475
TREATMENT	0.9499	(0.69, 1.31)	0.7512

1. *STATISTIACLLY SIGNIFICANT
2. INCIDENCE DENSITY RATIO: FEMALE RELATIVE TO MALES, SB 207499 RELATIVE TO PLACEBO, BASELINE NON-SMOKERS TO SMOKERS

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14A.7F

SUMMARY OF POISSON REGRESSION ON PROGNOSTIC FACTORS FOR TIME TO FIRST EXACERBATION - PP
PROTOCOL 157

FACTOR	INCIDENCE DENSITY RATIO	95% CI	P-VALUE
% PREDICTED FEV1	0.9770	(0.97, 0.99)	0.0000
AGE	1.0020	(0.99, 1.02)	0.7818
GENDER	1.1758	(0.89, 1.55)	0.2507
SMOKING STATUS	0.9005	(0.70, 1.15)	0.4070
TREATMENT	0.8642	(0.68, 1.10)	0.2321

1. *STATISTIACLLY SIGNIFICANT
2. INCIDENCE DENSITY RATIO: FEMALE RELATIVE TO MALES, SB 207499 RELATIVE TO PLACEBO, BASELINE NON-SMOKERS TO SMOKERS

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.1A

SUMMARY OF AVERAGE CHANGE FROM BASELINE OVER 52 WEEKS (REPEATED MEASURES ANALYSIS) IN PRE-BD TROUGH FEV1 (L) BY SMOKING STATUS - ITT
PROTOCOL 157

		BASELINE			CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
SMOKING STATUS BASELINE/ON-THERAPY	TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
S/-	PLACEBO	180	1.509	0.041	-0.050	0.015	-0.079	-0.022	.	.	.	
	SB 207499	179	1.403	0.040	-0.002	0.014	-0.030	0.026	0.049	0.014	0.083	0.006*
N/-	PLACEBO	236	1.365	0.032	-0.049	0.012	-0.072	-0.025	.	.	.	
	SB 207499	216	1.288	0.034	-0.011	0.013	-0.036	0.014	0.038	0.009	0.066	0.011*
S/S	PLACEBO	143	1.507	0.050	-0.052	0.018	-0.087	-0.017	.	.	.	
	SB 207499	148	1.383	0.050	-0.006	0.018	-0.041	0.029	0.046	0.007	0.085	0.021*
N/N	PLACEBO	216	1.351	0.033	-0.046	0.013	-0.071	-0.021	.	.	.	
	SB 207499	205	1.296	0.034	-0.009	0.013	-0.035	0.017	0.037	0.007	0.067	0.016*
S/N or N/S	PLACEBO	57	1.513	0.065	-0.064	0.022	-0.107	-0.021	.	.	.	
	SB 207499	42	1.398	0.078	-0.036	0.025	-0.086	0.014	0.028	-0.030	0.086	0.344
All Patients	PLACEBO	416	1.421	0.024	-0.047	0.009	-0.064	-0.029	.	.	.	
	SB 207499	395	1.340	0.025	-0.006	0.009	-0.024	0.012	0.041	0.019	0.063	0.000*

1. MEANS ARE ADJUSTED FOR BASELINE VALUE, COUNTRY AND WEEK
2. STATISTICS ARE REPORTED BASED ON THE MAXIMUM OF THREE REPORTED VALUES OF FEV1 (L)
3. * SIGNIFICANTLY DIFFERENT FROM PLACEBO
4. SMOKING STATUS: S= SMOKER ; N= NON-SMOKER ; - = EITHER

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.1AX

SUMMARY OF AVERAGE CHANGE FROM BASELINE OVER 52 WEEKS (REPEATED MEASURES ANALYSIS) IN PRE-BD TROUGH FEV1 (L) BY REVERSIBILITY - ITT
PROTOCOL 157

			BASELINE		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
POPULATION	TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
NON-REVERSIBLE	PLACEBO	406	1.424	0.025	-0.047	0.009	-0.065	-0.029	.	.	.	
	SB 207499	383	1.346	0.025	-0.008	0.009	-0.026	0.011	0.039	0.017	0.061	0.001*
REVERSIBLE	PLACEBO	8	1.126	0.134	.	.	.	.	.	.	.	
	SB 207499	10	1.074	0.134	.	.	.	.	.	.	.	

1. MEANS ARE ADJUSTED FOR BASELINE VALUE, COUNTRY AND WEEK
2. STATISTICS ARE REPORTED BASED ON THE MAXIMUM OF THREE REPORTED VALUES OF FEV1 (L)
3. * SIGNIFICANTLY DIFFERENT FROM PLACEBO

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.1B

SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN PRE-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP - ITT
PROTOCOL 157

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	420	1.416	0.024	.	.	.	.	.	.	.	.
	SB 207499	403	1.337	0.025	.	.	.	.	.	.	.	.
WEEK 4	PLACEBO	415	1.338	0.011	-0.031	0.011	-0.053	-0.010	.	.	.	.
	SB 207499	391	1.376	0.011	0.007	0.011	-0.015	0.029	0.038	0.011	0.066	0.006
WEEK 8	PLACEBO	400	1.351	0.011	-0.023	0.011	-0.045	-0.002	.	.	.	.
	SB 207499	380	1.376	0.011	0.001	0.011	-0.021	0.023	0.024	-0.003	0.052	0.083
WEEK 12	PLACEBO	388	1.342	0.012	-0.035	0.012	-0.058	-0.012	.	.	.	.
	SB 207499	356	1.390	0.012	0.012	0.012	-0.011	0.036	0.048	0.019	0.077	0.001
WEEK 20	PLACEBO	377	1.327	0.013	-0.052	0.013	-0.077	-0.027	.	.	.	.
	SB 207499	333	1.376	0.014	-0.004	0.014	-0.030	0.023	0.048	0.016	0.081	0.003
WEEK 28	PLACEBO	366	1.333	0.013	-0.051	0.013	-0.075	-0.026	.	.	.	.
	SB 207499	317	1.385	0.013	0.001	0.013	-0.026	0.027	0.051	0.019	0.083	0.002
WEEK 36	PLACEBO	349	1.334	0.014	-0.053	0.014	-0.081	-0.026	.	.	.	.
	SB 207499	303	1.377	0.015	-0.011	0.015	-0.040	0.018	0.042	0.007	0.078	0.018
WEEK 44	PLACEBO	334	1.317	0.014	-0.068	0.014	-0.095	-0.041	.	.	.	.
	SB 207499	291	1.381	0.015	-0.004	0.015	-0.033	0.025	0.064	0.029	0.099	0.000
WEEK 52	PLACEBO	323	1.341	0.014	-0.052	0.014	-0.079	-0.025	.	.	.	.
	SB 207499	275	1.386	0.015	-0.007	0.015	-0.036	0.022	0.045	0.011	0.080	0.010
ENDPOINT	PLACEBO	420	1.306	0.012	-0.061	0.012	-0.084	-0.039	.	.	.	.
	SB 207499	403	1.352	0.012	-0.015	0.012	-0.038	0.008	0.046	0.017	0.076	0.002

1. MEANS ARE ADJUSTED FOR BASELINE VALUE AND COUNTRY
2. STATISITCS ARE REPORTED BASED ON THE MAXIMUM OF THREE REPORTED VALUES OF FEV1 (L)
3. BASELINE = VISIT 3; WEEK 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 5, 6, 7, 8, 9, 10, 11, 12; ENDPOINT = LOCF
4. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14.1BS

SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN PRE-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP
- ITT BASELINE SMOKERS
PROTOCOL 157

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	183	1.502	0.041	.	.	.	.	.	.	.	.
	SB 207499	182	1.403	0.039	.	.	.	.	.	.	.	.
WEEK 4	PLACEBO	180	1.403	0.017	-0.048	0.017	-0.082	-0.014	.	.	.	.
	SB 207499	176	1.455	0.017	0.004	0.017	-0.029	0.038	0.052	0.011	0.094	0.014
WEEK 8	PLACEBO	174	1.420	0.018	-0.032	0.018	-0.068	0.003	.	.	.	.
	SB 207499	172	1.453	0.018	0.000	0.018	-0.035	0.035	0.032	-0.011	0.076	0.144
WEEK 12	PLACEBO	172	1.411	0.020	-0.038	0.020	-0.077	0.001	.	.	.	.
	SB 207499	165	1.468	0.019	0.019	0.019	-0.020	0.057	0.057	0.010	0.104	0.018
WEEK 20	PLACEBO	164	1.391	0.022	-0.060	0.022	-0.102	-0.018	.	.	.	.
	SB 207499	154	1.454	0.022	0.003	0.022	-0.040	0.045	0.063	0.011	0.114	0.018
WEEK 28	PLACEBO	159	1.403	0.021	-0.054	0.021	-0.095	-0.013	.	.	.	.
	SB 207499	147	1.469	0.021	0.012	0.021	-0.028	0.053	0.066	0.016	0.116	0.010
WEEK 36	PLACEBO	154	1.391	0.024	-0.066	0.024	-0.113	-0.019	.	.	.	.
	SB 207499	140	1.454	0.024	-0.003	0.024	-0.049	0.043	0.063	0.007	0.119	0.027
WEEK 44	PLACEBO	150	1.387	0.024	-0.066	0.024	-0.113	-0.019	.	.	.	.
	SB 207499	135	1.450	0.023	-0.004	0.023	-0.050	0.043	0.063	0.007	0.119	0.028
WEEK 52	PLACEBO	143	1.399	0.025	-0.057	0.025	-0.105	-0.008	.	.	.	.
	SB 207499	131	1.448	0.024	-0.008	0.024	-0.054	0.039	0.049	-0.007	0.104	0.084
ENDPOINT	PLACEBO	183	1.386	0.019	-0.062	0.019	-0.100	-0.024	.	.	.	.
	SB 207499	182	1.432	0.019	-0.016	0.019	-0.053	0.021	0.046	-0.000	0.092	0.051

1. MEANS ARE ADJUSTED FOR BASELINE VALUE AND COUNTRY
2. STATISITCS ARE REPORTED BASED ON THE MAXIMUM OF THREE REPORTED VALUES OF FEV1 (L)
3. BASELINE = VISIT 3; WEEK 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 5, 6, 7, 8, 9, 10, 11, 12; ENDPOINT = LOCF
4. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14.1BT

SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN PRE-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP
- ITT BASELINE NON-SMOKERS
PROTOCOL 157

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	237	1.362	0.032	.	.	.	.	.	.	.	.
	SB 207499	221	1.283	0.033	.	.	.	.	.	.	.	.
WEEK 4	PLACEBO	235	1.285	0.015	-0.020	0.015	-0.050	0.010	.	.	.	.
	SB 207499	215	1.317	0.016	0.012	0.016	-0.019	0.044	0.032	-0.005	0.068	0.086
WEEK 8	PLACEBO	226	1.289	0.015	-0.024	0.015	-0.053	0.006	.	.	.	.
	SB 207499	208	1.310	0.016	-0.003	0.016	-0.034	0.028	0.021	-0.015	0.057	0.252
WEEK 12	PLACEBO	216	1.281	0.016	-0.037	0.016	-0.069	-0.005	.	.	.	.
	SB 207499	191	1.325	0.017	0.007	0.017	-0.026	0.041	0.044	0.007	0.082	0.021
WEEK 20	PLACEBO	213	1.264	0.018	-0.056	0.018	-0.091	-0.021	.	.	.	.
	SB 207499	179	1.302	0.019	-0.018	0.019	-0.056	0.019	0.038	-0.004	0.080	0.075
WEEK 28	PLACEBO	207	1.273	0.018	-0.052	0.018	-0.087	-0.016	.	.	.	.
	SB 207499	170	1.315	0.019	-0.010	0.019	-0.048	0.028	0.041	-0.001	0.084	0.058
WEEK 36	PLACEBO	195	1.288	0.019	-0.043	0.019	-0.080	-0.005	.	.	.	.
	SB 207499	163	1.320	0.021	-0.011	0.021	-0.052	0.030	0.031	-0.015	0.077	0.180
WEEK 44	PLACEBO	184	1.250	0.019	-0.079	0.019	-0.115	-0.042	.	.	.	.
	SB 207499	156	1.320	0.020	-0.009	0.020	-0.049	0.031	0.070	0.025	0.115	0.002
WEEK 52	PLACEBO	180	1.288	0.019	-0.051	0.019	-0.088	-0.015	.	.	.	.
	SB 207499	144	1.333	0.020	-0.007	0.020	-0.047	0.033	0.045	0.000	0.089	0.048
ENDPOINT	PLACEBO	237	1.242	0.016	-0.062	0.016	-0.093	-0.030	.	.	.	.
	SB 207499	221	1.288	0.017	-0.015	0.017	-0.048	0.017	0.046	0.008	0.084	0.017

1. MEANS ARE ADJUSTED FOR BASELINE VALUE AND COUNTRY
2. STATISITCS ARE REPORTED BASED ON THE MAXIMUM OF THREE REPORTED VALUES OF FEV1 (L)
3. BASELINE = VISIT 3; WEEK 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 5, 6, 7, 8, 9, 10, 11,12; ENDPOINT = LOCF
4. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14.1BU

SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN PRE-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP
- ITT BASELINE/ON THERAPY SMOKING STATUS: S/S
PROTOCOL 157

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	146	1.504	0.049	.	.	.	.	.	.	.	.
	SB 207499	151	1.394	0.048	.	.	.	.	.	.	.	.
WEEK 4	PLACEBO	143	1.416	0.021	-0.052	0.021	-0.093	-0.010	.	.	.	.
	SB 207499	146	1.461	0.021	-0.006	0.021	-0.048	0.035	0.045	-0.002	0.093	0.060
WEEK 8	PLACEBO	139	1.442	0.022	-0.030	0.022	-0.073	0.013	.	.	.	.
	SB 207499	142	1.472	0.022	0.000	0.022	-0.043	0.043	0.030	-0.019	0.079	0.226
WEEK 12	PLACEBO	137	1.441	0.024	-0.031	0.024	-0.079	0.017	.	.	.	.
	SB 207499	136	1.500	0.025	0.029	0.025	-0.019	0.077	0.060	0.005	0.115	0.033
WEEK 20	PLACEBO	131	1.419	0.026	-0.056	0.026	-0.107	-0.005	.	.	.	.
	SB 207499	126	1.489	0.026	0.014	0.026	-0.038	0.066	0.070	0.011	0.129	0.020
WEEK 28	PLACEBO	128	1.403	0.025	-0.078	0.025	-0.128	-0.029	.	.	.	.
	SB 207499	119	1.469	0.026	-0.012	0.026	-0.063	0.039	0.066	0.008	0.124	0.025
WEEK 36	PLACEBO	125	1.396	0.030	-0.083	0.030	-0.141	-0.024	.	.	.	.
	SB 207499	114	1.456	0.031	-0.022	0.031	-0.082	0.038	0.060	-0.001	0.121	0.053
WEEK 44	PLACEBO	123	1.392	0.030	-0.083	0.030	-0.143	-0.024	.	.	.	.
	SB 207499	110	1.475	0.031	-0.001	0.031	-0.062	0.059	0.082	0.020	0.144	0.009
WEEK 52	PLACEBO	118	1.417	0.029	-0.059	0.029	-0.117	-0.001	.	.	.	.
	SB 207499	107	1.468	0.030	-0.008	0.030	-0.067	0.052	0.051	-0.009	0.112	0.097
ENDPOINT	PLACEBO	146	1.402	0.023	-0.061	0.023	-0.106	-0.017	.	.	.	.
	SB 207499	151	1.445	0.022	-0.018	0.022	-0.062	0.026	0.043	-0.008	0.095	0.099

1. MEANS ARE ADJUSTED FOR BASELINE VALUE AND COUNTRY
2. STATISITCS ARE REPORTED BASED ON THE MAXIMUM OF THREE REPORTED VALUES OF FEV1 (L)
3. BASELINE = VISIT 3; WEEK 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 5, 6, 7, 8, 9, 10, 11, 12; ENDPOINT = LOCF
4. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14.1BV

SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN PRE-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP
- ITT BASELINE/ON THERAPY SMOKING STATUS: N/N
PROTOCOL 157

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	217	1.346	0.033	.	.	.	.	.	.	.	.
	SB 207499	209	1.290	0.034	.	.	.	.	.	.	.	.
WEEK 4	PLACEBO	215	1.279	0.016	-0.015	0.016	-0.047	0.016	.	.	.	.
	SB 207499	204	1.311	0.017	0.016	0.017	-0.017	0.049	0.031	-0.006	0.069	0.103
WEEK 8	PLACEBO	207	1.279	0.016	-0.023	0.016	-0.054	0.008	.	.	.	.
	SB 207499	197	1.299	0.016	-0.003	0.016	-0.036	0.029	0.020	-0.018	0.057	0.302
WEEK 12	PLACEBO	197	1.270	0.017	-0.035	0.017	-0.069	-0.002	.	.	.	.
	SB 207499	182	1.317	0.018	0.011	0.018	-0.024	0.046	0.046	0.007	0.085	0.021
WEEK 20	PLACEBO	195	1.251	0.019	-0.060	0.019	-0.096	-0.023	.	.	.	.
	SB 207499	170	1.292	0.020	-0.019	0.020	-0.058	0.020	0.041	-0.003	0.084	0.067
WEEK 28	PLACEBO	190	1.265	0.018	-0.051	0.018	-0.086	-0.015	.	.	.	.
	SB 207499	163	1.309	0.020	-0.006	0.020	-0.045	0.032	0.044	0.001	0.087	0.044
WEEK 36	PLACEBO	180	1.284	0.020	-0.039	0.020	-0.079	0.000	.	.	.	.
	SB 207499	157	1.307	0.021	-0.017	0.021	-0.059	0.025	0.023	-0.025	0.070	0.346
WEEK 44	PLACEBO	170	1.252	0.019	-0.069	0.019	-0.106	-0.031	.	.	.	.
	SB 207499	151	1.306	0.020	-0.015	0.020	-0.055	0.026	0.054	0.009	0.100	0.019
WEEK 52	PLACEBO	166	1.284	0.020	-0.047	0.020	-0.087	-0.008	.	.	.	.
	SB 207499	139	1.326	0.022	-0.006	0.022	-0.049	0.036	0.041	-0.005	0.087	0.079
ENDPOINT	PLACEBO	217	1.236	0.017	-0.059	0.017	-0.092	-0.025	.	.	.	.
	SB 207499	209	1.279	0.017	-0.016	0.017	-0.050	0.018	0.043	0.003	0.083	0.036

1. MEANS ARE ADJUSTED FOR BASELINE VALUE AND COUNTRY
2. STATISITCS ARE REPORTED BASED ON THE MAXIMUM OF THREE REPORTED VALUES OF FEV1 (L)
3. BASELINE = VISIT 3; WEEK 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 5, 6, 7, 8, 9, 10, 11, 12; ENDPOINT = LOCF
4. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14.1BW

SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN PRE-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP
- ITT BASELINE/ON THERAPY SMOKING STATUS: N/S OR S/N
PROTOCOL 157

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	57	1.513	0.065	.	.	.	.	.	.	.	.
	SB 207499	42	1.398	0.078	.	.	.	.	.	.	.	.
WEEK 4	PLACEBO	57	1.340	0.027	-0.059	0.027	-0.113	-0.006	.	.	.	.
	SB 207499	41	1.403	0.032	0.003	0.032	-0.060	0.067	0.063	-0.013	0.139	0.102
WEEK 8	PLACEBO	54	1.355	0.032	-0.037	0.032	-0.100	0.026	.	.	.	.
	SB 207499	41	1.397	0.037	0.004	0.037	-0.070	0.078	0.042	-0.047	0.130	0.351
WEEK 12	PLACEBO	54	1.335	0.029	-0.059	0.029	-0.116	-0.001	.	.	.	.
	SB 207499	38	1.329	0.033	-0.065	0.033	-0.131	0.001	-0.006	-0.086	0.074	0.880
WEEK 20	PLACEBO	51	1.304	0.033	-0.076	0.033	-0.141	-0.011	.	.	.	.
	SB 207499	37	1.298	0.038	-0.083	0.038	-0.159	-0.007	-0.007	-0.099	0.086	0.888
WEEK 28	PLACEBO	48	1.332	0.035	-0.054	0.035	-0.124	0.016	.	.	.	.
	SB 207499	35	1.341	0.041	-0.044	0.041	-0.125	0.037	0.009	-0.091	0.110	0.854
WEEK 36	PLACEBO	44	1.301	0.045	-0.086	0.045	-0.176	0.004	.	.	.	.
	SB 207499	32	1.358	0.051	-0.029	0.051	-0.131	0.074	0.057	-0.073	0.187	0.383
WEEK 44	PLACEBO	41	1.311	0.040	-0.072	0.040	-0.153	0.009	.	.	.	.
	SB 207499	30	1.372	0.047	-0.011	0.047	-0.105	0.083	0.061	-0.057	0.179	0.301
WEEK 52	PLACEBO	39	1.345	0.043	-0.047	0.043	-0.134	0.040	.	.	.	.
	SB 207499	29	1.400	0.050	0.008	0.050	-0.092	0.109	0.056	-0.069	0.180	0.376
ENDPOINT	PLACEBO	57	1.342	0.032	-0.057	0.032	-0.121	0.008	.	.	.	.
	SB 207499	42	1.381	0.038	-0.018	0.038	-0.094	0.057	0.038	-0.051	0.128	0.398

1. MEANS ARE ADJUSTED FOR BASELINE VALUE AND COUNTRY
2. STATISITCS ARE REPORTED BASED ON THE MAXIMUM OF THREE REPORTED VALUES OF FEV1 (L)
3. BASELINE = VISIT 3; WEEK 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 5, 6, 7, 8, 9, 10, 11, 12; ENDPOINT = LOCF
4. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14.1BX

SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN TROUGH FEV1 BY WEEK AND TREATMENT GROUP
- ITT NON-REVERSIBLE PATIENTS
PROTOCOL 157

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	410	1.419	0.024	.	.	.	.	.	.	.	.
	SB 207499	391	1.343	0.025	.	.	.	.	.	.	.	.
WEEK 4	PLACEBO	405	1.343	0.011	-0.032	0.011	-0.054	-0.010	.	.	.	.
	SB 207499	379	1.380	0.011	0.006	0.011	-0.017	0.028	0.037	0.010	0.065	0.008
WEEK 8	PLACEBO	392	1.357	0.011	-0.023	0.011	-0.044	-0.001	.	.	.	.
	SB 207499	368	1.378	0.011	-0.001	0.011	-0.024	0.021	0.021	-0.006	0.049	0.130
WEEK 12	PLACEBO	379	1.347	0.012	-0.036	0.012	-0.059	-0.012	.	.	.	.
	SB 207499	345	1.395	0.012	0.012	0.012	-0.012	0.036	0.048	0.018	0.077	0.002
WEEK 20	PLACEBO	368	1.335	0.013	-0.050	0.013	-0.076	-0.024	.	.	.	.
	SB 207499	322	1.380	0.014	-0.004	0.014	-0.032	0.023	0.046	0.013	0.078	0.007
WEEK 28	PLACEBO	357	1.341	0.013	-0.049	0.013	-0.075	-0.024	.	.	.	.
	SB 207499	307	1.390	0.014	-0.000	0.014	-0.027	0.027	0.049	0.017	0.082	0.003
WEEK 36	PLACEBO	341	1.339	0.014	-0.057	0.014	-0.084	-0.029	.	.	.	.
	SB 207499	293	1.385	0.015	-0.011	0.015	-0.041	0.019	0.045	0.009	0.081	0.013
WEEK 44	PLACEBO	326	1.326	0.014	-0.067	0.014	-0.095	-0.039	.	.	.	.
	SB 207499	282	1.386	0.015	-0.007	0.015	-0.037	0.022	0.060	0.024	0.095	0.001
WEEK 52	PLACEBO	315	1.347	0.014	-0.054	0.014	-0.082	-0.026	.	.	.	.
	SB 207499	266	1.392	0.015	-0.009	0.015	-0.039	0.021	0.045	0.010	0.080	0.012
ENDPOINT	PLACEBO	410	1.310	0.012	-0.062	0.012	-0.086	-0.039	.	.	.	.
	SB 207499	391	1.356	0.012	-0.017	0.012	-0.040	0.007	0.046	0.016	0.076	0.002

1. MEANS ARE ADJUSTED FOR BASELINE VALUE AND COUNTRY
2. BASELINE = VISIT 3; WEEK 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 5, 6, 7, 8, 9, 10, 11, 12; ENDPOINT = LOCF
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14.1BY

SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN TROUGH FEV1 BY WEEK AND TREATMENT GROUP
- ITT REVERSIBLE PATIENTS
PROTOCOL 157

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	8	1.126	0.134	.	.	.	.	.	.	.	.
	SB 207499	10	1.074	0.134	.	.	.	.	.	.	.	.
WEEK 4	PLACEBO	8	1.179	0.055	0.030	0.055	-0.105	0.164	.	.	.	.
	SB 207499	10	1.218	0.056	0.069	0.056	-0.068	0.206	0.039	-0.167	0.245	0.660
WEEK 8	PLACEBO	7	1.293	0.052	0.156	0.052	0.023	0.290	.	.	.	.
	SB 207499	10	1.249	0.046	0.113	0.046	-0.005	0.231	-0.043	-0.240	0.153	0.593
WEEK 12	PLACEBO	7	1.246	0.053	0.102	0.053	-0.035	0.239	.	.	.	.
	SB 207499	9	1.170	0.053	0.026	0.053	-0.110	0.161	-0.076	-0.286	0.134	0.392
WEEK 20	PLACEBO	7	1.205	0.035	0.060	0.035	-0.029	0.150	.	.	.	.
	SB 207499	9	1.142	0.035	-0.002	0.035	-0.091	0.087	-0.062	-0.200	0.075	0.297
WEEK 28	PLACEBO	7	1.165	0.038	0.055	0.038	-0.051	0.162	.	.	.	.
	SB 207499	8	1.142	0.041	0.032	0.041	-0.082	0.147	-0.023	-0.200	0.155	0.740
WEEK 36	PLACEBO	7	1.234	0.048	0.124	0.048	-0.009	0.258	.	.	.	.
	SB 207499	8	1.042	0.052	-0.068	0.052	-0.211	0.076	-0.192	-0.415	0.031	0.075
WEEK 44	PLACEBO	7	1.149	0.149	0.027	0.149	-0.446	0.501	.	.	.	.
	SB 207499	7	1.147	0.171	0.025	0.171	-0.520	0.570	-0.002	-0.886	0.882	0.994
WEEK 52	PLACEBO	7	1.221	0.055	0.099	0.055	-0.076	0.273	.	.	.	.
	SB 207499	7	1.012	0.063	-0.110	0.063	-0.310	0.091	-0.208	-0.534	0.117	0.134
ENDPOINT	PLACEBO	8	1.204	0.083	0.055	0.083	-0.147	0.257	.	.	.	.
	SB 207499	10	1.165	0.084	0.016	0.084	-0.190	0.223	-0.039	-0.349	0.271	0.770

1. MEANS ARE ADJUSTED FOR BASELINE VALUE AND COUNTRY
2. BASELINE = VISIT 3; WEEK 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 5, 6, 7, 8, 9, 10, 11, 12; ENDPOINT = LOCF
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.1C

DESCRIPTIVE STATISTICS FOR PRE-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP - ITT

PROTOCOL 157

			BASELINE		WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	420	1.404	0.446	1.404	0.446	1.365	0.490	2.920	.	.	.	.	.
	SB 207499	403	1.329	0.444	1.329	0.444	1.280	0.490	2.800	.	.	.	.	.
WEEK 4	PLACEBO	415	1.407	0.447	1.382	0.458	1.330	0.490	2.840	-0.025	0.193	-0.030	-0.680	0.740
	SB 207499	391	1.329	0.447	1.345	0.473	1.280	0.430	3.180	0.017	0.199	0.010	-0.990	0.980
WEEK 8	PLACEBO	400	1.414	0.445	1.397	0.463	1.345	0.490	3.130	-0.017	0.195	-0.020	-0.550	0.740
	SB 207499	380	1.333	0.442	1.345	0.466	1.290	0.350	2.990	0.012	0.194	0.010	-0.760	0.820
WEEK 12	PLACEBO	388	1.417	0.446	1.385	0.467	1.350	0.480	3.340	-0.033	0.213	-0.040	-0.620	0.910
	SB 207499	356	1.334	0.446	1.351	0.482	1.260	0.460	2.930	0.017	0.192	0.010	-0.960	0.880
WEEK 20	PLACEBO	377	1.414	0.447	1.371	0.474	1.360	0.520	3.380	-0.043	0.237	-0.050	-0.730	1.030
	SB 207499	333	1.339	0.445	1.347	0.476	1.300	0.430	2.830	0.008	0.200	0.010	-0.990	0.800
WEEK 28	PLACEBO	366	1.419	0.446	1.373	0.484	1.320	0.510	3.810	-0.046	0.228	-0.050	-0.710	0.970
	SB 207499	317	1.343	0.446	1.349	0.487	1.310	0.450	3.160	0.006	0.194	0.000	-0.580	0.670
WEEK 36	PLACEBO	349	1.419	0.445	1.371	0.483	1.350	0.460	3.400	-0.048	0.244	-0.060	-0.890	0.820
	SB 207499	303	1.352	0.448	1.348	0.484	1.270	0.470	2.960	-0.004	0.207	-0.020	-0.860	0.700
WEEK 44	PLACEBO	334	1.416	0.449	1.358	0.489	1.295	0.450	3.180	-0.058	0.237	-0.060	-0.820	1.010
	SB 207499	291	1.351	0.443	1.357	0.477	1.300	0.490	2.920	0.007	0.212	0.000	-0.640	0.720
WEEK 52	PLACEBO	323	1.419	0.445	1.366	0.472	1.340	0.500	2.950	-0.053	0.222	-0.060	-0.690	0.660
	SB 207499	275	1.363	0.445	1.361	0.462	1.310	0.450	2.860	-0.001	0.209	0.010	-0.660	0.790
ENDPOINT	PLACEBO	420	1.404	0.446	1.346	0.468	1.305	0.500	3.180	-0.058	0.221	-0.060	-0.800	0.660
	SB 207499	403	1.329	0.444	1.321	0.459	1.260	0.350	2.960	-0.008	0.211	0.000	-1.010	0.790

1. STATISITCS ARE REPORTED BASED ON THE VALUE CORRESPONDING TO THE MAXIMUM FEV1 (L)
2. MEAN VALUES ARE SAMPLE MEANS
3. BASELINE = VISIT 3; WEEK 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 5, 6, 7, 8, 9, 10, 11, 12; ENDPOINT = LOCF

CONFIDENTIAL

SB 207499

TABLE 14.1CS

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN PRE-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP - ITT
BASELINE SMOKERS
PROTOCOL 157

		BASELINE			WEEKLY ASSESSMENT				CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	183	1.497	0.449	1.497	0.449	1.500	0.620	2.920	.	.	.	.	.
	SB 207499	182	1.398	0.482	1.398	0.482	1.345	0.490	2.800	.	.	.	.	.
WEEK 4	PLACEBO	180	1.502	0.450	1.459	0.452	1.425	0.570	2.780	-0.043	0.201	-0.050	-0.680	0.740
	SB 207499	176	1.398	0.487	1.414	0.509	1.390	0.450	3.180	0.016	0.191	0.010	-0.690	0.560
WEEK 8	PLACEBO	174	1.510	0.448	1.488	0.468	1.485	0.500	3.130	-0.022	0.206	-0.020	-0.550	0.740
	SB 207499	172	1.394	0.478	1.410	0.501	1.370	0.490	2.990	0.017	0.193	0.015	-0.600	0.700
WEEK 12	PLACEBO	172	1.508	0.450	1.475	0.471	1.455	0.570	3.300	-0.033	0.238	-0.045	-0.620	0.910
	SB 207499	165	1.388	0.478	1.418	0.506	1.320	0.570	2.920	0.030	0.182	0.020	-0.470	0.830
WEEK 20	PLACEBO	164	1.508	0.455	1.472	0.478	1.440	0.600	3.210	-0.036	0.261	-0.040	-0.730	1.000
	SB 207499	154	1.391	0.478	1.424	0.506	1.345	0.580	2.830	0.032	0.194	0.030	-0.650	0.800
WEEK 28	PLACEBO	159	1.514	0.453	1.475	0.497	1.420	0.510	3.120	-0.038	0.239	-0.050	-0.710	0.920
	SB 207499	147	1.395	0.484	1.424	0.521	1.370	0.540	3.160	0.029	0.193	0.010	-0.560	0.670
WEEK 36	PLACEBO	154	1.509	0.452	1.462	0.492	1.435	0.510	3.400	-0.047	0.258	-0.060	-0.890	0.760
	SB 207499	140	1.400	0.491	1.415	0.525	1.295	0.470	2.960	0.015	0.206	0.000	-0.470	0.700
WEEK 44	PLACEBO	150	1.506	0.455	1.456	0.489	1.430	0.570	3.180	-0.050	0.259	-0.060	-0.820	1.010
	SB 207499	135	1.395	0.482	1.410	0.507	1.350	0.540	2.920	0.016	0.212	0.010	-0.590	0.670
WEEK 52	PLACEBO	143	1.504	0.449	1.451	0.460	1.450	0.500	2.670	-0.053	0.247	-0.050	-0.650	0.610
	SB 207499	131	1.403	0.485	1.410	0.497	1.370	0.540	2.860	0.007	0.212	0.010	-0.660	0.500
ENDPOINT	PLACEBO	183	1.497	0.449	1.439	0.467	1.430	0.500	3.180	-0.059	0.236	-0.060	-0.650	0.610
	SB 207499	182	1.398	0.482	1.396	0.487	1.370	0.540	2.960	-0.001	0.212	0.010	-0.690	0.500

1. STATISITCS ARE REPORTED BASED ON THE VALUE CORRESPONDING TO THE MAXIMUM FEV1 (L)
2. MEAN VALUES ARE SAMPLE MEANS
3. BASELINE=VISIT 3; WEEK 4, 8, 12, 20, 28, 36, 44, 52 =VISIT 5, 6, 7, 8, 9, 10, 11,12; ENDPOINT=LOCF

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.1CT

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN PRE-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP - ITT
BASELINE NON-SMOKERS
PROTOCOL 157

		BASELINE			WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	237	1.332	0.431	1.332	0.431	1.270	0.490	2.840	.	.	.	.	.
	SB 207499	221	1.272	0.403	1.272	0.403	1.220	0.500	2.560	.	.	.	.	.
WEEK 4	PLACEBO	235	1.335	0.432	1.324	0.454	1.250	0.490	2.840	-0.012	0.186	-0.020	-0.550	0.650
	SB 207499	215	1.272	0.403	1.289	0.433	1.240	0.430	2.480	0.017	0.205	0.010	-0.990	0.980
WEEK 8	PLACEBO	226	1.340	0.429	1.327	0.447	1.250	0.490	2.950	-0.013	0.187	-0.010	-0.430	0.550
	SB 207499	208	1.283	0.404	1.291	0.429	1.230	0.350	2.520	0.008	0.196	0.000	-0.760	0.820
WEEK 12	PLACEBO	216	1.345	0.430	1.313	0.453	1.230	0.480	3.340	-0.032	0.191	-0.035	-0.480	0.830
	SB 207499	191	1.287	0.411	1.294	0.454	1.230	0.460	2.930	0.007	0.201	0.000	-0.960	0.880
WEEK 20	PLACEBO	213	1.342	0.428	1.293	0.457	1.220	0.520	3.380	-0.049	0.217	-0.060	-0.660	1.030
	SB 207499	179	1.294	0.411	1.281	0.439	1.260	0.430	2.430	-0.013	0.202	-0.020	-0.990	0.560
WEEK 28	PLACEBO	207	1.347	0.427	1.295	0.461	1.240	0.580	3.810	-0.052	0.218	-0.060	-0.570	0.970
	SB 207499	170	1.298	0.406	1.285	0.448	1.225	0.450	2.760	-0.013	0.193	-0.020	-0.580	0.640
WEEK 36	PLACEBO	195	1.348	0.427	1.298	0.465	1.260	0.460	3.240	-0.049	0.234	-0.050	-0.810	0.820
	SB 207499	163	1.311	0.405	1.290	0.440	1.230	0.470	2.890	-0.020	0.206	-0.020	-0.860	0.590
WEEK 44	PLACEBO	184	1.342	0.432	1.279	0.476	1.210	0.450	3.170	-0.064	0.217	-0.060	-0.690	0.600
	SB 207499	156	1.313	0.405	1.312	0.447	1.275	0.490	2.810	-0.001	0.212	-0.010	-0.640	0.720
WEEK 52	PLACEBO	180	1.351	0.431	1.298	0.471	1.210	0.510	2.950	-0.052	0.200	-0.060	-0.690	0.660
	SB 207499	144	1.325	0.403	1.317	0.425	1.290	0.450	2.690	-0.008	0.206	-0.010	-0.610	0.790
ENDPOINT	PLACEBO	237	1.332	0.431	1.275	0.457	1.190	0.510	2.950	-0.058	0.209	-0.060	-0.800	0.660
	SB 207499	221	1.272	0.403	1.259	0.427	1.220	0.350	2.690	-0.013	0.211	-0.010	-1.010	0.790

1. STATISITCS ARE REPORTED BASED ON THE VALUE CORRESPONDING TO THE MAXIMUM FEV1 (L)
2. MEAN VALUES ARE SAMPLE MEANS
3. BASELINE = VISIT 3; WEEK 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 5, 6, 7, 8, 9, 10, 11, 12; ENDPOINT = LOCF

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.1CU

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN PRE-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP - ITT
BASELINE/ON THERAPY SMOKING STATUS: S/S
PROTOCOL 157

		BASELINE		WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	146	1.526	0.463	1.526	0.463	1.550	0.620	2.920	.	.	.	.	.
	SB 207499	151	1.402	0.486	1.402	0.486	1.350	0.490	2.800	.	.	.	.	.
WEEK 4	PLACEBO	143	1.533	0.465	1.491	0.461	1.460	0.570	2.780	-0.042	0.209	-0.050	-0.680	0.740
	SB 207499	146	1.403	0.492	1.415	0.518	1.395	0.450	3.180	0.011	0.194	0.015	-0.690	0.560
WEEK 8	PLACEBO	139	1.541	0.461	1.520	0.467	1.520	0.500	3.130	-0.022	0.200	-0.010	-0.550	0.740
	SB 207499	142	1.405	0.487	1.419	0.512	1.370	0.490	2.990	0.014	0.195	0.025	-0.600	0.550
WEEK 12	PLACEBO	137	1.539	0.463	1.508	0.479	1.500	0.610	3.300	-0.031	0.247	-0.040	-0.620	0.910
	SB 207499	136	1.403	0.489	1.440	0.517	1.335	0.570	2.920	0.037	0.190	0.025	-0.470	0.830
WEEK 20	PLACEBO	131	1.538	0.471	1.506	0.496	1.480	0.620	3.210	-0.031	0.267	-0.040	-0.730	1.000
	SB 207499	126	1.411	0.489	1.452	0.515	1.390	0.580	2.830	0.042	0.196	0.040	-0.650	0.800
WEEK 28	PLACEBO	128	1.543	0.472	1.499	0.508	1.445	0.510	3.120	-0.044	0.252	-0.050	-0.710	0.920
	SB 207499	119	1.416	0.495	1.444	0.535	1.370	0.540	3.160	0.028	0.199	0.010	-0.560	0.670
WEEK 36	PLACEBO	125	1.532	0.471	1.490	0.494	1.500	0.510	3.400	-0.042	0.247	-0.060	-0.600	0.760
	SB 207499	114	1.420	0.501	1.436	0.544	1.295	0.470	2.960	0.017	0.214	0.000	-0.470	0.700
WEEK 44	PLACEBO	123	1.534	0.475	1.473	0.503	1.440	0.570	3.180	-0.061	0.261	-0.060	-0.820	1.010
	SB 207499	110	1.410	0.490	1.431	0.522	1.330	0.540	2.920	0.020	0.216	0.010	-0.590	0.670
WEEK 52	PLACEBO	118	1.526	0.464	1.464	0.464	1.450	0.500	2.670	-0.062	0.244	-0.060	-0.650	0.610
	SB 207499	107	1.421	0.492	1.419	0.498	1.370	0.540	2.860	-0.001	0.212	0.010	-0.660	0.500
ENDPOINT	PLACEBO	146	1.526	0.463	1.468	0.473	1.450	0.500	3.180	-0.058	0.235	-0.055	-0.650	0.610
	SB 207499	151	1.402	0.486	1.399	0.487	1.370	0.540	2.960	-0.004	0.213	0.010	-0.690	0.500

1. STATISITCS ARE REPORTED BASED ON THE VALUE CORRESPONDING TO THE MAXIMUM FEV1 (L)
2. MEAN VALUES ARE SAMPLE MEANS
3. BASELINE = VISIT 3; WEEK 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 5, 6, 7, 8, 9, 10, 11, 12; ENDPOINT = LOCF

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.1CV

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN PRE-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP - ITT
BASELINE/ON THERAPY SMOKING STATUS: N/N
PROTOCOL 157

		BASELINE			WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	217	1.312	0.417	1.312	0.417	1.260	0.490	2.450	.	.	.	.	.
	SB 207499	209	1.276	0.406	1.276	0.406	1.220	0.500	2.560	.	.	.	.	.
WEEK 4	PLACEBO	215	1.315	0.417	1.304	0.434	1.240	0.490	2.740	-0.010	0.190	-0.020	-0.550	0.650
	SB 207499	204	1.273	0.405	1.291	0.439	1.245	0.430	2.480	0.018	0.207	0.010	-0.990	0.980
WEEK 8	PLACEBO	207	1.319	0.413	1.307	0.428	1.230	0.490	2.710	-0.012	0.192	0.000	-0.430	0.550
	SB 207499	197	1.285	0.407	1.292	0.433	1.230	0.350	2.520	0.007	0.196	0.000	-0.760	0.820
WEEK 12	PLACEBO	197	1.323	0.414	1.291	0.426	1.220	0.480	2.440	-0.032	0.193	-0.030	-0.480	0.830
	SB 207499	182	1.287	0.413	1.296	0.461	1.230	0.460	2.930	0.009	0.201	0.000	-0.960	0.880
WEEK 20	PLACEBO	195	1.325	0.416	1.275	0.437	1.210	0.520	2.680	-0.050	0.221	-0.060	-0.660	1.030
	SB 207499	170	1.294	0.413	1.282	0.445	1.270	0.430	2.430	-0.012	0.202	-0.020	-0.990	0.560
WEEK 28	PLACEBO	190	1.329	0.414	1.281	0.430	1.240	0.580	2.960	-0.049	0.210	-0.050	-0.570	0.610
	SB 207499	163	1.299	0.408	1.291	0.451	1.230	0.450	2.760	-0.008	0.194	-0.020	-0.580	0.640
WEEK 36	PLACEBO	180	1.332	0.415	1.289	0.451	1.260	0.460	3.170	-0.043	0.232	-0.045	-0.740	0.820
	SB 207499	157	1.313	0.406	1.287	0.443	1.220	0.470	2.890	-0.026	0.207	-0.030	-0.860	0.590
WEEK 44	PLACEBO	170	1.330	0.420	1.273	0.461	1.205	0.450	2.680	-0.057	0.214	-0.060	-0.690	0.600
	SB 207499	151	1.311	0.408	1.302	0.448	1.270	0.490	2.810	-0.009	0.208	-0.010	-0.640	0.720
WEEK 52	PLACEBO	166	1.338	0.419	1.289	0.461	1.205	0.510	2.940	-0.050	0.202	-0.060	-0.690	0.660
	SB 207499	139	1.324	0.406	1.314	0.430	1.290	0.450	2.690	-0.010	0.209	-0.010	-0.610	0.790
ENDPOINT	PLACEBO	217	1.312	0.417	1.256	0.442	1.170	0.510	2.940	-0.056	0.212	-0.060	-0.800	0.660
	SB 207499	209	1.276	0.406	1.259	0.432	1.220	0.350	2.690	-0.017	0.215	-0.010	-1.010	0.790

1. STATISITCS ARE REPORTED BASED ON THE VALUE CORRESPONDING TO THE MAXIMUM FEV1 (L)
2. MEAN VALUES ARE SAMPLE MEANS
3. BASELINE = VISIT 3; WEEK 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 5, 6, 7, 8, 9, 10, 11, 12; ENDPOINT = LOCF

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.1CW

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN PRE-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP - ITT
BASELINE/ON THERAPY SMOKING STATUS: N/S OR S/N
PROTOCOL 157

			BASELINE		WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	57	1.443	0.435	1.443	0.435	1.350	0.690	2.840	.	.	.	.	.
	SB 207499	42	1.339	0.440	1.339	0.440	1.325	0.600	2.590	.	.	.	.	.
WEEK 4	PLACEBO	57	1.443	0.435	1.403	0.487	1.310	0.650	2.840	-0.040	0.162	-0.060	-0.490	0.280
	SB 207499	41	1.338	0.445	1.368	0.439	1.320	0.560	2.490	0.030	0.174	0.000	-0.280	0.520
WEEK 8	PLACEBO	54	1.451	0.443	1.426	0.512	1.295	0.530	2.950	-0.025	0.195	-0.060	-0.370	0.570
	SB 207499	41	1.315	0.417	1.344	0.428	1.370	0.540	2.580	0.029	0.186	0.010	-0.250	0.700
WEEK 12	PLACEBO	54	1.450	0.444	1.411	0.513	1.265	0.570	3.340	-0.039	0.192	-0.045	-0.340	0.540
	SB 207499	38	1.313	0.410	1.301	0.409	1.255	0.600	2.410	-0.012	0.148	-0.015	-0.390	0.260
WEEK 20	PLACEBO	51	1.437	0.429	1.389	0.476	1.370	0.600	3.380	-0.048	0.216	-0.050	-0.710	0.540
	SB 207499	37	1.303	0.411	1.285	0.420	1.300	0.660	2.610	-0.019	0.190	0.000	-0.380	0.480
WEEK 28	PLACEBO	48	1.448	0.422	1.407	0.548	1.340	0.630	3.810	-0.041	0.230	-0.095	-0.480	0.970
	SB 207499	35	1.300	0.416	1.302	0.442	1.350	0.580	2.680	0.002	0.171	0.010	-0.280	0.440
WEEK 36	PLACEBO	44	1.451	0.417	1.364	0.520	1.280	0.740	3.240	-0.087	0.286	-0.085	-0.890	0.500
	SB 207499	32	1.299	0.433	1.331	0.411	1.375	0.610	2.440	0.032	0.170	0.020	-0.290	0.330
WEEK 44	PLACEBO	41	1.419	0.415	1.367	0.501	1.290	0.570	3.170	-0.052	0.254	-0.030	-0.640	0.350
	SB 207499	30	1.333	0.425	1.365	0.426	1.405	0.570	2.330	0.033	0.215	0.030	-0.420	0.560
WEEK 52	PLACEBO	39	1.436	0.434	1.400	0.493	1.300	0.640	2.950	-0.036	0.235	-0.040	-0.600	0.330
	SB 207499	29	1.333	0.432	1.377	0.467	1.270	0.640	2.620	0.044	0.199	0.030	-0.440	0.410
ENDPOINT	PLACEBO	57	1.443	0.435	1.378	0.484	1.300	0.600	2.950	-0.066	0.223	-0.060	-0.600	0.330
	SB 207499	42	1.339	0.440	1.355	0.456	1.260	0.640	2.620	0.015	0.187	-0.005	-0.440	0.410

1. STATISTICS ARE REPORTED BASED ON THE VALUE CORRESPONDING TO THE MAXIMUM FEV1 (L)
2. MEAN VALUES ARE SAMPLE MEANS
3. BASELINE = VISIT 3; WEEK 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 5, 6, 7, 8, 9, 10, 11, 12; ENDPOINT = LOCF

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.1I

DESCRIPTIVE STATISTICS FOR PRE-BD TROUGH FEV1 (L) AT ENDPOINT BY COUNTRY AND TREATMENT GROUP - ITT

PROTOCOL 157

COUNTRY	TREATMENT GROUP	N	BASELINE MEAN	BASELINE SD	ENDPOINT ASSESSMENT MEAN	ENDPOINT ASSESSMENT SD	ENDPOINT ASSESSMENT MEDIAN	ENDPOINT ASSESSMENT MIN	ENDPOINT ASSESSMENT MAX	CHANGE FROM BASELINE MEAN	CHANGE FROM BASELINE SD	CHANGE FROM BASELINE MEDIAN	CHANGE FROM BASELINE MIN	CHANGE FROM BASELINE MAX
Australia	PLACEBO	17	1.391	0.494	1.269	0.466	1.280	0.610	2.150	-0.122	0.208	-0.110	-0.600	0.240
	SB 207499	11	1.246	0.520	1.245	0.462	1.110	0.810	2.260	-0.002	0.131	-0.020	-0.220	0.180
Belgium	PLACEBO	11	1.249	0.494	1.217	0.550	1.140	0.550	2.210	-0.032	0.148	-0.060	-0.250	0.300
	SB 207499	9	1.424	0.575	1.480	0.521	1.320	0.930	2.540	0.056	0.228	0.060	-0.240	0.500
Czech Republic	PLACEBO	16	1.604	0.429	1.424	0.429	1.290	0.880	2.340	-0.180	0.174	-0.200	-0.450	0.220
	SB 207499	19	1.394	0.549	1.358	0.526	1.380	0.590	2.400	-0.036	0.192	-0.030	-0.470	0.370
Denmark	PLACEBO	11	1.186	0.316	1.106	0.305	0.980	0.780	1.660	-0.080	0.206	-0.040	-0.490	0.120
	SB 207499	8	1.311	0.367	1.394	0.409	1.455	0.770	1.830	0.083	0.107	0.075	-0.090	0.240
Finland	PLACEBO	14	1.721	0.294	1.598	0.338	1.530	1.100	2.390	-0.123	0.193	-0.155	-0.420	0.310
	SB 207499	10	1.600	0.322	1.718	0.397	1.780	0.950	2.180	0.118	0.204	0.115	-0.190	0.490
France	PLACEBO	17	1.336	0.476	1.278	0.431	1.120	0.810	2.200	-0.058	0.155	-0.050	-0.360	0.160
	SB 207499	11	1.313	0.225	1.220	0.287	1.140	0.820	1.690	-0.093	0.212	-0.110	-0.460	0.240
Germany	PLACEBO	73	1.450	0.428	1.457	0.446	1.380	0.570	2.950	0.006	0.247	-0.010	-0.740	0.610
	SB 207499	69	1.300	0.420	1.358	0.425	1.310	0.530	2.560	0.059	0.236	0.080	-0.660	0.790
Italy	PLACEBO	39	1.415	0.411	1.296	0.524	1.170	0.510	2.940	-0.119	0.295	-0.130	-0.690	0.660
	SB 207499	51	1.323	0.387	1.272	0.413	1.230	0.560	2.210	-0.050	0.243	-0.040	-0.860	0.600
Netherlands	PLACEBO	14	1.446	0.471	1.343	0.458	1.385	0.630	2.160	-0.104	0.228	-0.095	-0.800	0.160
	SB 207499	21	1.313	0.414	1.271	0.413	1.220	0.650	2.250	-0.041	0.277	0.030	-1.010	0.390
New Zealand	PLACEBO	12	1.211	0.430	1.141	0.416	1.150	0.620	1.820	-0.070	0.084	-0.070	-0.200	0.080
	SB 207499	11	1.126	0.316	1.023	0.320	0.940	0.580	1.640	-0.104	0.139	-0.120	-0.300	0.100
Poland	PLACEBO	3	1.610	0.685	1.593	0.625	1.610	0.960	2.210	-0.017	0.064	0.010	-0.090	0.030
	SB 207499	8	1.535	0.504	1.583	0.598	1.540	0.810	2.620	0.048	0.216	0.070	-0.310	0.270
Russia	PLACEBO	34	1.540	0.575	1.497	0.635	1.375	0.590	3.180	-0.044	0.264	-0.060	-0.600	0.530
	SB 207499	30	1.433	0.641	1.469	0.668	1.320	0.590	2.960	0.036	0.142	0.050	-0.240	0.230
Slovakia	PLACEBO	13	1.376	0.392	1.340	0.321	1.370	0.780	1.780	-0.036	0.154	0.010	-0.300	0.230
	SB 207499	12	1.471	0.355	1.428	0.335	1.460	0.830	2.000	-0.043	0.256	0.020	-0.600	0.270
South Africa	PLACEBO	24	1.525	0.369	1.459	0.420	1.505	0.740	2.360	-0.066	0.191	-0.055	-0.440	0.380
	SB 207499	25	1.481	0.380	1.396	0.374	1.450	0.720	2.160	-0.085	0.243	-0.060	-0.690	0.340
Spain	PLACEBO	48	1.284	0.349	1.214	0.379	1.130	0.600	2.190	-0.070	0.189	-0.090	-0.440	0.370
	SB 207499	48	1.243	0.332	1.221	0.375	1.170	0.520	2.100	-0.022	0.176	-0.010	-0.450	0.250

1. STATISTICS ARE REPORTED BASED ON THE VALUE CORRESPONDING TO THE MAXIMUM FEV1 (L)

CONFIDENTIAL

SB 207499

TABLE 14.1I

DESCRIPTIVE STATISTICS FOR PRE-BD TROUGH FEV1 (L) AT ENDPOINT BY COUNTRY AND TREATMENT GROUP - ITT

PROTOCOL 157

COUNTRY	TREATMENT GROUP	N	BASELINE MEAN	BASELINE SD	ENDPOINT ASSESSMENT MEAN	ENDPOINT ASSESSMENT SD	ENDPOINT ASSESSMENT MEDIAN	ENDPOINT ASSESSMENT MIN	ENDPOINT ASSESSMENT MAX	CHANGE FROM BASELINE MEAN	CHANGE FROM BASELINE SD	CHANGE FROM BASELINE MEDIAN	CHANGE FROM BASELINE MIN	CHANGE FROM BASELINE MAX
Sweden	PLACEBO	20	1.520	0.512	1.409	0.472	1.530	0.680	2.170	-0.111	0.221	-0.060	-0.570	0.220
	SB 207499	13	1.201	0.573	1.165	0.563	1.180	0.450	2.300	-0.035	0.188	-0.080	-0.280	0.390
Taiwan	PLACEBO	12	1.206	0.267	1.164	0.368	1.110	0.760	1.720	-0.042	0.184	-0.045	-0.300	0.360
	SB 207499	11	1.292	0.324	1.295	0.326	1.220	0.790	1.760	0.004	0.095	-0.020	-0.110	0.200
United Kingdom	PLACEBO	42	1.258	0.459	1.273	0.486	1.145	0.500	2.540	0.015	0.210	0.025	-0.450	0.410
	SB 207499	36	1.251	0.527	1.236	0.520	1.080	0.350	2.290	-0.016	0.184	-0.015	-0.450	0.270

1. STATISTICS ARE REPORTED BASED ON THE VALUE CORRESPONDING TO THE MAXIMUM FEV1 (L)

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.1J

DESCRIPTIVE STATISTICS FOR PRE-BD TROUGH FEV1 (L) AT ENDPOINT BY GENDER AND TREATMENT GROUP - ITT

PROTOCOL 157

SEX	TREATMENT GROUP	N	BASELINE MEAN	BASELINE SD	ENDPOINT ASSESSMENT MEAN	ENDPOINT ASSESSMENT SD	ENDPOINT ASSESSMENT MEDIAN	ENDPOINT ASSESSMENT MIN	ENDPOINT ASSESSMENT MAX	CHANGE FROM BASELINE MEAN	CHANGE FROM BASELINE SD	CHANGE FROM BASELINE MEDIAN	CHANGE FROM BASELINE MIN	CHANGE FROM BASELINE MAX
FEMALE	PLACEBO	108	1.098	0.317	1.081	0.349	1.030	0.500	2.160	-0.017	0.193	-0.040	-0.490	0.610
	SB 207499	80	1.082	0.398	1.097	0.407	1.010	0.350	2.050	0.016	0.154	0.015	-0.400	0.320
MALE	PLACEBO	312	1.510	0.435	1.438	0.470	1.410	0.510	3.180	-0.072	0.229	-0.060	-0.800	0.660
	SB 207499	323	1.390	0.434	1.377	0.455	1.330	0.520	2.960	-0.014	0.223	-0.010	-1.010	0.790

1. STATISTICS ARE REPORTED BASED ON THE VALUE CORRESPONDING TO THE MAXIMUM FEV1 (L)

CONFIDENTIAL

SB 207499

TABLE 14.1K

DESCRIPTIVE STATISTICS FOR PRE-BD TROUGH FEV1 (L) AT ENDPOINT BY ATS SEVERITY AND TREATMENT GROUP - ITT

PROTOCOL 157

SEVERITY	TREATMENT GROUP	N	BASELINE MEAN	BASELINE SD	ENDPOINT ASSESSMENT MEAN	ENDPOINT ASSESSMENT SD	ENDPOINT ASSESSMENT MEDIAN	ENDPOINT ASSESSMENT MIN	ENDPOINT ASSESSMENT MAX	CHANGE FROM BASELINE MEAN	CHANGE FROM BASELINE SD	CHANGE FROM BASELINE MEDIAN	CHANGE FROM BASELINE MIN	CHANGE FROM BASELINE MAX
MILD	PLACEBO	258	1.599	0.397	1.540	0.432	1.530	0.620	3.180	-0.059	0.245	-0.060	-0.800	0.660
	SB 207499	209	1.582	0.408	1.565	0.430	1.550	0.520	2.960	-0.017	0.224	-0.010	-1.010	0.500
MODERATE	PLACEBO	139	1.114	0.322	1.055	0.343	0.960	0.500	2.340	-0.059	0.180	-0.060	-0.500	0.420
	SB 207499	148	1.111	0.273	1.125	0.304	1.090	0.530	2.000	0.015	0.196	0.020	-0.600	0.790
SEVERE	PLACEBO	21	0.910	0.255	0.883	0.260	0.880	0.510	1.410	-0.028	0.152	-0.020	-0.280	0.280
	SB 207499	44	0.872	0.299	0.835	0.305	0.760	0.350	2.170	-0.037	0.200	-0.035	-0.860	0.450
UNKNOWN	PLACEBO	2	1.625	0.757	1.420	0.537	1.420	1.040	1.800	-0.205	0.219	-0.205	-0.360	-0.050
	SB 207499	2	1.060	0.438	1.050	0.354	1.050	0.800	1.300	-0.010	0.085	-0.010	-0.070	0.050

1. STATISTICS ARE REPORTED BASED ON THE VALUE CORRESPONDING TO THE MAXIMUM FEV1 (L)
2. ATS SEVERITY: MILD / MODERATE / SEVERE= PERCENT PREDICTED > 50% / 35%-50% / < 35%

CONFIDENTIAL

SB 207499

TABLE 14.1M

DESCRIPTIVE STATISTICS FOR PRE-BD TROUGH FEV1 (L) AT ENDPOINT BY REVERSIBILITY AND TREATMENT GROUP - ITT

ITT

PROTOCOL 157

POPULATION	TREATMENT GROUP	N	BASELINE MEAN	BASELINE SD	ENDPOINT ASSESSMENT MEAN	ENDPOINT ASSESSMENT SD	ENDPOINT ASSESSMENT MEDIAN	ENDPOINT ASSESSMENT MIN	ENDPOINT ASSESSMENT MAX	CHANGE FROM BASELINE MEAN	CHANGE FROM BASELINE SD	CHANGE FROM BASELINE MEDIAN	CHANGE FROM BASELINE MIN	CHANGE FROM BASELINE MAX
NON-REVERSIBLE	PLACEBO	410	1.408	0.446	1.349	0.469	1.310	0.500	3.180	-0.059	0.222	-0.060	-0.800	0.660
	SB 207499	391	1.335	0.445	1.326	0.460	1.260	0.350	2.960	-0.010	0.211	0.000	-1.010	0.790
REVERSIBLE	PLACEBO	8	1.170	0.324	1.193	0.428	1.210	0.580	1.880	0.022	0.170	0.050	-0.250	0.260
	SB 207499	10	1.132	0.383	1.196	0.453	1.175	0.450	1.730	0.064	0.234	0.050	-0.210	0.600

1. STATISTICS ARE REPORTED BASED ON THE VALUE CORRESPONDING TO THE MAXIMUM FEV1 (L)
2. REVERSIBILITY IS DEFINED AS <= 15 OR <=200 ml (OR BOTH) INCREASE IN FEV1 AFTER THE ADMINISTRATION OF SALBUTAMOL 400 mcg VIA MDI AT VISIT 1 (SCREENING)

CONFIDENTIAL

SB 207499

TABLE 14.1N

SUMMARY OF TESTS OF SIGNIFICANCE FOR INTERACTION TERMS FOR CHANGE FROM BASELINE IN PRE-BD TROUGH FEV1 (L) - ITT

PROTOCOL 157

FACTOR	P-VALUE
TREATMENT-BY-COUNTRY	0.7755
TREATMENT-BY-VISIT	0.5414

1. STATISTICS ARE REPORTED BASED ON THE VALUE CORRESPONDING TO THE MAXIMUM FEV1 (L)
2. P-VALUES ARE BASED ON A REPEATED MEASURES MODEL WITH ONLY THE DISPLAYED TWO-FACTOR INTERACTIONS AND ALL MAIN EFFECTS

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.2A

SUMMARY OF AVERAGE CHANGE FROM BASELINE OVER 52 WEEKS (REPEATED MEASURES ANALYSIS) IN TOTAL SCORE OF THE SGRQ - ITT
PROTOCOL 157

	BASELINE		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
PLACEBO	346	38.456	1.048	-1.495	0.748	-2.965	-0.025	.	.	.	
SB 207499	299	38.811	1.122	-1.293	0.800	-2.864	0.279	0.202	-1.700	2.104	0.835

1. MEANS ARE ADJUSTED FOR BASELINE VALUE, COUNTRY AND WEEK
2. * SIGNIFICANTLY DIFFERENT FROM PLACEBO

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.2AX

SUMMARY OF AVERAGE CHANGE FROM BASELINE OVER 52 WEEKS (REPEATED MEASURES ANALYSIS) IN TOTAL SCORE OF THE SGRQ BY REVERSIBILITY - ITT
PROTOCOL 157

			BASELINE		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
POPULATION	TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
NON-REVERSIBLE	PLACEBO	337	38.223	1.065	-1.499	0.766	-3.003	0.004	.	.	.	
	SB 207499	289	38.276	1.139	-1.406	0.819	-3.015	0.203	0.093	-1.843	2.029	0.925
REVERSIBLE	PLACEBO	8	50.444	4.903	-1.816	4.331	-12.41	8.781	.	.	.	
	SB 207499	8	47.080	5.746	3.568	5.035	-8.752	15.888	5.384	-13.07	23.837	0.502

1. MEANS ARE ADJUSTED FOR BASELINE VALUE, COUNTRY AND WEEK
2. * SIGNIFICANTLY DIFFERENT FROM PLACEBO

CONFIDENTIAL

SB 207499

TABLE 14.2B

SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN TOTAL SCORE OF THE SGRQ BY WEEK AND TREATMENT GROUP - ITT
PROTOCOL 157

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	384	39.158	0.987	.	.	.	.	.	.	.	.
	SB 207499	360	39.485	1.023	.	.	.	.	.	.	.	.
WEEK 28	PLACEBO	336	36.911	0.811	-1.822	0.811	-3.415	-0.228	.	.	.	.
	SB 207499	287	37.327	0.879	-1.407	0.879	-3.132	0.319	0.415	-1.645	2.475	0.692
WEEK 52	PLACEBO	290	37.271	0.903	-1.235	0.903	-3.009	0.539	.	.	.	.
	SB 207499	263	36.984	0.947	-1.522	0.947	-3.383	0.338	-0.287	-2.552	1.978	0.804
ENDPOINT	PLACEBO	384	38.882	0.799	-0.637	0.799	-2.206	0.931	.	.	.	.
	SB 207499	360	38.383	0.827	-1.137	0.827	-2.761	0.488	-0.499	-2.513	1.514	0.627

1. MEANS ARE ADJUSTED FOR BASELINE VALUE AND COUNTRY
2. BASELINE = VISIT 3; WEEK 28, 52 =VISIT 9, 12; ENDPOINT = LOCF
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.2BS

SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN TOTAL SCORE OF THE SGRQ BY WEEK AND TREATMENT GROUP
- ITT BASELINE SMOKERS
PROTOCOL 157

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	165	38.650	1.610	.	.	.	.	.	.	.	.
	SB 207499	164	39.887	1.519	.	.	.	.	.	.	.	.
WEEK 28	PLACEBO	146	38.382	1.268	-2.652	1.268	-5.149	-0.156	.	.	.	.
	SB 207499	137	39.008	1.244	-2.026	1.244	-4.476	0.424	0.626	-2.379	3.632	0.682
WEEK 52	PLACEBO	130	39.254	1.543	-1.568	1.543	-4.608	1.471	.	.	.	.
	SB 207499	126	38.175	1.451	-2.647	1.451	-5.505	0.212	-1.079	-4.532	2.375	0.539
ENDPOINT	PLACEBO	165	40.335	1.302	-1.122	1.302	-3.684	1.440	.	.	.	.
	SB 207499	164	40.010	1.224	-1.447	1.224	-3.856	0.962	-0.325	-3.342	2.692	0.832

1. MEANS ARE ADJUSTED FOR BASELINE VALUE AND COUNTRY
2. BASELINE = VISIT 3; WEEK 28, 52 =VISIT 9, 12; ENDPOINT = LOCF
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.2BT

SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN TOTAL SCORE OF THE SGRQ BY WEEK AND TREATMENT GROUP
- ITT BASELINE NON-SMOKERS
PROTOCOL 157

		WEEKLY ASSESSMENT			CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	219	39.342	1.402	.	.	.	.	.	.	.	.
	SB 207499	196	38.844	1.524	.	.	.	.	.	.	.	.
WEEK 28	PLACEBO	190	35.864	1.219	-0.954	1.219	-3.353	1.445	.	.	.	.
	SB 207499	150	36.164	1.366	-0.654	1.366	-3.342	2.033	0.300	-2.594	3.193	0.839
WEEK 52	PLACEBO	160	35.511	1.256	-0.999	1.256	-3.472	1.474	.	.	.	.
	SB 207499	137	35.848	1.370	-0.662	1.370	-3.359	2.034	0.337	-2.746	3.420	0.830
ENDPOINT	PLACEBO	219	37.679	1.138	-0.305	1.138	-2.542	1.932	.	.	.	.
	SB 207499	196	36.980	1.236	-1.003	1.236	-3.433	1.426	-0.698	-3.482	2.086	0.622

1. MEANS ARE ADJUSTED FOR BASELINE VALUE AND COUNTRY
2. BASELINE = VISIT 3; WEEK 28, 52 =VISIT 9, 12; ENDPOINT = LOCF
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.2BU

SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN TOTAL SCORE OF THE SGRQ BY WEEK AND TREATMENT GROUP
- ITT BASELINE/ON-THERAPY SMOKING STATUS: S/S
PROTOCOL 157

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	134	38.711	1.904	.	.	.	.	.	.	.	.
	SB 207499	130	40.408	1.871	.	.	.	.	.	.	.	.
WEEK 28	PLACEBO	120	38.764	1.605	-2.157	1.605	-5.320	1.006	.	.	.	.
	SB 207499	112	39.423	1.627	-1.499	1.627	-4.706	1.708	0.658	-2.850	4.167	0.712
WEEK 52	PLACEBO	110	39.928	1.893	-0.891	1.893	-4.625	2.842	.	.	.	.
	SB 207499	104	39.757	1.889	-1.062	1.889	-4.788	2.664	-0.171	-3.982	3.640	0.930
ENDPOINT	PLACEBO	134	40.620	1.529	-0.615	1.529	-3.628	2.397	.	.	.	.
	SB 207499	130	40.724	1.498	-0.511	1.498	-3.461	2.439	0.104	-3.284	3.492	0.952

1. MEANS ARE ADJUSTED FOR BASELINE VALUE AND COUNTRY
2. BASELINE = VISIT 3; WEEK 28, 52 =VISIT 9, 12; ENDPOINT = LOCF
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.2BV

SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN TOTAL SCORE OF THE SGRQ BY WEEK AND TREATMENT GROUP
- ITT BASELINE/ON-THERAPY SMOKING STATUS: N/N
PROTOCOL 157

		WEEKLY ASSESSMENT			CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	197	39.002	1.514	.	.	.	.	.	.	.	.
	SB 207499	185	38.860	1.604	.	.	.	.	.	.	.	.
WEEK 28	PLACEBO	173	36.945	1.329	0.099	1.329	-2.516	2.715	.	.	.	.
	SB 207499	145	36.402	1.483	-0.444	1.483	-3.363	2.475	-0.543	-3.486	2.399	0.717
WEEK 52	PLACEBO	147	35.850	1.366	-0.534	1.366	-3.224	2.156	.	.	.	.
	SB 207499	133	35.709	1.435	-0.675	1.435	-3.501	2.152	-0.141	-3.310	3.029	0.930
ENDPOINT	PLACEBO	197	37.975	1.211	0.046	1.211	-2.335	2.428	.	.	.	.
	SB 207499	185	36.830	1.282	-1.098	1.282	-3.620	1.424	-1.145	-4.039	1.749	0.437

1. MEANS ARE ADJUSTED FOR BASELINE VALUE AND COUNTRY
2. BASELINE = VISIT 3; WEEK 28, 52 =VISIT 9, 12; ENDPOINT = LOCF
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.2BW

SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN TOTAL SCORE OF THE SGRQ BY WEEK AND TREATMENT GROUP
- ITT BASELINE/ON-THERAPY SMOKING STATUS: N/S OR S/N
PROTOCOL 157

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	49	38.337	2.664	.	.	.	.	.	.	.	.
	SB 207499	34	36.099	3.117	.	.	.	.	.	.	.	.
WEEK 28	PLACEBO	43	37.133	2.100	-2.868	2.100	-7.077	1.340	.	.	.	.
	SB 207499	30	40.655	2.563	0.653	2.563	-4.483	5.790	3.522	-2.936	9.980	0.279
WEEK 52	PLACEBO	32	38.426	2.717	-1.695	2.717	-7.187	3.797	.	.	.	.
	SB 207499	26	34.352	3.223	-5.769	3.223	-12.284	0.746	-4.074	-12.262	4.114	0.321
ENDPOINT	PLACEBO	49	38.357	2.542	-1.712	2.542	-6.789	3.365	.	.	.	.
	SB 207499	34	37.520	3.001	-2.549	3.001	-8.543	3.445	-0.837	-8.241	6.567	0.822

1. MEANS ARE ADJUSTED FOR BASELINE VALUE AND COUNTRY
2. BASELINE = VISIT 3; WEEK 28, 52 =VISIT 9, 12; ENDPOINT = LOCF
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.2BX

SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN TOTAL SCORE OF THE SGRQ BY WEEK AND TREATMENT GROUP
- ITT NON-REVERSIBLE PATIENTS
PROTOCOL 157

		WEEKLY ASSESSMENT			CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	374	38.974	1.003	.	.	.	.	.	.	.	.
	SB 207499	347	39.099	1.039	.	.	.	.	.	.	.	.
WEEK 28	PLACEBO	328	36.604	0.827	-1.775	0.827	-3.400	-0.150	.	.	.	.
	SB 207499	277	36.939	0.898	-1.439	0.898	-3.203	0.324	0.336	-1.760	2.431	0.753
WEEK 52	PLACEBO	283	36.890	0.922	-1.325	0.922	-3.136	0.487	.	.	.	.
	SB 207499	254	36.473	0.970	-1.742	0.970	-3.647	0.164	-0.417	-2.726	1.893	0.723
ENDPOINT	PLACEBO	374	38.570	0.815	-0.713	0.815	-2.313	0.888	.	.	.	.
	SB 207499	347	38.017	0.844	-1.266	0.844	-2.924	0.391	-0.553	-2.600	1.494	0.596

1. MEANS ARE ADJUSTED FOR BASELINE VALUE AND COUNTRY
2. BASELINE = VISIT 3; WEEK 28, 52 =VISIT 9, 12; ENDPOINT = LOCF
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.2BY

SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN TOTAL SCORE OF THE SGRQ BY WEEK AND TREATMENT GROUP
- ITT REVERSIBLE PATIENTS
PROTOCOL 157

		WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	9	42.131	7.652	.	.	.	.	.	.	.	.
	SB 207499	11	44.845	7.652	.	.	.	.	.	.	.	.
WEEK 28	PLACEBO	7	45.106	5.997	-3.893	5.997	-19.309	11.523	.	.	.	.
	SB 207499	8	44.841	6.853	-4.158	6.853	-21.773	13.458	-0.265	-26.150	25.620	0.980
WEEK 52	PLACEBO	7	46.832	5.344	0.645	5.344	-14.192	15.483	.	.	.	.
	SB 207499	7	53.307	6.822	7.120	6.822	-11.820	26.061	6.475	-22.451	35.400	0.568
ENDPOINT	PLACEBO	9	47.244	4.255	2.098	4.255	-7.714	11.911	.	.	.	.
	SB 207499	11	49.730	4.219	4.585	4.219	-5.145	14.315	2.486	-13.135	18.108	0.723

1. MEANS ARE ADJUSTED FOR BASELINE VALUE AND COUNTRY
2. BASELINE = VISIT 3; WEEK 28, 52 =VISIT 9, 12; ENDPOINT = LOCF
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.2C

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN TOTAL SCORE OF THE SGRQ BY WEEK AND TREATMENT GROUP - ITT
PROTOCOL 157

			BASELINE		WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	384	39.472	18.263	39.472	18.263	37.607	0.000	87.785	.	.	.	.	.
	SB 207499	360	39.570	18.439	39.570	18.439	37.137	0.000	97.817	.	.	.	.	.
WEEK 28	PLACEBO	336	38.818	18.148	37.151	18.549	36.307	1.050	88.872	-1.667	13.201	-1.455	-47.970	35.198
	SB 207499	287	38.634	18.531	37.135	19.413	36.371	0.000	86.489	-1.499	14.348	-0.925	-60.789	46.443
WEEK 52	PLACEBO	290	38.582	18.234	36.579	19.356	34.404	0.000	88.452	-2.003	14.260	-1.271	-46.651	39.708
	SB 207499	263	38.422	18.318	35.998	19.341	33.512	0.000	91.828	-2.424	13.986	-2.494	-59.144	35.319
ENDPOINT	PLACEBO	384	39.472	18.263	38.569	20.061	37.110	0.000	88.452	-0.903	14.491	-0.651	-46.651	39.708
	SB 207499	360	39.570	18.439	37.936	19.388	36.685	0.000	91.828	-1.635	14.881	-2.034	-59.144	55.409

1. MEAN VALUES ARE SAMPLE MEANS
2. BASELINE = VISIT 3; WEEK 28, 52 = VISIT 9, 12; ENDPOINT = LOCF

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.2CS

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN TOTAL SCORE OF THE SGRQ BY WEEK AND TREATMENT GROUP
- ITT BASELINE SMOKERS
PROTOCOL 157

			BASELINE		WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	165	40.768	18.158	40.768	18.158	38.971	0.000	87.424	.	.	.	.	.
	SB 207499	164	42.151	18.343	42.151	18.343	40.824	5.071	90.347	.	.	.	.	.
WEEK 28	PLACEBO	146	40.842	18.165	38.696	18.725	37.651	1.050	88.872	-2.146	13.099	-1.916	-47.970	27.260
	SB 207499	137	41.239	18.206	39.370	19.176	39.462	0.000	86.489	-1.869	13.061	-1.832	-49.004	31.266
WEEK 52	PLACEBO	130	40.666	18.105	39.283	19.823	35.187	0.000	88.452	-1.383	14.327	-1.347	-40.583	39.708
	SB 207499	126	40.983	17.596	38.528	19.707	35.215	0.000	91.828	-2.455	13.527	-4.130	-39.515	35.319
ENDPOINT	PLACEBO	165	40.768	18.158	40.051	19.878	38.773	0.000	88.452	-0.717	14.373	-0.341	-45.047	39.708
	SB 207499	164	42.151	18.343	40.484	19.883	39.190	0.000	91.828	-1.667	13.817	-2.147	-49.004	35.319

1. MEAN VALUES ARE SAMPLE MEANS
2. BASELINE = VISIT 3; WEEK 28, 52 = VISIT 9, 12; ENDPOINT = LOCF

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.2CT

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN TOTAL SCORE OF THE SGRQ BY WEEK AND TREATMENT GROUP
- ITT BASELINE NON-SMOKERS
PROTOCOL 157

			BASELINE		WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	219	38.496	18.323	38.496	18.323	37.575	0.000	87.785	.	.	.	.	.
	SB 207499	196	37.411	18.286	37.411	18.286	36.163	0.000	97.817	.	.	.	.	.
WEEK 28	PLACEBO	190	37.262	18.029	35.963	18.374	34.945	1.050	85.890	-1.299	13.302	-0.777	-47.115	35.198
	SB 207499	150	36.255	18.565	35.093	19.467	34.063	0.000	79.884	-1.162	15.466	-0.276	-60.789	46.443
WEEK 52	PLACEBO	160	36.889	18.220	34.383	18.744	32.819	0.867	77.267	-2.506	14.230	-1.127	-46.651	27.177
	SB 207499	137	36.067	18.714	33.671	18.769	31.714	0.000	76.860	-2.396	14.444	-1.310	-59.144	31.333
ENDPOINT	PLACEBO	219	38.496	18.323	37.452	20.171	35.965	0.867	85.890	-1.044	14.611	-0.765	-46.651	31.789
	SB 207499	196	37.411	18.286	35.804	18.749	33.917	0.000	90.615	-1.607	15.751	-1.385	-59.144	55.409

1. MEAN VALUES ARE SAMPLE MEANS
2. BASELINE = VISIT 3; WEEK 28, 52 = VISIT 9, 12; ENDPOINT = LOCF

CONFIDENTIAL

SB 207499

TABLE 14.2CU

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN TOTAL SCORE OF THE SGRQ BY WEEK AND TREATMENT GROUP
- ITT BASELINE/ON-THERAPY SMOKING STATUS: S/S
PROTOCOL 157

		BASELINE		WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	134	40.563	17.999	40.563	17.999	39.318	0.000	87.424	.	.	.	.	.
	SB 207499	130	41.928	18.488	41.928	18.488	39.496	5.071	90.347	.	.	.	.	.
WEEK 28	PLACEBO	120	40.626	17.794	38.189	18.751	36.969	1.050	88.872	-2.436	13.641	-1.916	-47.970	27.260
	SB 207499	112	41.238	18.123	39.757	19.366	40.482	0.000	86.489	-1.481	13.561	-1.488	-49.004	31.266
WEEK 52	PLACEBO	110	40.686	17.811	38.908	19.768	35.102	0.000	86.173	-1.777	14.360	-1.955	-40.583	39.708
	SB 207499	104	40.961	17.450	39.414	19.376	35.215	0.734	91.828	-1.547	13.785	-2.147	-39.515	35.319
ENDPOINT	PLACEBO	134	40.563	17.999	39.240	19.992	37.890	0.000	86.173	-1.323	14.575	-1.059	-45.047	39.708
	SB 207499	130	41.928	18.488	40.723	19.824	38.291	0.734	91.828	-1.205	13.842	-1.708	-49.004	35.319

1. MEAN VALUES ARE SAMPLE MEANS
2. BASELINE = VISIT 3; WEEK 28, 52 = VISIT 9, 12; ENDPOINT = LOCF

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.2CV

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN TOTAL SCORE OF THE SGRQ BY WEEK AND TREATMENT GROUP
- ITT BASELINE/ON-THERAPY SMOKING STATUS: N/N
PROTOCOL 157

			BASELINE		WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	197	38.160	18.590	38.160	18.590	36.562	0.000	87.785	.	.	.	.	.
	SB 207499	185	37.683	18.512	37.683	18.512	36.384	0.000	97.817	.	.	.	.	.
WEEK 28	PLACEBO	173	37.141	18.230	36.395	18.332	35.466	1.050	85.890	-0.746	13.049	-0.211	-47.115	35.198
	SB 207499	145	36.492	18.709	34.935	19.495	33.391	0.000	79.884	-1.558	15.491	-0.519	-60.789	46.443
WEEK 52	PLACEBO	147	36.557	18.506	34.641	18.922	33.491	0.867	77.267	-1.916	14.375	-0.667	-46.651	27.177
	SB 207499	133	36.192	18.867	33.777	18.796	31.714	0.000	76.860	-2.415	14.557	-1.310	-59.144	31.333
ENDPOINT	PLACEBO	197	38.160	18.590	37.523	20.100	36.093	0.867	85.890	-0.637	14.538	-0.138	-46.651	31.789
	SB 207499	185	37.683	18.512	35.970	18.989	32.985	0.000	90.615	-1.712	16.020	-1.459	-59.144	55.409

1. MEAN VALUES ARE SAMPLE MEANS
2. BASELINE = VISIT 3; WEEK 28, 52 = VISIT 9, 12; ENDPOINT = LOCF

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.2CW

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN TOTAL SCORE OF THE SGRQ BY WEEK AND TREATMENT GROUP
- ITT BASELINE/ON-THERAPY SMOKING STATUS: S/N OR N/S
PROTOCOL 157

			BASELINE		WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	49	40.325	17.621	40.325	17.621	39.209	8.711	77.383	.	.	.	.	.
	SB 207499	34	39.700	18.421	39.700	18.421	31.783	11.077	76.756	.	.	.	.	.
WEEK 28	PLACEBO	43	40.516	18.577	37.291	19.143	33.886	4.492	80.476	-3.225	12.563	-5.234	-28.513	25.998
	SB 207499	30	39.264	18.490	37.980	18.509	35.725	0.000	79.207	-1.284	11.608	-2.104	-22.278	22.229
WEEK 52	PLACEBO	32	40.482	18.209	37.149	19.788	34.044	7.079	88.452	-3.333	13.947	-1.498	-38.850	17.802
	SB 207499	26	39.677	18.104	33.694	20.683	35.604	0.000	67.649	-5.983	11.473	-9.347	-22.862	26.743
ENDPOINT	PLACEBO	49	40.325	17.621	39.532	20.324	35.085	4.492	88.452	-0.793	14.706	-0.765	-38.850	26.636
	SB 207499	34	39.700	18.421	37.578	20.604	40.806	0.000	78.694	-2.122	14.087	-8.397	-22.862	30.340

1. MEAN VALUES ARE SAMPLE MEANS
2. BASELINE = VISIT 3; WEEK 28, 52 = VISIT 9, 12; ENDPOINT = LOCF

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.2I

DESCRIPTIVE STATISTICS FOR TOTAL SCORE OF THE SGRQ AT ENDPOINT BY COUNTRY AND TREATMENT GROUP - ITT

PROTOCOL 157

COUNTRY	TREATMENT GROUP	N	BASELINE MEAN	BASELINE SD	ENDPOINT ASSESSMENT MEAN	ENDPOINT ASSESSMENT SD	ENDPOINT ASSESSMENT MEDIAN	ENDPOINT ASSESSMENT MIN	ENDPOINT ASSESSMENT MAX	CHANGE FROM BASELINE MEAN	CHANGE FROM BASELINE SD	CHANGE FROM BASELINE MEDIAN	CHANGE FROM BASELINE MIN	CHANGE FROM BASELINE MAX
Australia	PLACEBO	16	39.647	18.791	38.308	24.967	31.859	2.750	85.890	-1.339	12.816	-2.327	-33.37	19.406
	SB 207499	12	46.351	15.332	46.106	16.915	49.723	13.511	63.927	-0.245	9.234	-0.603	-14.87	16.250
Belgium	PLACEBO	11	45.883	16.838	48.934	16.555	48.092	22.289	76.906	3.051	10.535	3.790	-23.03	20.577
	SB 207499	8	43.833	7.893	30.024	6.491	31.704	20.336	38.793	-13.81	9.416	-14.19	-31.27	-2.053
Czech Republic	PLACEBO	15	46.514	20.118	40.031	15.794	35.163	18.293	71.417	-6.484	19.782	-2.652	-40.40	19.599
	SB 207499	18	47.727	19.131	45.666	17.602	44.483	14.812	70.392	-2.061	17.625	0.780	-59.14	23.760
Denmark	PLACEBO	11	45.671	15.112	47.598	12.679	47.451	23.272	66.792	1.927	11.611	3.038	-22.33	21.113
	SB 207499	5	39.072	17.319	42.314	16.685	43.711	23.194	67.897	3.243	11.676	3.191	-13.43	16.456
Finland	PLACEBO	14	34.207	20.287	34.145	19.182	30.530	3.795	61.187	-0.062	10.887	-3.062	-20.48	20.344
	SB 207499	9	26.772	11.456	24.696	20.856	17.206	1.882	61.546	-2.076	14.927	-3.903	-18.43	26.743
France	PLACEBO	10	37.540	17.005	39.717	21.574	30.197	13.919	74.655	2.177	11.751	2.139	-12.45	25.946
	SB 207499	8	33.574	20.133	31.993	23.234	34.816	0.000	60.866	-1.581	11.402	-4.260	-19.03	14.651
Germany	PLACEBO	62	44.164	16.970	41.028	20.604	39.604	2.645	82.448	-3.136	17.271	-3.410	-46.65	39.708
	SB 207499	66	43.702	21.223	39.640	21.699	40.678	0.734	82.025	-4.062	15.620	-3.533	-49.00	29.769
Italy	PLACEBO	36	28.358	17.090	24.988	18.279	20.587	0.000	77.267	-3.370	13.165	-1.833	-33.76	31.789
	SB 207499	43	31.935	20.472	30.833	19.183	28.801	0.000	77.383	-1.102	18.582	0.787	-56.45	46.443
Netherlands	PLACEBO	13	39.695	13.153	45.062	17.357	42.187	14.869	76.377	5.367	9.882	1.990	-8.989	25.447
	SB 207499	15	38.246	20.496	42.819	22.121	41.252	14.814	86.091	4.573	18.278	3.567	-17.27	44.831
New Zealand	PLACEBO	13	36.830	15.086	40.276	15.319	39.319	16.035	75.041	3.447	10.116	3.717	-13.51	26.833
	SB 207499	11	35.774	12.576	39.092	14.977	32.213	22.189	71.547	3.318	15.707	0.857	-28.37	35.319
Poland	PLACEBO	3	31.812	25.369	31.607	20.832	40.374	7.824	46.621	-0.205	5.439	-0.341	-5.575	5.300
	SB 207499	8	46.817	22.038	43.785	20.333	42.535	4.707	72.492	-3.032	7.771	-5.833	-10.29	11.169
Russia	PLACEBO	30	49.711	16.753	41.758	18.508	41.165	6.332	75.555	-7.953	17.948	-10.92	-45.05	35.527
	SB 207499	26	49.126	15.234	45.600	19.317	41.937	18.354	91.828	-3.526	11.747	-5.406	-21.43	16.388
Slovakia	PLACEBO	13	23.754	8.638	31.450	13.228	29.403	8.939	50.451	7.696	11.894	9.821	-14.16	22.317
	SB 207499	12	28.855	4.462	33.893	13.858	35.040	9.510	59.337	5.037	13.786	4.598	-20.77	32.145
South Africa	PLACEBO	23	38.245	15.437	37.510	16.669	35.085	5.773	71.911	-0.735	14.875	4.690	-33.15	18.978
	SB 207499	22	39.185	13.763	38.474	11.398	35.302	20.929	65.574	-0.711	8.006	-0.718	-13.02	12.714
Spain	PLACEBO	48	30.374	16.774	31.158	18.372	28.794	2.845	71.151	0.783	13.261	0.198	-36.65	27.177
	SB 207499	44	31.844	14.051	32.065	19.012	29.784	0.000	90.615	0.221	14.696	-0.777	-26.63	55.409
Sweden	PLACEBO	20	41.522	13.580	39.164	16.881	36.434	9.791	80.007	-2.359	11.396	-5.409	-18.82	17.501

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.2I

DESCRIPTIVE STATISTICS FOR TOTAL SCORE OF THE SGRQ AT ENDPOINT BY COUNTRY AND TREATMENT GROUP - ITT

PROTOCOL 157

COUNTRY	TREATMENT GROUP	N	BASELINE MEAN	BASELINE SD	ENDPOINT ASSESSMENT MEAN	ENDPOINT ASSESSMENT SD	ENDPOINT ASSESSMENT MEDIAN	ENDPOINT ASSESSMENT MIN	ENDPOINT ASSESSMENT MAX	CHANGE FROM BASELINE MEAN	CHANGE FROM BASELINE SD	CHANGE FROM BASELINE MEDIAN	CHANGE FROM BASELINE MIN	CHANGE FROM BASELINE MAX
Sweden	SB 207499	18	40.502	13.863	36.716	13.966	39.510	9.074	58.748	-3.785	12.182	-6.109	-18.12	30.340
Taiwan	PLACEBO	8	31.772	15.114	29.811	11.556	34.342	10.941	45.633	-1.961	7.458	-2.092	-12.32	10.941
	SB 207499	7	39.747	16.516	27.718	15.203	30.253	0.000	41.460	-12.03	14.087	-15.70	-31.15	10.227
United Kingdom	PLACEBO	38	49.794	19.539	51.862	24.169	56.834	3.544	88.452	2.068	15.063	3.183	-38.85	30.716
	SB 207499	28	45.756	20.392	45.802	21.364	43.801	4.765	85.920	0.046	16.433	-1.891	-26.04	29.974

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.3A

SUMMARY OF AVERAGE CHANGE FROM BASELINE OVER 52 WEEKS (REPEATED MEASURES ANALYSIS) IN POST-BD TROUGH FEV1 (L)
BY SMOKING STATUS AND TREATMENT GROUP - ITT
PROTOCOL 157

			BASELINE		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
SMOKING STATUS BASELINE/ON-THERAPY	TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
S/-	PLACEBO	178	1.601	0.043	-0.004	0.015	-0.035	0.026	.	.	.	
	SB 207499	177	1.506	0.041	0.030	0.015	0.000	0.059	0.034	-0.002	0.070	0.061
N/-	PLACEBO	233	1.463	0.034	-0.004	0.013	-0.029	0.022	.	.	.	
	SB 207499	213	1.372	0.036	0.033	0.014	0.006	0.061	0.037	0.007	0.068	0.017*
S/S	PLACEBO	141	1.602	0.051	-0.008	0.019	-0.045	0.028	.	.	.	
	SB 207499	146	1.495	0.051	0.022	0.019	-0.015	0.058	0.030	-0.010	0.070	0.145
N/N	PLACEBO	213	1.451	0.035	0.000	0.014	-0.027	0.027	.	.	.	
	SB 207499	202	1.384	0.036	0.034	0.014	0.005	0.062	0.033	0.001	0.065	0.041*
S/N or N/S	PLACEBO	57	1.600	0.070	-0.018	0.025	-0.068	0.032	.	.	.	
	SB 207499	42	1.468	0.084	0.009	0.029	-0.050	0.067	0.026	-0.041	0.094	0.444
All Patients	PLACEBO	411	1.518	0.025	-0.002	0.009	-0.021	0.016	.	.	.	
	SB 207499	390	1.432	0.026	0.032	0.010	0.013	0.051	0.034	0.011	0.057	0.004*

1. MEANS ARE ADJUSTED FOR BASELINE VALUE, COUNTRY AND WEEK
2. STATISTICS ARE REPORTED BASED ON THE MAXIMUM OF THREE REPORTED VALUES OF FEV1 (L)
3. * SIGNIFICANTLY DIFFERENT FROM PLACEBO
4. SMOKING STATUS: S= SMOKER ; N= NON-SMOKER ; - = EITHER

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.3B

SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN POST-BD TROUGH FEV1(L) BY WEEK AND TREATMENT GROUP - ITT
PROTOCOL 157

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	414	1.420	0.024	.	.	.	.	.	.	.	.
	SB 207499	397	1.332	0.025	.	.	.	.	.	.	.	.
WEEK 4	PLACEBO	392	1.461	0.011	0.015	0.011	-0.008	0.037	.	.	.	.
	SB 207499	371	1.485	0.012	0.038	0.012	0.015	0.061	0.024	-0.005	0.052	0.106
WEEK 8	PLACEBO	387	1.471	0.011	0.017	0.011	-0.004	0.038	.	.	.	.
	SB 207499	365	1.495	0.011	0.041	0.011	0.019	0.063	0.024	-0.003	0.051	0.086
WEEK 12	PLACEBO	377	1.456	0.012	0.005	0.012	-0.019	0.028	.	.	.	.
	SB 207499	344	1.507	0.013	0.056	0.013	0.031	0.080	0.051	0.021	0.081	0.001
WEEK 20	PLACEBO	371	1.452	0.013	-0.004	0.013	-0.029	0.021	.	.	.	.
	SB 207499	328	1.494	0.013	0.037	0.013	0.011	0.064	0.042	0.010	0.073	0.010
WEEK 28	PLACEBO	359	1.461	0.014	-0.002	0.014	-0.029	0.025	.	.	.	.
	SB 207499	311	1.502	0.015	0.039	0.015	0.010	0.067	0.041	0.006	0.076	0.021
WEEK 36	PLACEBO	342	1.439	0.015	-0.024	0.015	-0.052	0.005	.	.	.	.
	SB 207499	298	1.494	0.015	0.031	0.015	0.001	0.062	0.055	0.018	0.092	0.003
WEEK 44	PLACEBO	326	1.446	0.014	-0.021	0.014	-0.049	0.008	.	.	.	.
	SB 207499	284	1.518	0.015	0.051	0.015	0.021	0.081	0.072	0.035	0.109	0.000
WEEK 52	PLACEBO	316	1.452	0.015	-0.017	0.015	-0.046	0.013	.	.	.	.
	SB 207499	269	1.499	0.016	0.029	0.016	-0.002	0.061	0.046	0.009	0.083	0.016
ENDPOINT	PLACEBO	414	1.421	0.012	-0.029	0.012	-0.054	-0.005	.	.	.	.
	SB 207499	397	1.474	0.012	0.024	0.012	-0.000	0.048	0.053	0.023	0.084	0.001

1. MEANS ARE ADJUSTED FOR BASELINE VALUE AND COUNTRY
2. STATISITCS ARE REPORTED BASED ON THE MAXIMUM OF THREE REPORTED VALUES OF FEV1 (L)
3. BASELINE = VISIT 3; WEEK 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 5, 6, 7, 8, 9, 10, 11, 12; ENDPOINT = LOCF
4. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.3BS

SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN POST-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP
- ITT BASELINE SMOKERS
PROTOCOL 157

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	181	1.506	0.041	.	.	.	.	.	.	.	.
	SB 207499	180	1.403	0.040	.	.	.	.	.	.	.	.
WEEK 4	PLACEBO	175	1.540	0.018	0.006	0.018	-0.029	0.042	.	.	.	.
	SB 207499	169	1.567	0.018	0.033	0.018	-0.002	0.067	0.027	-0.016	0.069	0.218
WEEK 8	PLACEBO	170	1.540	0.018	0.005	0.018	-0.030	0.041	.	.	.	.
	SB 207499	167	1.569	0.018	0.034	0.018	-0.001	0.069	0.029	-0.014	0.071	0.191
WEEK 12	PLACEBO	168	1.525	0.020	-0.002	0.020	-0.042	0.038	.	.	.	.
	SB 207499	160	1.580	0.020	0.053	0.020	0.014	0.092	0.055	0.007	0.103	0.024
WEEK 20	PLACEBO	162	1.536	0.021	0.007	0.021	-0.034	0.048	.	.	.	.
	SB 207499	152	1.570	0.021	0.041	0.021	0.000	0.082	0.034	-0.015	0.084	0.175
WEEK 28	PLACEBO	156	1.539	0.022	0.003	0.022	-0.041	0.047	.	.	.	.
	SB 207499	145	1.577	0.022	0.041	0.022	-0.003	0.084	0.038	-0.016	0.092	0.166
WEEK 36	PLACEBO	151	1.517	0.025	-0.016	0.025	-0.066	0.034	.	.	.	.
	SB 207499	139	1.582	0.025	0.049	0.025	-0.000	0.098	0.064	0.006	0.123	0.032
WEEK 44	PLACEBO	148	1.507	0.024	-0.021	0.024	-0.069	0.027	.	.	.	.
	SB 207499	134	1.583	0.024	0.055	0.024	0.008	0.102	0.076	0.019	0.132	0.009
WEEK 52	PLACEBO	141	1.516	0.027	-0.013	0.027	-0.065	0.039	.	.	.	.
	SB 207499	128	1.562	0.026	0.033	0.026	-0.018	0.083	0.046	-0.013	0.106	0.129
ENDPOINT	PLACEBO	181	1.498	0.021	-0.034	0.021	-0.074	0.007	.	.	.	.
	SB 207499	180	1.546	0.020	0.015	0.020	-0.024	0.054	0.049	-0.001	0.098	0.054

1. MEANS ARE ADJUSTED FOR BASELINE VALUE AND COUNTRY
2. STATISITCS ARE REPORTED BASED ON THE MAXIMUM OF THREE REPORTED VALUES OF FEV1 (L)
3. BASELINE = VISIT 3; WEEK 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 5, 6, 7, 8, 9, 10, 11, 12; ENDPOINT = LOCF
4. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.3BT

SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN POST-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP
- ITT BASELINE NON-SMOKERS
PROTOCOL 157

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	233	1.360	0.033	.	.	.	.	.	.	.	.
	SB 207499	217	1.270	0.034	.	.	.	.	.	.	.	.
WEEK 4	PLACEBO	217	1.394	0.016	0.019	0.016	-0.013	0.051	.	.	.	.
	SB 207499	202	1.419	0.017	0.044	0.017	0.010	0.078	0.025	-0.014	0.064	0.210
WEEK 8	PLACEBO	217	1.411	0.015	0.024	0.015	-0.005	0.053	.	.	.	.
	SB 207499	198	1.434	0.016	0.046	0.016	0.016	0.077	0.023	-0.013	0.059	0.212
WEEK 12	PLACEBO	209	1.392	0.017	0.004	0.017	-0.031	0.038	.	.	.	.
	SB 207499	184	1.443	0.019	0.055	0.019	0.018	0.092	0.051	0.011	0.091	0.013
WEEK 20	PLACEBO	209	1.386	0.018	-0.012	0.018	-0.047	0.024	.	.	.	.
	SB 207499	176	1.435	0.020	0.037	0.020	-0.002	0.076	0.048	0.006	0.091	0.025
WEEK 28	PLACEBO	203	1.393	0.020	-0.011	0.020	-0.050	0.028	.	.	.	.
	SB 207499	166	1.440	0.022	0.036	0.022	-0.007	0.079	0.047	-0.000	0.094	0.050
WEEK 36	PLACEBO	191	1.379	0.020	-0.025	0.020	-0.065	0.015	.	.	.	.
	SB 207499	159	1.431	0.022	0.027	0.022	-0.017	0.070	0.052	0.004	0.099	0.032
WEEK 44	PLACEBO	178	1.389	0.020	-0.024	0.020	-0.064	0.016	.	.	.	.
	SB 207499	150	1.464	0.023	0.051	0.023	0.007	0.096	0.075	0.026	0.124	0.003
WEEK 52	PLACEBO	175	1.400	0.022	-0.018	0.022	-0.062	0.025	.	.	.	.
	SB 207499	141	1.449	0.024	0.030	0.024	-0.018	0.078	0.048	0.000	0.096	0.049
ENDPOINT	PLACEBO	233	1.358	0.017	-0.027	0.017	-0.060	0.006	.	.	.	.
	SB 207499	217	1.418	0.017	0.033	0.017	-0.001	0.068	0.060	0.021	0.100	0.003

1. MEANS ARE ADJUSTED FOR BASELINE VALUE AND COUNTRY
2. STATISITCS ARE REPORTED BASED ON THE MAXIMUM OF THREE REPORTED VALUES OF FEV1 (L)
3. BASELINE = VISIT 3; WEEK 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 5, 6, 7, 8, 9, 10, 11,12; ENDPOINT = LOCF
4. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14.3BU

SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN POST-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP
- ITT BASELINE/ON THERAPY SMOKING STATUS: S/S
PROTOCOL 157

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	144	1.509	0.049	.	.	.	.	.	.	.	.
	SB 207499	149	1.394	0.048	.	.	.	.	.	.	.	.
WEEK 4	PLACEBO	138	1.542	0.022	-0.004	0.022	-0.046	0.039	.	.	.	.
	SB 207499	140	1.565	0.021	0.020	0.021	-0.022	0.062	0.024	-0.024	0.071	0.332
WEEK 8	PLACEBO	135	1.552	0.022	-0.001	0.022	-0.045	0.043	.	.	.	.
	SB 207499	137	1.577	0.022	0.025	0.022	-0.018	0.068	0.026	-0.023	0.075	0.305
WEEK 12	PLACEBO	134	1.552	0.025	0.005	0.025	-0.044	0.054	.	.	.	.
	SB 207499	131	1.592	0.025	0.044	0.025	-0.004	0.093	0.039	-0.016	0.094	0.160
WEEK 20	PLACEBO	129	1.554	0.025	0.004	0.025	-0.044	0.053	.	.	.	.
	SB 207499	124	1.585	0.025	0.035	0.025	-0.015	0.085	0.030	-0.026	0.087	0.289
WEEK 28	PLACEBO	125	1.546	0.028	-0.011	0.028	-0.066	0.044	.	.	.	.
	SB 207499	118	1.585	0.028	0.029	0.028	-0.028	0.085	0.039	-0.024	0.103	0.223
WEEK 36	PLACEBO	122	1.542	0.032	-0.010	0.032	-0.073	0.053	.	.	.	.
	SB 207499	113	1.587	0.033	0.035	0.033	-0.030	0.099	0.044	-0.021	0.110	0.181
WEEK 44	PLACEBO	121	1.520	0.031	-0.028	0.031	-0.089	0.032	.	.	.	.
	SB 207499	109	1.602	0.032	0.054	0.032	-0.009	0.116	0.082	0.019	0.146	0.011
WEEK 52	PLACEBO	116	1.531	0.030	-0.015	0.030	-0.075	0.045	.	.	.	.
	SB 207499	104	1.582	0.031	0.036	0.031	-0.025	0.098	0.051	-0.012	0.114	0.111
ENDPOINT	PLACEBO	144	1.506	0.023	-0.039	0.023	-0.085	0.007	.	.	.	.
	SB 207499	149	1.550	0.023	0.006	0.023	-0.040	0.051	0.044	-0.008	0.097	0.098

1. MEANS ARE ADJUSTED FOR BASELINE VALUE AND COUNTRY
2. STATISITCS ARE REPORTED BASED ON THE MAXIMUM OF THREE REPORTED VALUES OF FEV1 (L)
3. BASELINE = VISIT 3; WEEK 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 5, 6, 7, 8, 9, 10, 11, 12; ENDPOINT = LOCF
4. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14.3BV

SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN POST-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP
- ITT BASELINE/ON THERAPY SMOKING STATUS: N/N
PROTOCOL 157

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	213	1.344	0.033	.	.	.	.	.	.	.	.
	SB 207499	205	1.277	0.034	.	.	.	.	.	.	.	.
WEEK 4	PLACEBO	198	1.390	0.017	0.023	0.017	-0.011	0.057	.	.	.	.
	SB 207499	191	1.412	0.018	0.046	0.018	0.011	0.081	0.023	-0.018	0.064	0.276
WEEK 8	PLACEBO	199	1.405	0.016	0.026	0.016	-0.005	0.057	.	.	.	.
	SB 207499	188	1.425	0.016	0.046	0.016	0.014	0.078	0.020	-0.018	0.057	0.302
WEEK 12	PLACEBO	191	1.384	0.018	0.006	0.018	-0.030	0.041	.	.	.	.
	SB 207499	175	1.432	0.019	0.054	0.019	0.016	0.092	0.048	0.007	0.090	0.023
WEEK 20	PLACEBO	191	1.379	0.019	-0.010	0.019	-0.048	0.028	.	.	.	.
	SB 207499	167	1.427	0.021	0.038	0.021	-0.003	0.078	0.048	0.004	0.092	0.034
WEEK 28	PLACEBO	186	1.385	0.021	-0.009	0.021	-0.051	0.033	.	.	.	.
	SB 207499	160	1.431	0.023	0.037	0.023	-0.008	0.082	0.046	-0.003	0.095	0.067
WEEK 36	PLACEBO	176	1.378	0.021	-0.020	0.021	-0.061	0.021	.	.	.	.
	SB 207499	153	1.419	0.023	0.021	0.023	-0.024	0.066	0.041	-0.008	0.090	0.100
WEEK 44	PLACEBO	164	1.393	0.021	-0.014	0.021	-0.055	0.028	.	.	.	.
	SB 207499	145	1.452	0.023	0.046	0.023	0.000	0.091	0.059	0.009	0.109	0.021
WEEK 52	PLACEBO	162	1.400	0.023	-0.012	0.023	-0.058	0.034	.	.	.	.
	SB 207499	136	1.441	0.025	0.029	0.025	-0.021	0.079	0.041	-0.009	0.091	0.105
ENDPOINT	PLACEBO	213	1.357	0.017	-0.019	0.017	-0.054	0.015	.	.	.	.
	SB 207499	205	1.411	0.018	0.034	0.018	-0.002	0.070	0.054	0.012	0.095	0.011

1. MEANS ARE ADJUSTED FOR BASELINE VALUE AND COUNTRY
2. STATISITCS ARE REPORTED BASED ON THE MAXIMUM OF THREE REPORTED VALUES OF FEV1 (L)
3. BASELINE = VISIT 3; WEEK 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 5, 6, 7, 8, 9, 10, 11, 12; ENDPOINT = LOCF
4. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14.3BW

SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN POST-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP
- ITT BASELINE/ON THERAPY SMOKING STATUS: N/S OR S/N
PROTOCOL 157

		WEEKLY ASSESSMENT			CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	57	1.513	0.065	.	.	.	.	.	.	.	.
	SB 207499	42	1.398	0.078	.	.	.	.	.	.	.	.
WEEK 4	PLACEBO	56	1.495	0.032	0.010	0.032	-0.054	0.074	.	.	.	.
	SB 207499	40	1.516	0.038	0.031	0.038	-0.044	0.106	0.021	-0.068	0.110	0.641
WEEK 8	PLACEBO	53	1.474	0.029	0.000	0.029	-0.058	0.059	.	.	.	.
	SB 207499	40	1.507	0.034	0.033	0.034	-0.035	0.101	0.033	-0.049	0.115	0.428
WEEK 12	PLACEBO	52	1.433	0.033	-0.030	0.033	-0.097	0.036	.	.	.	.
	SB 207499	38	1.529	0.038	0.065	0.038	-0.010	0.140	0.096	0.005	0.187	0.040
WEEK 20	PLACEBO	51	1.445	0.034	-0.018	0.034	-0.087	0.050	.	.	.	.
	SB 207499	37	1.484	0.040	0.020	0.040	-0.060	0.101	0.039	-0.060	0.137	0.436
WEEK 28	PLACEBO	48	1.472	0.030	-0.008	0.030	-0.068	0.051	.	.	.	.
	SB 207499	33	1.480	0.035	-0.000	0.035	-0.071	0.070	0.008	-0.080	0.096	0.854
WEEK 36	PLACEBO	44	1.386	0.044	-0.081	0.044	-0.169	0.007	.	.	.	.
	SB 207499	32	1.515	0.050	0.047	0.050	-0.054	0.148	0.128	0.000	0.257	0.050
WEEK 44	PLACEBO	41	1.422	0.041	-0.037	0.041	-0.119	0.044	.	.	.	.
	SB 207499	30	1.525	0.047	0.066	0.047	-0.029	0.161	0.103	-0.016	0.222	0.088
WEEK 52	PLACEBO	38	1.472	0.056	-0.002	0.056	-0.115	0.111	.	.	.	.
	SB 207499	29	1.520	0.065	0.047	0.065	-0.085	0.178	0.049	-0.115	0.213	0.553
ENDPOINT	PLACEBO	57	1.454	0.040	-0.032	0.040	-0.112	0.049	.	.	.	.
	SB 207499	42	1.506	0.048	0.021	0.048	-0.074	0.116	0.053	-0.060	0.165	0.355

1. MEANS ARE ADJUSTED FOR BASELINE VALUE AND COUNTRY
2. STATISITCS ARE REPORTED BASED ON THE MAXIMUM OF THREE REPORTED VALUES OF FEV1 (L)
3. BASELINE = VISIT 3; WEEK 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 5, 6, 7, 8, 9, 10, 11, 12; ENDPOINT = LOCF
4. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14.3C

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN IN POST-BD TROUGH FEV1(L) BY WEEK AND TREATMENT GROUP - ITT
PROTOCOL 157

		BASELINE		WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	414	1.408	0.447	1.490	0.459	1.470	0.500	3.150	.	.	.	.	.
	SB 207499	397	1.324	0.445	1.409	0.460	1.350	0.520	2.920	.	.	.	.	.
WEEK 4	PLACEBO	392	1.482	0.462	1.503	0.471	1.465	0.490	2.950	0.020	0.200	0.010	-1.010	0.800
	SB 207499	371	1.409	0.464	1.459	0.479	1.380	0.480	3.220	0.050	0.205	0.030	-0.980	1.320
WEEK 8	PLACEBO	387	1.494	0.461	1.516	0.468	1.490	0.570	3.200	0.022	0.188	0.010	-0.740	0.720
	SB 207499	365	1.411	0.459	1.463	0.474	1.430	0.470	3.150	0.052	0.192	0.050	-0.920	0.960
WEEK 12	PLACEBO	377	1.494	0.461	1.502	0.474	1.480	0.570	3.350	0.008	0.212	-0.010	-0.890	0.980
	SB 207499	344	1.404	0.460	1.466	0.503	1.400	0.440	3.020	0.062	0.201	0.040	-1.020	0.970
WEEK 20	PLACEBO	371	1.496	0.462	1.501	0.481	1.460	0.490	3.450	0.005	0.217	0.000	-0.770	0.840
	SB 207499	328	1.412	0.458	1.465	0.488	1.400	0.520	2.980	0.053	0.211	0.050	-0.920	0.650
WEEK 28	PLACEBO	359	1.501	0.460	1.502	0.498	1.440	0.610	3.590	0.001	0.232	-0.020	-0.690	1.330
	SB 207499	311	1.420	0.461	1.466	0.514	1.400	0.550	3.700	0.046	0.223	0.040	-0.570	1.520
WEEK 36	PLACEBO	342	1.498	0.456	1.483	0.497	1.450	0.530	3.450	-0.015	0.242	-0.040	-0.920	0.920
	SB 207499	298	1.422	0.462	1.467	0.500	1.410	0.520	3.070	0.045	0.227	0.030	-0.790	0.720
WEEK 44	PLACEBO	326	1.499	0.459	1.487	0.499	1.440	0.460	3.240	-0.012	0.233	-0.030	-0.670	0.990
	SB 207499	284	1.429	0.459	1.492	0.501	1.465	0.520	2.980	0.063	0.227	0.050	-0.670	0.800
WEEK 52	PLACEBO	316	1.499	0.454	1.484	0.486	1.445	0.510	3.200	-0.016	0.220	-0.040	-0.730	0.710
	SB 207499	269	1.434	0.460	1.471	0.488	1.430	0.560	2.920	0.037	0.236	0.030	-0.790	1.230
ENDPOINT	PLACEBO	414	1.490	0.459	1.464	0.482	1.420	0.490	3.240	-0.025	0.224	-0.040	-1.050	0.860
	SB 207499	397	1.409	0.460	1.442	0.482	1.390	0.470	3.070	0.033	0.222	0.030	-0.790	1.230

1. STATISITCS ARE REPORTED BASED ON TO THE MAXIMUM OF THREE REPORTED VALUES OF FEV1 (L)
2. MEAN VALUES ARE SAMPLE MEANS
3. BASELINE = VISIT 3; WEEK 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 5, 6, 7, 8, 9, 10, 11, 12; ENDPOINT = LOCF

CONFIDENTIAL

SB 207499

TABLE 14.3CS

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN POST-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP
- ITT BASELINE SMOKERS
PROTOCOL 157

		BASELINE			WEEKLY ASSESSMENT				CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	181	1.502	0.447	1.577	0.459	1.590	0.690	3.020	.	.	.	.	.
	SB 207499	180	1.395	0.484	1.485	0.491	1.420	0.620	2.920	.	.	.	.	.
WEEK 4	PLACEBO	175	1.576	0.464	1.592	0.453	1.610	0.600	2.860	0.016	0.209	0.010	-0.650	0.800
	SB 207499	169	1.490	0.500	1.540	0.513	1.460	0.610	3.220	0.050	0.192	0.020	-0.600	0.610
WEEK 8	PLACEBO	170	1.585	0.462	1.599	0.461	1.630	0.610	3.200	0.013	0.206	0.020	-0.740	0.720
	SB 207499	167	1.483	0.489	1.534	0.506	1.460	0.600	3.150	0.051	0.187	0.050	-0.500	0.820
WEEK 12	PLACEBO	168	1.581	0.460	1.592	0.460	1.590	0.610	3.170	0.011	0.236	0.020	-0.890	0.980
	SB 207499	160	1.468	0.491	1.542	0.528	1.475	0.620	2.950	0.073	0.188	0.050	-0.410	0.660
WEEK 20	PLACEBO	162	1.586	0.466	1.599	0.480	1.570	0.630	3.390	0.013	0.243	0.005	-0.740	0.840
	SB 207499	152	1.468	0.485	1.532	0.514	1.445	0.580	2.980	0.064	0.199	0.075	-0.550	0.650
WEEK 28	PLACEBO	156	1.589	0.464	1.605	0.493	1.590	0.610	3.520	0.016	0.240	0.010	-0.690	0.930
	SB 207499	145	1.480	0.493	1.538	0.559	1.480	0.580	3.700	0.058	0.228	0.050	-0.440	1.520
WEEK 36	PLACEBO	151	1.584	0.457	1.571	0.490	1.540	0.630	3.450	-0.012	0.270	-0.040	-0.920	0.880
	SB 207499	139	1.478	0.502	1.538	0.542	1.440	0.520	3.070	0.060	0.222	0.040	-0.520	0.720
WEEK 44	PLACEBO	148	1.579	0.458	1.567	0.483	1.535	0.630	3.240	-0.011	0.256	-0.045	-0.670	0.990
	SB 207499	134	1.473	0.492	1.544	0.529	1.510	0.590	2.980	0.071	0.220	0.065	-0.470	0.790
WEEK 52	PLACEBO	141	1.577	0.451	1.561	0.458	1.600	0.590	2.720	-0.015	0.252	-0.040	-0.730	0.710
	SB 207499	128	1.476	0.497	1.517	0.523	1.475	0.560	2.920	0.040	0.236	0.020	-0.790	0.740
ENDPOINT	PLACEBO	181	1.577	0.459	1.548	0.466	1.590	0.590	3.240	-0.029	0.246	-0.040	-0.730	0.710
	SB 207499	180	1.485	0.491	1.514	0.506	1.455	0.560	3.070	0.028	0.225	0.020	-0.790	0.740

1. MEAN VALUES ARE SAMPLE MEANS
2. STATISITCS ARE REPORTED BASED ON THE VALUE CORRESPONDING TO THE MAXIMUM FEV1 (L)
3. BASELINE = VISIT 3; WEEK 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 5, 6, 7, 8, 9, 10, 11, 12; ENDPOINT = LOCF

CONFIDENTIAL

SB 207499

TABLE 14.3CT

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN POST-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP
- ITT BASELINE NON-SMOKERS
PROTOCOL 157

		BASELINE			WEEKLY ASSESSMENT				CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	233	1.336	0.433	1.422	0.449	1.350	0.500	3.150	.	.	.	.	.
	SB 207499	217	1.266	0.402	1.346	0.424	1.290	0.520	2.700	.	.	.	.	.
WEEK 4	PLACEBO	217	1.407	0.448	1.430	0.473	1.360	0.490	2.950	0.024	0.193	0.010	-1.010	0.790
	SB 207499	202	1.341	0.422	1.391	0.438	1.350	0.480	2.590	0.049	0.215	0.045	-0.980	1.320
WEEK 8	PLACEBO	217	1.422	0.449	1.451	0.464	1.380	0.570	3.160	0.029	0.173	0.010	-0.520	0.610
	SB 207499	198	1.350	0.424	1.403	0.436	1.385	0.470	2.640	0.053	0.196	0.060	-0.920	0.960
WEEK 12	PLACEBO	209	1.424	0.451	1.430	0.474	1.350	0.570	3.350	0.006	0.190	-0.010	-0.600	0.920
	SB 207499	184	1.348	0.425	1.400	0.473	1.340	0.440	3.020	0.052	0.211	0.030	-1.020	0.970
WEEK 20	PLACEBO	209	1.427	0.448	1.425	0.470	1.330	0.490	3.450	-0.002	0.195	0.000	-0.770	0.820
	SB 207499	176	1.363	0.429	1.407	0.458	1.370	0.520	2.830	0.044	0.222	0.030	-0.920	0.640
WEEK 28	PLACEBO	203	1.433	0.447	1.423	0.488	1.350	0.620	3.590	-0.010	0.225	-0.030	-0.680	1.330
	SB 207499	166	1.367	0.425	1.403	0.464	1.335	0.550	2.830	0.036	0.220	0.030	-0.570	0.870
WEEK 36	PLACEBO	191	1.430	0.444	1.414	0.492	1.390	0.530	3.410	-0.017	0.219	-0.040	-0.640	0.920
	SB 207499	159	1.373	0.420	1.405	0.453	1.380	0.590	2.920	0.032	0.230	0.030	-0.790	0.680
WEEK 44	PLACEBO	178	1.433	0.450	1.421	0.504	1.305	0.460	3.190	-0.012	0.214	-0.020	-0.620	0.860
	SB 207499	150	1.389	0.426	1.446	0.472	1.405	0.520	2.980	0.057	0.234	0.030	-0.670	0.800
WEEK 52	PLACEBO	175	1.437	0.448	1.421	0.500	1.330	0.510	3.200	-0.016	0.192	-0.040	-0.390	0.710
	SB 207499	141	1.396	0.422	1.429	0.452	1.400	0.580	2.830	0.033	0.237	0.030	-0.490	1.230
ENDPOINT	PLACEBO	233	1.422	0.449	1.399	0.486	1.320	0.490	3.200	-0.023	0.207	-0.040	-1.050	0.860
	SB 207499	217	1.346	0.424	1.382	0.455	1.330	0.470	2.830	0.036	0.220	0.050	-0.790	1.230

1. MEAN VALUES ARE SAMPLE MEANS
2. STATISITCS ARE REPORTED BASED ON THE VALUE CORRESPONDING TO THE MAXIMUM FEV1 (L)
3. BASELINE = VISIT 3; WEEK 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 5, 6, 7, 8, 9, 10, 11,12; ENDPOINT = LOCF

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.3CU

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN POST-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP
- ITT BASELINE/ON THERAPY SMOKING STATUS: S/S
PROTOCOL 157

		BASELINE			WEEKLY ASSESSMENT				CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	144	1.532	0.462	1.602	0.466	1.605	0.690	3.020	.	.	.	.	.
	SB 207499	149	1.400	0.489	1.489	0.493	1.430	0.620	2.920	.	.	.	.	.
WEEK 4	PLACEBO	138	1.601	0.472	1.618	0.453	1.620	0.600	2.860	0.017	0.208	0.005	-0.650	0.800
	SB 207499	140	1.491	0.502	1.539	0.520	1.475	0.610	3.220	0.048	0.192	0.025	-0.600	0.570
WEEK 8	PLACEBO	135	1.611	0.467	1.626	0.463	1.660	0.630	3.200	0.015	0.213	0.020	-0.740	0.720
	SB 207499	137	1.495	0.496	1.541	0.517	1.460	0.600	3.150	0.046	0.181	0.050	-0.400	0.590
WEEK 12	PLACEBO	134	1.610	0.469	1.630	0.460	1.635	0.730	3.170	0.020	0.245	0.020	-0.890	0.980
	SB 207499	131	1.483	0.503	1.554	0.536	1.510	0.630	2.950	0.071	0.191	0.050	-0.410	0.630
WEEK 20	PLACEBO	129	1.610	0.475	1.633	0.490	1.610	0.720	3.390	0.023	0.236	0.020	-0.570	0.840
	SB 207499	124	1.487	0.495	1.546	0.524	1.455	0.580	2.980	0.059	0.204	0.070	-0.550	0.650
WEEK 28	PLACEBO	125	1.612	0.478	1.626	0.504	1.590	0.610	3.520	0.014	0.250	0.000	-0.690	0.930
	SB 207499	118	1.498	0.506	1.555	0.577	1.460	0.580	3.700	0.057	0.246	0.040	-0.440	1.520
WEEK 36	PLACEBO	122	1.600	0.471	1.605	0.490	1.600	0.630	3.450	0.005	0.261	-0.035	-0.520	0.880
	SB 207499	113	1.500	0.512	1.552	0.561	1.420	0.520	3.070	0.052	0.231	0.030	-0.520	0.720
WEEK 44	PLACEBO	121	1.601	0.473	1.587	0.496	1.560	0.630	3.240	-0.014	0.260	-0.050	-0.670	0.990
	SB 207499	109	1.491	0.501	1.560	0.537	1.520	0.590	2.980	0.069	0.224	0.080	-0.470	0.790
WEEK 52	PLACEBO	116	1.591	0.460	1.574	0.454	1.595	0.590	2.720	-0.017	0.253	-0.040	-0.730	0.710
	SB 207499	104	1.495	0.505	1.532	0.517	1.480	0.620	2.920	0.037	0.213	0.035	-0.480	0.540
ENDPOINT	PLACEBO	144	1.602	0.466	1.580	0.464	1.590	0.590	3.240	-0.022	0.243	-0.040	-0.730	0.710
	SB 207499	149	1.489	0.493	1.519	0.501	1.460	0.610	3.070	0.030	0.207	0.040	-0.480	0.540

1. MEAN VALUES ARE SAMPLE MEANS
2. STATISITCS ARE REPORTED BASED ON THE VALUE CORRESPONDING TO THE MAXIMUM FEV1 (L)
3. BASELINE = VISIT 3; WEEK 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 5, 6, 7, 8, 9, 10, 11, 12; ENDPOINT = LOCF

CONFIDENTIAL

SB 207499

TABLE 14.3CV

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN POST-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP
- ITT BASELINE/ON THERAPY SMOKING STATUS: N/N
PROTOCOL 157

		BASELINE		WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	213	1.315	0.419	1.401	0.431	1.330	0.500	2.560	.	.	.	.	.
	SB 207499	205	1.269	0.405	1.352	0.427	1.290	0.520	2.700	.	.	.	.	.
WEEK 4	PLACEBO	198	1.387	0.429	1.413	0.459	1.345	0.490	2.860	0.027	0.197	0.010	-1.010	0.790
	SB 207499	191	1.345	0.426	1.394	0.444	1.360	0.480	2.590	0.048	0.217	0.040	-0.980	1.320
WEEK 8	PLACEBO	199	1.404	0.430	1.437	0.445	1.380	0.570	2.670	0.033	0.177	0.020	-0.520	0.610
	SB 207499	188	1.353	0.427	1.406	0.439	1.390	0.470	2.640	0.053	0.199	0.060	-0.920	0.960
WEEK 12	PLACEBO	191	1.405	0.432	1.413	0.451	1.340	0.570	2.520	0.008	0.195	-0.010	-0.600	0.920
	SB 207499	175	1.349	0.428	1.400	0.479	1.340	0.440	3.020	0.051	0.207	0.030	-1.020	0.970
WEEK 20	PLACEBO	191	1.411	0.432	1.412	0.451	1.330	0.490	2.720	0.001	0.200	0.000	-0.770	0.820
	SB 207499	167	1.365	0.432	1.411	0.464	1.370	0.520	2.830	0.046	0.222	0.050	-0.920	0.640
WEEK 28	PLACEBO	186	1.416	0.429	1.410	0.468	1.350	0.620	3.310	-0.006	0.228	-0.020	-0.680	1.330
	SB 207499	160	1.368	0.426	1.407	0.468	1.335	0.550	2.830	0.038	0.222	0.035	-0.570	0.870
WEEK 36	PLACEBO	176	1.416	0.427	1.404	0.478	1.395	0.530	3.410	-0.011	0.219	-0.040	-0.500	0.920
	SB 207499	153	1.377	0.421	1.403	0.455	1.380	0.590	2.920	0.026	0.229	0.030	-0.790	0.680
WEEK 44	PLACEBO	164	1.423	0.435	1.417	0.491	1.310	0.460	2.900	-0.005	0.216	-0.020	-0.620	0.860
	SB 207499	145	1.389	0.429	1.439	0.474	1.400	0.520	2.980	0.050	0.232	0.020	-0.670	0.800
WEEK 52	PLACEBO	162	1.426	0.432	1.416	0.492	1.335	0.510	3.200	-0.009	0.192	-0.035	-0.360	0.710
	SB 207499	136	1.396	0.426	1.426	0.458	1.395	0.580	2.830	0.031	0.240	0.040	-0.490	1.230
ENDPOINT	PLACEBO	213	1.401	0.431	1.385	0.473	1.320	0.490	3.200	-0.016	0.209	-0.030	-1.050	0.860
	SB 207499	205	1.352	0.427	1.386	0.461	1.320	0.470	2.830	0.034	0.223	0.050	-0.790	1.230

1. MEAN VALUES ARE SAMPLE MEANS
2. STATISITCS ARE REPORTED BASED ON THE VALUE CORRESPONDING TO THE MAXIMUM FEV1 (L)
3. BASELINE = VISIT 3; WEEK 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 5, 6, 7, 8, 9, 10, 11, 12; ENDPOINT = LOCF

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.3CW

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN POST-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP
- ITT BASELINE/ON THERAPY SMOKING STATUS: N/S OR S/N
PROTOCOL 157

		BASELINE			WEEKLY ASSESSMENT				CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	57	1.443	0.435	1.536	0.483	1.420	0.750	3.150	.	.	.	.	.
	SB 207499	42	1.339	0.440	1.416	0.465	1.395	0.670	2.620	.	.	.	.	.
WEEK 4	PLACEBO	56	1.527	0.482	1.534	0.498	1.425	0.610	2.950	0.007	0.195	0.025	-0.480	0.520
	SB 207499	40	1.428	0.469	1.489	0.454	1.360	0.620	2.730	0.061	0.192	-0.010	-0.230	0.610
WEEK 8	PLACEBO	53	1.532	0.493	1.532	0.516	1.380	0.610	3.160	0.000	0.158	0.000	-0.420	0.460
	SB 207499	40	1.397	0.439	1.465	0.447	1.500	0.610	2.670	0.068	0.195	0.045	-0.500	0.820
WEEK 12	PLACEBO	52	1.521	0.484	1.500	0.523	1.385	0.610	3.350	-0.021	0.176	-0.045	-0.410	0.550
	SB 207499	38	1.386	0.420	1.467	0.460	1.445	0.620	2.680	0.082	0.208	0.035	-0.330	0.660
WEEK 20	PLACEBO	51	1.530	0.478	1.503	0.504	1.430	0.630	3.450	-0.027	0.229	-0.040	-0.740	0.740
	SB 207499	37	1.372	0.417	1.437	0.439	1.350	0.740	2.830	0.065	0.190	0.050	-0.400	0.510
WEEK 28	PLACEBO	48	1.540	0.473	1.536	0.531	1.475	0.760	3.590	-0.005	0.198	-0.050	-0.460	0.520
	SB 207499	33	1.393	0.423	1.435	0.450	1.480	0.660	2.730	0.043	0.125	0.050	-0.250	0.320
WEEK 36	PLACEBO	44	1.545	0.467	1.460	0.529	1.370	0.760	3.260	-0.085	0.270	-0.065	-0.920	0.620
	SB 207499	32	1.362	0.441	1.474	0.445	1.550	0.700	2.670	0.112	0.184	0.045	-0.190	0.590
WEEK 44	PLACEBO	41	1.504	0.460	1.475	0.499	1.380	0.690	3.190	-0.029	0.220	-0.010	-0.630	0.570
	SB 207499	30	1.397	0.431	1.505	0.477	1.465	0.720	2.550	0.108	0.218	0.005	-0.160	0.600
WEEK 52	PLACEBO	38	1.532	0.485	1.496	0.520	1.395	0.660	2.760	-0.036	0.231	-0.025	-0.440	0.470
	SB 207499	29	1.397	0.439	1.461	0.514	1.400	0.560	2.590	0.064	0.299	0.020	-0.790	0.740
ENDPOINT	PLACEBO	57	1.536	0.483	1.467	0.511	1.350	0.630	2.760	-0.070	0.229	-0.060	-0.630	0.470
	SB 207499	42	1.416	0.465	1.445	0.493	1.340	0.560	2.590	0.028	0.268	0.010	-0.790	0.740

1. MEAN VALUES ARE SAMPLE MEANS
2. STATISITCS ARE REPORTED BASED ON THE VALUE CORRESPONDING TO THE MAXIMUM FEV1 (L)
3. BASELINE = VISIT 3; WEEK 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 5, 6, 7, 8, 9, 10, 11, 12; ENDPOINT = LOCF

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.4A

SUMMARY OF AVERAGE CHANGE FROM BASELINE OVER 52 WEEKS (REPEATED MEASURES ANALYSIS) IN SUMMARY SYMPTOM SCORE
ITT
PROTOCOL 157

		BASELINE		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
PLACEBO	411	5.104	0.155	-0.150	0.076	-0.298	-0.001	.	.	.	
SB 207499	403	5.114	0.157	-0.120	0.077	-0.272	0.031	0.029	-0.139	0.198	0.733

1. MEANS ARE ADJUSTED FOR BASELINE VALUE, COUNTRY AND WEEK
2. * SIGNIFICANTLY DIFFERENT FROM PLACEBO

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.4B

SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN SUMMARY SYMPTOM SCORE BY WEEK AND TREATMENT GROUP - ITT
PROTOCOL 157

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	412	5.106	0.154	.	.	.	.	.	.	.	.
	SB 207499	403	5.113	0.157	.	.	.	.	.	.	.	.
WEEK 2	PLACEBO	385	5.223	0.070	0.024	0.070	-0.114	0.161	.	.	.	.
	SB 207499	366	5.317	0.072	0.117	0.072	-0.024	0.259	0.094	-0.083	0.271	0.298
WEEK 4	PLACEBO	371	5.101	0.091	-0.033	0.091	-0.210	0.145	.	.	.	.
	SB 207499	349	5.125	0.094	-0.009	0.094	-0.193	0.175	0.024	-0.204	0.251	0.839
WEEK 8	PLACEBO	368	5.086	0.108	-0.117	0.108	-0.329	0.095	.	.	.	.
	SB 207499	344	5.154	0.113	-0.048	0.113	-0.270	0.173	0.069	-0.203	0.341	0.620
WEEK 12	PLACEBO	358	5.010	0.111	-0.113	0.111	-0.330	0.105	.	.	.	.
	SB 207499	314	5.081	0.118	-0.042	0.118	-0.272	0.189	0.071	-0.208	0.350	0.618
WEEK 20	PLACEBO	335	5.051	0.129	-0.130	0.129	-0.385	0.124	.	.	.	.
	SB 207499	295	4.990	0.138	-0.192	0.138	-0.463	0.080	-0.061	-0.386	0.263	0.711
WEEK 28	PLACEBO	335	5.017	0.132	-0.141	0.132	-0.401	0.118	.	.	.	.
	SB 207499	291	4.922	0.141	-0.236	0.141	-0.513	0.041	-0.095	-0.429	0.240	0.577
WEEK 36	PLACEBO	320	5.005	0.133	-0.149	0.133	-0.410	0.112	.	.	.	.
	SB 207499	277	4.850	0.142	-0.304	0.142	-0.584	-0.024	-0.155	-0.495	0.185	0.370
WEEK 44	PLACEBO	300	5.065	0.147	-0.155	0.147	-0.443	0.134	.	.	.	.
	SB 207499	261	4.952	0.157	-0.268	0.157	-0.575	0.040	-0.113	-0.484	0.258	0.550
WEEK 52	PLACEBO	292	4.869	0.159	-0.292	0.159	-0.604	0.020	.	.	.	.
	SB 207499	248	4.872	0.166	-0.289	0.166	-0.614	0.037	0.003	-0.372	0.379	0.987
ENDPOINT	PLACEBO	412	4.968	0.117	-0.215	0.117	-0.444	0.015	.	.	.	.
	SB 207499	403	5.010	0.119	-0.172	0.119	-0.405	0.060	0.042	-0.250	0.335	0.776

1. MEANS ARE ADJUSTED FOR BASELINE VALUE AND COUNTRY
2. BASELINE = VISIT 3; WEEK 2, 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 4, 5, 6, 7, 8, 9, 10, 11, 12; ENDPOINT = LOCF
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14.4C

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN IN SUMMARY SYMPTOM SCORE BY WEEK AND TREATMENT GROUP - ITT
PROTOCOL 157

WEEK	TREATMENT GROUP	N	BASELINE MEAN	BASELINE SD	WEEKLY ASSESSMENT MEAN	WEEKLY ASSESSMENT SD	WEEKLY ASSESSMENT MEDIAN	WEEKLY ASSESSMENT MIN	WEEKLY ASSESSMENT MAX	CHANGE FROM BASELINE MEAN	CHANGE FROM BASELINE SD	CHANGE FROM BASELINE MEDIAN	CHANGE FROM BASELINE MIN	CHANGE FROM BASELINE MAX
BASELINE	PLACEBO	412	5.199	2.883	5.199	2.883	5.280	0.000	12.500	.	.	.	.	.
	SB 207499	403	5.166	2.996	5.166	2.996	5.091	0.000	13.000	.	.	.	.	.
WEEK 2	PLACEBO	385	5.243	2.870	5.209	2.979	5.214	0.000	12.917	-0.034	1.194	0.000	-4.861	3.643
	SB 207499	366	5.153	2.948	5.225	2.859	5.379	0.000	12.500	0.072	1.317	0.000	-6.536	5.417
WEEK 4	PLACEBO	371	5.156	2.931	5.049	3.109	5.000	0.000	14.000	-0.108	1.589	0.000	-7.000	5.307
	SB 207499	349	5.110	2.936	5.014	2.792	5.000	0.000	11.167	-0.096	1.619	0.000	-7.846	5.109
WEEK 8	PLACEBO	368	5.262	2.845	5.083	3.024	5.179	0.000	14.000	-0.179	1.854	0.000	-7.071	4.573
	SB 207499	344	5.139	2.956	5.046	2.822	5.000	0.000	11.923	-0.093	2.018	0.000	-8.461	7.994
WEEK 12	PLACEBO	358	5.144	2.849	4.996	3.079	5.214	0.000	14.000	-0.148	1.832	0.000	-7.000	4.929
	SB 207499	314	5.099	2.979	5.031	2.807	5.036	0.000	12.143	-0.068	2.047	-0.077	-7.857	7.780
WEEK 20	PLACEBO	335	5.194	2.840	5.027	3.089	5.000	0.000	14.000	-0.167	2.030	0.000	-7.000	6.560
	SB 207499	295	5.167	2.946	4.948	2.918	5.000	0.000	13.000	-0.220	2.343	-0.107	-7.250	8.571
WEEK 28	PLACEBO	335	5.146	2.833	4.941	3.173	5.000	0.000	14.000	-0.206	2.221	0.000	-7.214	7.308
	SB 207499	291	5.173	2.876	4.840	2.921	5.000	0.000	12.857	-0.333	2.280	-0.286	-7.637	7.071
WEEK 36	PLACEBO	320	5.132	2.876	4.899	3.006	4.929	0.000	14.000	-0.233	2.271	-0.071	-8.071	7.237
	SB 207499	277	5.180	2.908	4.759	2.946	4.333	0.000	12.000	-0.421	2.203	-0.286	-9.077	6.071
WEEK 44	PLACEBO	300	5.191	2.898	4.900	3.166	4.890	0.000	14.000	-0.291	2.272	0.000	-8.071	7.308
	SB 207499	261	5.252	2.920	4.828	2.958	5.000	0.000	12.500	-0.423	2.512	-0.214	-10.462	9.417
WEEK 52	PLACEBO	292	5.162	2.919	4.796	3.094	4.750	0.000	14.000	-0.366	2.195	-0.071	-8.214	6.000
	SB 207499	248	5.160	2.877	4.807	2.932	4.786	0.000	12.000	-0.353	2.526	-0.149	-10.962	6.214
ENDPOINT	PLACEBO	412	5.199	2.883	4.918	3.128	5.000	0.000	14.000	-0.281	2.150	0.000	-8.214	6.560
	SB 207499	403	5.166	2.996	4.943	2.967	4.929	0.000	13.000	-0.223	2.354	-0.043	-10.962	6.214

1. MEAN VALUES ARE SAMPLE MEANS
2. BASELINE = VISIT 3; WEEK 2, 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 4, 5, 6, 7, 8, 9, 10, 11, 12; ENDPOINT = LOCF

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.5A

SUMMARY OF AVERAGE CHANGE FROM BASELINE OVER 52 WEEKS (REPEATED MEASURES ANALYSIS) IN TROUGH FVC (L)
ITT
PROTOCOL 157

		BASELINE		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
PLACEBO	416	2.937	0.043	-0.068	0.016	-0.100	-0.037	.	.	.	
SB 207499	395	2.842	0.044	-0.026	0.017	-0.059	0.006	0.042	0.002	0.082	0.037*

1. MEANS ARE ADJUSTED FOR BASELINE VALUE, COUNTRY AND WEEK
2. STATISTICS ARE REPORTED BASED ON THE MAXIMUM OF THREE REPORTED VALUES OF FEV1 (L)
3. * SIGNIFICANTLY DIFFERENT FROM PLACEBO

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.5B

SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN TROUGH FVC (L) BY WEEK AND TREATMENT GROUP - ITT
PROTOCOL 157

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	420	2.940	0.042	.	.	.	.	.	.	.	.
	SB 207499	403	2.846	0.043	.	.	.	.	.	.	.	.
WEEK 4	PLACEBO	415	2.790	0.019	-0.041	0.019	-0.078	-0.003	.	.	.	.
	SB 207499	391	2.835	0.020	0.005	0.020	-0.034	0.044	0.045	-0.002	0.093	0.063
WEEK 8	PLACEBO	400	2.814	0.019	-0.029	0.019	-0.067	0.009	.	.	.	.
	SB 207499	380	2.836	0.020	-0.007	0.020	-0.047	0.032	0.022	-0.027	0.070	0.381
WEEK 12	PLACEBO	388	2.789	0.022	-0.059	0.022	-0.101	-0.016	.	.	.	.
	SB 207499	356	2.844	0.022	-0.004	0.022	-0.047	0.040	0.055	0.001	0.109	0.044
WEEK 20	PLACEBO	377	2.781	0.023	-0.076	0.023	-0.120	-0.031	.	.	.	.
	SB 207499	333	2.836	0.024	-0.020	0.024	-0.068	0.027	0.055	-0.002	0.112	0.056
WEEK 28	PLACEBO	366	2.801	0.023	-0.066	0.023	-0.111	-0.021	.	.	.	.
	SB 207499	317	2.859	0.024	-0.008	0.024	-0.056	0.039	0.057	-0.000	0.115	0.051
WEEK 36	PLACEBO	349	2.786	0.025	-0.083	0.025	-0.132	-0.035	.	.	.	.
	SB 207499	303	2.839	0.026	-0.030	0.026	-0.081	0.021	0.053	-0.009	0.115	0.092
WEEK 44	PLACEBO	334	2.777	0.026	-0.090	0.026	-0.140	-0.039	.	.	.	.
	SB 207499	291	2.834	0.027	-0.032	0.027	-0.086	0.022	0.057	-0.008	0.123	0.084
WEEK 52	PLACEBO	323	2.804	0.026	-0.079	0.026	-0.130	-0.028	.	.	.	.
	SB 207499	275	2.845	0.028	-0.038	0.028	-0.092	0.016	0.041	-0.024	0.106	0.216
ENDPOINT	PLACEBO	420	2.738	0.022	-0.093	0.022	-0.136	-0.050	.	.	.	.
	SB 207499	403	2.788	0.022	-0.043	0.022	-0.087	0.001	0.050	-0.005	0.105	0.076

1. MEANS ARE ADJUSTED FOR BASELINE VALUE AND COUNTRY
2. STATISITCS ARE REPORTED BASED ON THE MAXIMUM OF THREE REPORTED VALUES OF TROUGH FVC (L)
3. BASELINE = VISIT 3; WEEK 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 5, 6, 7, 8, 9, 10, 11, 12; ENDPOINT = LOCF
4. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.5C

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN TROUGH FVC(L) BY WEEK AND TREATMENT GROUP - ITT

PROTOCOL 157

WEEK	TREATMENT GROUP	N	BASELINE MEAN	BASELINE SD	WEEKLY ASSESSMENT MEAN	WEEKLY ASSESSMENT SD	WEEKLY ASSESSMENT MEDIAN	WEEKLY ASSESSMENT MIN	WEEKLY ASSESSMENT MAX	CHANGE FROM BASELINE MEAN	CHANGE FROM BASELINE SD	CHANGE FROM BASELINE MEDIAN	CHANGE FROM BASELINE MIN	CHANGE FROM BASELINE MAX
BASELINE	PLACEBO	420	2.867	0.840	2.867	0.840	2.790	1.090	6.050	.	.	.	.	.
	SB 207499	403	2.793	0.797	2.793	0.797	2.740	1.100	5.270	.	.	.	.	.
WEEK 4	PLACEBO	415	2.872	0.843	2.817	0.833	2.750	1.180	6.150	-0.055	0.342	-0.060	-1.310	1.490
	SB 207499	391	2.786	0.797	2.784	0.791	2.740	1.120	5.260	-0.002	0.363	0.030	-2.030	1.210
WEEK 8	PLACEBO	400	2.889	0.844	2.846	0.851	2.725	1.030	5.950	-0.043	0.337	-0.050	-0.820	1.340
	SB 207499	380	2.795	0.787	2.784	0.782	2.720	1.060	5.130	-0.011	0.369	-0.010	-2.100	1.290
WEEK 12	PLACEBO	388	2.898	0.843	2.823	0.851	2.715	1.160	6.010	-0.076	0.399	-0.060	-2.090	1.400
	SB 207499	356	2.793	0.796	2.781	0.789	2.750	1.100	5.270	-0.012	0.358	-0.010	-2.000	1.060
WEEK 20	PLACEBO	377	2.909	0.853	2.822	0.839	2.750	1.190	6.090	-0.087	0.395	-0.080	-1.780	1.370
	SB 207499	333	2.798	0.791	2.774	0.799	2.670	0.860	5.710	-0.024	0.410	-0.010	-2.080	1.760
WEEK 28	PLACEBO	366	2.919	0.848	2.823	0.843	2.750	1.170	5.850	-0.096	0.417	-0.075	-1.970	1.090
	SB 207499	317	2.807	0.786	2.781	0.800	2.710	0.910	5.400	-0.026	0.375	-0.030	-1.750	1.040
WEEK 36	PLACEBO	349	2.919	0.849	2.808	0.847	2.690	1.030	6.080	-0.111	0.436	-0.080	-2.050	1.180
	SB 207499	303	2.811	0.778	2.766	0.761	2.670	1.100	5.030	-0.046	0.403	-0.030	-1.680	1.490
WEEK 44	PLACEBO	334	2.913	0.860	2.795	0.865	2.680	0.840	6.320	-0.117	0.443	-0.090	-2.150	1.140
	SB 207499	291	2.813	0.778	2.760	0.774	2.690	1.050	4.880	-0.053	0.420	-0.020	-2.030	1.130
WEEK 52	PLACEBO	323	2.921	0.850	2.808	0.834	2.700	0.990	6.220	-0.114	0.426	-0.100	-1.720	1.180
	SB 207499	275	2.836	0.785	2.779	0.770	2.670	1.060	5.170	-0.057	0.425	-0.010	-1.840	1.250
ENDPOINT	PLACEBO	420	2.867	0.840	2.756	0.831	2.630	0.990	6.220	-0.111	0.420	-0.090	-1.720	1.180
	SB 207499	403	2.793	0.797	2.738	0.776	2.650	1.060	5.170	-0.055	0.426	-0.010	-1.860	1.760

1. STATISITCS ARE REPORTED BASED ON THE VALUE CORRESPONDING TO THE MAXIMUM FEV1 (L)
2. MEAN VALUES ARE SAMPLE MEANS
3. BASELINE = VISIT 3; WEEK 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 5, 6, 7, 8, 9, 10, 11, 12; ENDPOINT = LOCF

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.6A

SUMMARY OF AVERAGE CHANGE FROM BASELINE OVER 52 WEEKS (REPEATED MEASURES ANALYSIS) OF PERCENT OF DAYS SYMPTOM FREE - ITT
PROTOCOL 157

	BASELINE		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
PLACEBO	411	0.082	0.013	0.018	0.008	0.001	0.034	.	.	.	
SB 207499	403	0.072	0.014	0.009	0.009	-0.007	0.026	-0.008	-0.027	0.011	0.395

1. MEANS ARE ADJUSTED FOR BASELINE VALUE, COUNTRY AND WEEK
2. * SIGNIFICANTLY DIFFERENT FROM PLACEBO
3. A SYMPTOM FREE DAY IS DEFINED AS ONE 24-HOUR PERIOD DURING WHICH COUGH, BREATHLESSNESS AND SPUTUM ARE ABSENT

CONFIDENTIAL

SB 207499

TABLE 14.6B

SUMMARY STATISTICS FOR PERCENT OF DAYS SYMPTOM FREE BY WEEK AND TREATMENT GROUP
- ITT
PROTOCOL 157

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	412	0.082	0.013	.	.	.	.	.	.	.	.
	SB 207499	403	0.072	0.014	.	.	.	.	.	.	.	.
WEEK 2	PLACEBO	385	0.085	0.008	-0.001	0.008	-0.016	0.015	.	.	.	.
	SB 207499	366	0.084	0.008	-0.002	0.008	-0.018	0.014	-0.001	-0.021	0.018	0.881
WEEK 4	PLACEBO	371	0.104	0.010	0.014	0.010	-0.007	0.034	.	.	.	.
	SB 207499	349	0.085	0.011	-0.005	0.011	-0.026	0.016	-0.019	-0.044	0.007	0.163
WEEK 8	PLACEBO	368	0.102	0.011	0.018	0.011	-0.004	0.040	.	.	.	.
	SB 207499	344	0.085	0.012	0.001	0.012	-0.022	0.024	-0.017	-0.045	0.012	0.250
WEEK 12	PLACEBO	358	0.112	0.013	0.023	0.013	-0.002	0.049	.	.	.	.
	SB 207499	314	0.088	0.014	-0.000	0.014	-0.027	0.026	-0.024	-0.056	0.009	0.150
WEEK 20	PLACEBO	335	0.110	0.014	0.027	0.014	0.000	0.055	.	.	.	.
	SB 207499	295	0.089	0.015	0.007	0.015	-0.022	0.036	-0.020	-0.055	0.014	0.248
WEEK 28	PLACEBO	335	0.115	0.014	0.035	0.014	0.007	0.062	.	.	.	.
	SB 207499	291	0.097	0.015	0.018	0.015	-0.012	0.047	-0.017	-0.053	0.019	0.350
WEEK 36	PLACEBO	320	0.099	0.014	0.013	0.014	-0.015	0.041	.	.	.	.
	SB 207499	277	0.100	0.015	0.015	0.015	-0.015	0.045	0.001	-0.035	0.038	0.942
WEEK 44	PLACEBO	300	0.077	0.015	-0.003	0.015	-0.033	0.026	.	.	.	.
	SB 207499	261	0.092	0.016	0.012	0.016	-0.019	0.043	0.015	-0.022	0.053	0.427
WEEK 52	PLACEBO	292	0.115	0.018	0.032	0.018	-0.002	0.067	.	.	.	.
	SB 207499	248	0.122	0.018	0.040	0.018	0.004	0.076	0.007	-0.034	0.049	0.726
ENDPOINT	PLACEBO	412	0.107	0.012	0.018	0.012	-0.006	0.043	.	.	.	.
	SB 207499	403	0.097	0.013	0.008	0.013	-0.017	0.033	-0.010	-0.042	0.021	0.515

1. MEANS ARE ADJUSTED FOR BASELINE VALUE AND COUNTRY
2. A SYMPTOM FREE DAY IS DEFINED AS ONE 24-HOUR PERIOD DURING WHICH COUGH, BREATHLESSNESS AND SPUTUM ARE ABSENT
3. BASELINE = VISIT 3; WEEK 2, 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 4, 5, 6, 7, 8, 9, 10, 11, 12; ENDPOINT = LOCF
4. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14.6C

DESCRIPTIVE STATISTICS FOR PERCENT OF DAYS SYMPTOM FREE BY WEEK AND TREATMENT GROUP
- ITT
PROTOCOL 157

WEEK	TREATMENT GROUP	N	BASELINE MEAN	BASELINE SD	WEEKLY ASSESSMENT MEAN	WEEKLY ASSESSMENT SD	WEEKLY ASSESSMENT MEDIAN	WEEKLY ASSESSMENT MIN	WEEKLY ASSESSMENT MAX	CHANGE FROM BASELINE MEAN	CHANGE FROM BASELINE SD	CHANGE FROM BASELINE MEDIAN	CHANGE FROM BASELINE MIN	CHANGE FROM BASELINE MAX
BASELINE	PLACEBO	412	0.091	0.254	0.091	0.254	0.000	0.000	1.000	.	.	.	.	.
	SB 207499	403	0.087	0.250	0.087	0.250	0.000	0.000	1.000	.	.	.	.	.
WEEK 2	PLACEBO	385	0.086	0.245	0.089	0.251	0.000	0.000	1.000	0.002	0.143	0.000	-1.000	1.000
	SB 207499	366	0.085	0.247	0.088	0.258	0.000	0.000	1.000	0.004	0.133	0.000	-0.929	0.769
WEEK 4	PLACEBO	371	0.095	0.258	0.116	0.294	0.000	0.000	1.000	0.020	0.192	0.000	-1.000	1.000
	SB 207499	349	0.085	0.246	0.094	0.260	0.000	0.000	1.000	0.009	0.165	0.000	-0.846	1.000
WEEK 8	PLACEBO	368	0.082	0.239	0.104	0.276	0.000	0.000	1.000	0.022	0.199	0.000	-0.929	1.000
	SB 207499	344	0.086	0.250	0.093	0.265	0.000	0.000	1.000	0.007	0.194	0.000	-1.000	1.000
WEEK 12	PLACEBO	358	0.087	0.247	0.113	0.292	0.000	0.000	1.000	0.026	0.220	0.000	-1.000	1.000
	SB 207499	314	0.090	0.253	0.094	0.268	0.000	0.000	1.000	0.004	0.229	0.000	-1.000	1.000
WEEK 20	PLACEBO	335	0.085	0.249	0.117	0.297	0.000	0.000	1.000	0.032	0.223	0.000	-1.000	1.000
	SB 207499	295	0.079	0.237	0.094	0.278	0.000	0.000	1.000	0.016	0.233	0.000	-1.000	1.000
WEEK 28	PLACEBO	335	0.084	0.244	0.125	0.307	0.000	0.000	1.000	0.041	0.219	0.000	-1.000	1.000
	SB 207499	291	0.075	0.227	0.104	0.289	0.000	0.000	1.000	0.029	0.245	0.000	-1.000	1.000
WEEK 36	PLACEBO	320	0.090	0.252	0.113	0.295	0.000	0.000	1.000	0.023	0.216	0.000	-1.000	1.000
	SB 207499	277	0.080	0.238	0.109	0.298	0.000	0.000	1.000	0.030	0.243	0.000	-1.000	1.000
WEEK 44	PLACEBO	300	0.087	0.247	0.097	0.275	0.000	0.000	1.000	0.010	0.219	0.000	-1.000	1.000
	SB 207499	261	0.073	0.228	0.106	0.297	0.000	0.000	1.000	0.033	0.248	0.000	-1.000	1.000
WEEK 52	PLACEBO	292	0.090	0.251	0.109	0.287	0.000	0.000	1.000	0.019	0.247	0.000	-1.000	1.000
	SB 207499	248	0.074	0.228	0.110	0.300	0.000	0.000	1.000	0.036	0.262	0.000	-1.000	1.000
ENDPOINT	PLACEBO	412	0.091	0.254	0.114	0.296	0.000	0.000	1.000	0.023	0.233	0.000	-1.000	1.000
	SB 207499	403	0.087	0.250	0.103	0.290	0.000	0.000	1.000	0.016	0.235	0.000	-1.000	1.000

1. A SYMPTOM FREE DAY IS DEFINED AS ONE 24-HOUR PERIOD DURING WHICH COUGH, BREATHLESSNESS AND SPUTUM ARE ABSENT
2. MEAN VALUES ARE SAMPLE MEANS.
3. BASELINE = VISIT 3; WEEK 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 5, 6, 7, 8, 9, 10, 11, 12; ENDPOINT = LOCF

CONFIDENTIAL

SB 207499

TABLE 14.7A

SUMMARY OF LEVEL II / III COPD EXACERBATION RATES PER PATIENT YEAR BY TREATMENT GOUP
- ALL RANDOMIZED PATIENTS
PROTOCOL 157

TREATMENT	N	RATE PER PATIENT YEAR	95% CI	INCIDENCE DENSITY RATIO	95% CI	P-VALUE
PLACEBO	437	0.448	(0.357, 0.563)	.		.
SB 207499	442	0.483	(0.384, 0.608)	1.0776	(0.827, 1.405)	0.5804

1. RATES ARE CALCULATED BY POISSON REGRESSION WITH TREATMENT DURATION AS AN OFFSET VARIABLE AND WITH TREATMENT AND COUNTRY AS THE ONLY COVARIATES.
2. INCIDENCE DENSITY RATIO IS SB207499 RELATIVE TO PLACEBO

CONFIDENTIAL

SB 207499

TABLE 14.7B

SUMMARY OF COPD EXACERBATION RATES PER PATIENT YEAR BY TREATMENT GROUP
- ALL RANDOMIZED PATIENTS
PROTOCOL 157

TREATMENT	N	RATE PER PATIENT YEAR	95% CI	INCIDENCE DENSITY RATIO	95% CI	P-VALUE
PLACEBO	437	0.909	(0.745, 1.110)	.		.
SB 207499	442	0.867	(0.712, 1.057)	0.9537	(0.775, 1.173)	0.6541

1. RATES ARE CALCULATED BY POISSON REGRESSION WITH TREATMENT DURATION AS AN OFFSET VARIABLE AND WITH TREATMENT AND COUNTRY AS THE ONLY COVARIATES.
2. INCIDENCE DENSITY RATIO IS SB207499 RELATIVE TO PLACEBO

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.7C

SUMMARY OF LEVEL II / III EXACERBATION-FREE SURVIVAL BY SMOKING STATUS AND TREATMENT
- ALL RANDOMIZED PATIENTS
PROTOCOL 157

SMOKING STATUS BASELINE/ON-THERAPY	TREATMENT GROUP	NUMBER OF PATIENTS EXAC.-FREE	EXACERBATION-FREE SURVIVAL AT 52 WEEKS PERCENT EXAC.-FREE	95% CI	P-VALUE
S/-	PLACEBO	136	70.2%	(63.2%, 77.1%)	.
	SB 207499	145	68.7%	(61.4%, 76.0%)	0.869
N/-	PLACEBO	182	69.2%	(63.0%, 75.3%)	.
	SB 207499	184	68.2%	(61.6%, 74.8%)	0.619
S/S	PLACEBO	114	75.3%	(67.9%, 82.7%)	.
	SB 207499	116	68.8%	(60.7%, 76.8%)	0.293
N/N	PLACEBO	158	67.4%	(60.8%, 73.9%)	.
	SB 207499	166	68.9%	(62.1%, 75.7%)	0.939
S/N or N/S	PLACEBO	38	63.5%	(50.2%, 76.8%)	.
	SB 207499	29	65.8%	(50.4%, 81.1%)	0.846
All Patients	PLACEBO	318	69.6%	(65.0%, 74.2%)	.
	SB 207499	329	68.4%	(63.5%, 73.3%)	0.637

1. EXACERBATION-FREE SURVIVAL IS ESTIMATED USING KAPLAN-MEIER ESTIMATE OF TIME-TO-FIRST EXACERBATION
2. P-VALUE IS BASED ON LOG-RANK TEST
3. SMOKING STATUS: S= SMOKER ; N= NON-SMOKER ; - = EITHER

CONFIDENTIAL

SB 207499

TABLE 14.7D

SUMMARY OF EXACERBATION-FREE SURVIVAL BY SMOKING STATUS AND TREATMENT
- ALL RANDOMIZED PATIENTS
PROTOCOL 157

SMOKING STATUS BASELINE/ON-THERAPY	TREATMENT GROUP	NUMBER OF PATIENTS EXAC.-FREE	EXACERBATION-FREE SURVIVAL AT 52 WEEKS PERCENT EXAC.-FREE	95% CI	P-VALUE
S/-	PLACEBO	99	49.1%	(41.5%, 56.7%)	.
	SB 207499	112	50.6%	(42.9%, 58.4%)	0.707
N/-	PLACEBO	141	52.0%	(45.3%, 58.6%)	.
	SB 207499	151	51.8%	(44.6%, 58.9%)	0.677
S/S	PLACEBO	83	53.2%	(44.8%, 61.7%)	.
	SB 207499	88	49.6%	(41.0%, 58.2%)	0.730
N/N	PLACEBO	119	49.3%	(42.4%, 56.3%)	.
	SB 207499	136	53.3%	(45.9%, 60.6%)	0.728
S/N or N/S	PLACEBO	31	50.6%	(36.8%, 64.4%)	.
	SB 207499	22	49.3%	(33.5%, 65.1%)	0.847
All Patients	PLACEBO	240	50.7%	(45.7%, 55.7%)	.
	SB 207499	263	51.2%	(46.0%, 56.5%)	0.952

1. EXACERBATION-FREE SURVIVAL IS ESTIMATED USING KAPLAN-MEIER ESTIMATE OF TIME-TO-FIRST EXACERBATION
2. P-VALUE IS BASED ON LOG-RANK TEST
3. SMOKING STATUS: S= SMOKER ; N= NON-SMOKER ; - = EITHER

CONFIDENTIAL

SB 207499

TABLE 14.7E

SUMMARY OF POISSON REGRESSION ON PROGNOSTIC FACTORS FOR LEVEL II / III EXACERBATIONS
- ALL RANDOMIZED PATIENTS
PROTOCOL 157

FACTOR	INCIDENCE DENSITY RATIO	95% CI	P-VALUE
% PREDICTED FEV1	0.9776	(0.96, 0.99)	0.0007
AGE	1.0250	(1.01, 1.04)	0.0091
GENDER	1.4452	(1.03, 2.03)	0.0335
SMOKING STATUS	1.0617	(0.77, 1.46)	0.7147
TREATMENT	0.9542	(0.70, 1.29)	0.7621

1. *STATISTIACLLY SIGNIFICANT
2. INCIDENCE DENSITY RATIO: FEMALE RELATIVE TO MALES, SB 207499 RELATIVE TO PLACEBO, BASELINE NON-SMOKERS TO SMOKERS

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.7F

SUMMARY OF POISSON REGRESSION ON PROGNOSTIC FACTORS FOR EXACERBATIONS
- ALL RANDOMIZED PATIENTS
PROTOCOL 157

FACTOR	INCIDENCE DENSITY RATIO	95% CI	P-VALUE
% PREDICTED FEV1	0.9779	(0.97, 0.99)	0.0000
AGE	1.0025	(0.99, 1.02)	0.7174
GENDER	1.2047	(0.93, 1.57)	0.1636
SMOKING STATUS	0.8827	(0.70, 1.12)	0.3055
TREATMENT	0.8611	(0.68, 1.08)	0.2040

1. *STATISTIACLLY SIGNIFICANT
2. INCIDENCE DENSITY RATIO: FEMALE RELATIVE TO MALES, SB 207499 RELATIVE TO PLACEBO, BASELINE NON-SMOKERS TO SMOKERS

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.7H

FREQUENCY AND RATE OF COPD EXACERBATIONS BY LEVEL, BASELINE/ON-THERAPY SMOKING STATUS AND TREATMENT GROUP
- ALL RANDOMIZED PATIENTS
PROTOCOL 157

SMOKING STATUS BASELINE/ON-THERAPY	TREATMENT GROUP	N	MEAN EXPOSURE (YEARS)	LEVEL	NUMBER OF PATIENTS	NUMBER OF EXACERBATIONS
S/-	PLACEBO	187	0.867	I	57	132
				II	47	77
				III	9	10
				II/III	51	87
				I/II/III	88	219
	SB 207499	195	0.789	I	47	91
				II	48	70
				III	5	5
				II/III	50	75
				I/II/III	83	166
N/-	PLACEBO	250	0.834	I	63	105
				II	63	113
				III	8	8
				II/III	68	121
				I/II/III	109	226
	SB 207499	247	0.726	I	48	85
				II	60	102
				III	10	13
				II/III	63	115
				I/II/III	96	200
S/S	PLACEBO	148	0.882	I	46	117
				II	32	54
				III	3	3
				II/III	34	57
				I/II/III	65	174
	SB 207499	157	0.802	I	41	81
				II	39	55
				III	4	4
				II/III	41	59
				I/II/III	69	140
N/N	PLACEBO	224	0.854	I	60	100
				II	62	112
				III	7	7
				II/III	66	119
				I/II/III	105	219

1. LEVELS ARE NOT MUTUALLY EXCLUSIVE ACROSS PATIENTS. EACH EXACERBATION HAS ONE UNIQUE LEVEL
 BUT PATIENTS CAN HAVE MULTIPLE EXACERBATIONS OF DIFFERENT LEVELS
2. SMOKING STATUS: S= SMOKER ; N= NON-SMOKER ; - = EITHER
3. RATES ARE CALCULATED BY POISSON REGRESSION WITH TREATMENT DURATION AS AN OFFSET VARIABLE

CONFIDENTIAL

SB 207499

TABLE 14.7H

FREQUENCY AND RATE OF COPD EXACERBATIONS BY LEVEL, BASELINE/ON-THERAPY SMOKING STATUS AND TREATMENT GROUP
- ALL RANDOMIZED PATIENTS
PROTOCOL 157

SMOKING STATUS BASELINE/ON-THERAPY	TREATMENT GROUP	N	MEAN EXPOSURE (YEARS)	LEVEL	NUMBER OF PATIENTS	NUMBER OF EXACERBATIONS
N/N	SB 207499	224	0.765	I	45	80
				II	55	96
				III	10	13
				II/III	58	109
				I/II/III	88	189
S/N or N/S	PLACEBO	57	0.852	I	13	19
				II	16	24
				III	7	8
				II/III	19	32
				I/II/III	26	51
	SB 207499	42	0.851	I	8	14
				II	13	20
				III	1	1
				II/III	13	21
				I/II/III	20	35
All Patients	PLACEBO	437	0.848	I	120	237
				II	110	190
				III	17	18
				II/III	119	208
				I/II/III	197	445
	SB 207499	442	0.754	I	95	176
				II	108	172
				III	15	18
				II/III	113	190
				I/II/III	179	366

1. LEVELS ARE NOT MUTUALLY EXCLUSIVE ACROSS PATIENTS. EACH EXACERBATION HAS ONE UNIQUE LEVEL BUT PATIENTS CAN HAVE MULTIPLE EXACERBATIONS OF DIFFERENT LEVELS
2. SMOKING STATUS: S= SMOKER ; N= NON-SMOKER ; - = EITHER
3. RATES ARE CALCULATED BY POISSON REGRESSION WITH TREATMENT DURATION AS AN OFFSET VARIABLE

CONFIDENTIAL

---------- COUNTRY=Poland ----------

WARNING: The generalized Hessian matrix is not positive definite. Iteration will be terminated.

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.7I

SUMMARY OF COPD EXACERBATION RATES PER PATIENT YEAR BY COUNTRY AND TREATMENT GROUP
- ALL RANDOMIZED PATIENTS
PROTOCOL 157

COUNTRY	TREATMENT	N	RATE PER PATIENT YEAR	95% CI	INCIDENCE DENSITY RATIO	95% CI	P-VALUE
Australia	PLACEBO	17	1.400	(0.673, 2.911)	.		.
	SB 207499	13	1.274	(0.720, 2.253)	0.9102	(0.360, 2.303)	0.8424
Belgium	PLACEBO	11	1.778	(1.016, 3.111)	.		.
	SB 207499	10	2.436	(1.287, 4.614)	1.3706	(0.586, 3.204)	0.4668
Czech Republic	PLACEBO	16	1.140	(0.640, 2.030)	.		.
	SB 207499	19	1.083	(0.484, 2.422)	0.9501	(0.353, 2.558)	0.9193
Denmark	PLACEBO	12	2.000	(1.154, 3.464)	.		.
	SB 207499	11	2.757	(1.586, 4.792)	1.3788	(0.632, 3.006)	0.4193
Finland	PLACEBO	14	0.824	(0.397, 1.712)	.		.
	SB 207499	12	0.111	(0.015, 0.830)	0.1351	(0.016, 1.146)	0.0665
France	PLACEBO	19	1.183	(0.703, 1.993)	.		.
	SB 207499	12	1.678	(0.954, 2.953)	1.4181	(0.657, 3.060)	0.3733
Germany	PLACEBO	76	1.166	(0.810, 1.679)	.		.
	SB 207499	75	0.949	(0.663, 1.358)	0.8134	(0.488, 1.356)	0.4283
Italy	PLACEBO	40	1.005	(0.620, 1.629)	.		.
	SB 207499	53	0.849	(0.486, 1.484)	0.8452	(0.404, 1.768)	0.6551
Netherlands	PLACEBO	15	0.973	(0.557, 1.701)	.		.
	SB 207499	22	1.185	(0.602, 2.331)	1.2173	(0.506, 2.927)	0.6606
New Zealand	PLACEBO	13	1.091	(0.727, 1.639)	.		.
	SB 207499	12	1.653	(0.834, 3.277)	1.5147	(0.683, 3.357)	0.3066
Poland	PLACEBO	3	.	(., .)	.		.
	SB 207499	9	.	(., .)	.		.
Russia	PLACEBO	34	1.444	(0.749, 2.784)	.		.
	SB 207499	31	0.892	(0.456, 1.746)	0.6180	(0.242, 1.581)	0.3153
Slovakia	PLACEBO	13	0.366	(0.105, 1.272)	.		.
	SB 207499	12	0.347	(0.122, 0.986)	0.9491	(0.187, 4.827)	0.9498
South Africa	PLACEBO	25	1.046	(0.534, 2.050)	.		.
	SB 207499	25	0.730	(0.424, 1.258)	0.6980	(0.294, 1.658)	0.4154
Spain	PLACEBO	51	1.392	(0.874, 2.218)	.		.
	SB 207499	51	1.621	(1.156, 2.273)	1.1647	(0.655, 2.071)	0.6035

1. RATES ARE CALCULATED BY POISSON REGRESSION WITH TREATMENT DURATION AS AN OFFSET VARIABLE
2. INCIDENCE DENSITY RATIO IS SB207499 RELATIVE TO PLACEBO

CONFIDENTIAL

SB 207499

TABLE 14.7I

SUMMARY OF COPD EXACERBATION RATES PER PATIENT YEAR BY COUNTRY AND TREATMENT GROUP
- ALL RANDOMIZED PATIENTS
PROTOCOL 157

COUNTRY	TREATMENT	N	RATE PER PATIENT YEAR	95% CI	INCIDENCE DENSITY RATIO	95% CI	P-VALUE
Sweden	PLACEBO	20	0.678	(0.313, 1.468)	.		.
	SB 207499	19	1.257	(0.765, 2.067)	1.8530	(0.740, 4.643)	0.1881
Taiwan	PLACEBO	13	0.240	(0.031, 1.846)	.		.
	SB 207499	14	0.111	(0.015, 0.833)	0.4605	(0.026, 8.124)	0.5964
United Kingdom	PLACEBO	45	1.762	(1.198, 2.590)	.		.
	SB 207499	42	1.508	(1.059, 2.148)	0.8561	(0.507, 1.444)	0.5604

1. RATES ARE CALCULATED BY POISSON REGRESSION WITH TREATMENT DURATION AS AN OFFSET VARIABLE
2. INCIDENCE DENSITY RATIO IS SB207499 RELATIVE TO PLACEBO

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.7J

SUMMARY OF COPD EXACERBATION RATES PER PATIENT YEAR BY GENDER AND TREATMENT GROUP
- ALL RANDOMIZED PATIENTS
PROTOCOL 157

GENDER	TREATMENT	N	RATE PER PATIENT YEAR	95% CI	INCIDENCE DENSITY RATIO	95% CI	P-VALUE
Female	PLACEBO	114	1.408	(1.080, 1.834)	.		.
	SB 207499	96	1.193	(0.893, 1.593)	0.8471	(0.572, 1.254)	0.4072
Male	PLACEBO	323	1.129	(0.938, 1.358)	.		.
	SB 207499	346	1.076	(0.906, 1.277)	0.9530	(0.741, 1.226)	0.7081

1. RATE IS CALCULATED BY POISSON REGRESSION WITH TREATMENT DURATION AS AN OFFSET VARIABLE
2. INCIDENCE DENSITY RATIO IS SB207499 RELATIVE TO PLACEBO

CONFIDENTIAL

SB 207499

TABLE 14.7K

SUMMARY OF COPD EXACERBATION RATES PER PATIENT YEAR BY ATS SEVERITY AND TREATMENT GROUP
- ALL RANDOMIZED PATIENTS
PROTOCOL 157

ATS SEVERITY	TREATMENT	N	RATE PER PATIENT YEAR	95% CI	INCIDENCE DENSITY RATIO	95% CI	P-VALUE
Mild	PLACEBO	267	1.033	(0.838, 1.274)	.		.
	SB 207499	233	0.879	(0.701, 1.103)	0.8509	(0.625, 1.158)	0.3051
Moderate	PLACEBO	146	1.388	(1.095, 1.760)	.		.
	SB 207499	160	1.305	(1.047, 1.626)	0.9398	(0.680, 1.299)	0.7073
Severe	PLACEBO	22	2.105	(1.204, 3.680)	.		.
	SB 207499	47	1.513	(1.018, 2.250)	0.7190	(0.362, 1.427)	0.3454
Unknown	PLACEBO	2	1.294	(0.840, 1.995)	.		.
	SB 207499	2	0.508	(0.130, 1.994)	0.3928	(0.094, 1.647)	0.2013

1. RATES ARE CALCULATED BY POISSON REGRESSION WITH TREATMENT DURATION AS AN OFFSET VARIABLE
2. INCIDENCE DENSITY RATIO IS SB207499 RELATIVE TO PLACEBO

CONFIDENTIAL

---------- POPULATION= ----------

WARNING: The generalized Hessian matrix is not positive definite. Iteration will be terminated.

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

---------- POPULATION=REVERSIBLE ----------

WARNING: The generalized Hessian matrix is not positive definite. Iteration will be terminated.

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.7N

SUMMARY OF LEVEL II/III COPD EXACERBATION RATES PER PATIENT YEAR BY REVERSIBILITY AND TREATMENT GROUP
- ALL RANDOMIZED PATIENTS
PROTOCOL 157

POPULATION	TREATMENT	N	RATE PER PATIENT YEAR	95% CI	INCIDENCE DENSITY RATIO	95% CI	P-VALUE
NON-REVERSIBLE	PLACEBO	426	0.452	(0.360, 0.569)	.		.
	SB 207499	425	0.489	(0.388, 0.618)	1.0819	(0.826, 1.416)	0.5670
REVERSIBLE	PLACEBO	9	.	(., .)	.		.
	SB 207499	15	.	(., .)	.		.

1. RATES ARE CALCULATED BY POISSON REGRESSION WITH TREATMENT DURATION AS AN OFFSET VARIABLE
2. INCIDENCE DENSITY RATIO IS SB207499 RELATIVE TO PLACEBO

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

---------- POPULATION= ----------

WARNING: The generalized Hessian matrix is not positive definite. Iteration will be terminated.

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

---------- POPULATION=REVERSIBLE ----------

WARNING: The generalized Hessian matrix is not positive definite. Iteration will be terminated.

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.7O

SUMMARY OF COPD EXACERBATION RATES PER PATIENT YEAR BY REVERSIBILITY AND TREATMENT GROUP
- ALL RANDOMIZED PATIENTS
PROTOCOL 157

POPULATION	TREATMENT	N	RATE PER PATIENT YEAR	95% CI	INCIDENCE DENSITY RATIO	95% CI	P-VALUE
NON-REVERSIBLE	PLACEBO	426	0.909	(0.743, 1.112)	.		.
	SB 207499	425	0.863	(0.706, 1.055)	0.9492	(0.769, 1.171)	0.6268
REVERSIBLE	PLACEBO	9	.	(., .)	.		.
	SB 207499	15	.	(., .)	.		.

1. RATES ARE CALCULATED BY POISSON REGRESSION WITH TREATMENT DURATION AS AN OFFSET VARIABLE
2. INCIDENCE DENSITY RATIO IS SB207499 RELATIVE TO PLACEBO

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.7R

SUMMARY OF MARGINAL REGRESSION ANALYSIS OF TIME TO MULTIPLE EXACERBATION
- ALL RANDOMIZED PATIENTS
PROTOCOL 157

FACTOR	RELATIVE RISK	95% CI	P-VALUE
TREATMENT	1.0032	(0.82, 1.23)	0.9753

1. RESULTS ARE BASED ON A MARGINAL REGRESSION ANALYSIS MODEL OF WEI, LIN AND WEISSFELD
2. RELATIVE RISK IS CALCULATED BASED ON THE FIRST FOUR EXACERBATIONS PER PATIENT

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.7S

DURATION (DAYS) OF EXACERBATION BY TREATMENT GROUP
- ALL RANDOMIZED PATIENTS
PROTOCOL 157

TREATMENT GROUP	N	DURATION (DAYS) OF EXACERBATIONS MEAN	STD DEV	COMPARISON WITH PLACEBO MEAN	STD DEV	P-VALUE
PLACEBO	197	44.249	65.066	.	.	.
SB 207499	179	35.978	52.048	8.271	59.228	0.325

1. P-VALUE IS OF WILCOXON RANK SUM STATISTIC

CONFIDENTIAL

SB 207499

TABLE 14.7T

SUMMARY OF LEVEL II / III COPD EXACERBATION RATES PER PATIENT YEAR BY SMOKING STATUS AND TREATMENT GOUP
- ALL RANDOMIZED PATIENTS
PROTOCOL 157

SMOKING STATUS BASELINE/ON-THERAPY	TREATMENT	N	RATE PER PATIENT YEAR	95% CI	INCIDENCE DENSITY RATIO	95% CI	P-VALUE
S/-	PLACEBO	187	0.537	(0.395, 0.729)	.		.
	SB 207499	195	0.487	(0.362, 0.655)	0.9076	(0.593, 1.389)	0.6555
N/-	PLACEBO	250	0.581	(0.450, 0.748)	.		.
	SB 207499	247	0.641	(0.493, 0.834)	1.1044	(0.766, 1.592)	0.5945
S/S	PLACEBO	148	0.437	(0.295, 0.647)	.		.
	SB 207499	157	0.469	(0.337, 0.651)	1.0730	(0.642, 1.793)	0.7879
N/N	PLACEBO	224	0.622	(0.482, 0.803)	.		.
	SB 207499	224	0.636	(0.484, 0.837)	1.0230	(0.704, 1.487)	0.9053
S/N or N/S	PLACEBO	57	0.659	(0.414, 1.049)	.		.
	SB 207499	42	0.587	(0.338, 1.021)	0.8915	(0.433, 1.837)	0.7555

1. RATES ARE CALCULATED BY POISSON REGRESSION WITH TREATMENT DURATION AS AN OFFSET VARIABLE AND WITH TREATMENT AS THE ONLY COVARIATE.
2. INCIDENCE DENSITY RATIO IS SB207499 RELATIVE TO PLACEBO

CONFIDENTIAL

SB 207499

TABLE 14.7U

SUMMARY OF EXACERBATION RATES PER PATIENT YEAR BY SMOKING STATUS AND TREATMENT GOUP
- ALL RANDOMIZED PATIENTS
PROTOCOL 157

SMOKING STATUS BASELINE/ON-THERAPY	TREATMENT	N	RATE PER PATIENT YEAR	95% CI	INCIDENCE DENSITY RATIO	95% CI	P-VALUE
S/-	PLACEBO	187	1.351	(1.079, 1.691)	.		.
	SB 207499	195	1.078	(0.869, 1.339)	0.7981	(0.584, 1.090)	0.1561
N/-	PLACEBO	250	1.084	(0.884, 1.331)	.		.
	SB 207499	247	1.115	(0.909, 1.367)	1.0284	(0.770, 1.373)	0.8495
S/S	PLACEBO	148	1.333	(1.020, 1.741)	.		.
	SB 207499	157	1.112	(0.875, 1.412)	0.8341	(0.583, 1.194)	0.3213
N/N	PLACEBO	224	1.145	(0.931, 1.408)	.		.
	SB 207499	224	1.104	(0.892, 1.366)	0.9638	(0.716, 1.297)	0.8079
S/N or N/S	PLACEBO	57	1.050	(0.728, 1.515)	.		.
	SB 207499	42	0.979	(0.655, 1.464)	0.9323	(0.541, 1.607)	0.8007

1. RATES ARE CALCULATED BY POISSON REGRESSION WITH TREATMENT DURATION AS AN OFFSET VARIABLE AND WITH TREATMENT AS THE ONLY COVARIATE.
2. INCIDENCE DENSITY RATIO IS SB207499 RELATIVE TO PLACEBO

CONFIDENTIAL

SB 207499

TABLE 14.7X

SUMMARY OF LEVEL II / III EXACERBATION-FREE SURVIVAL BY REVERSIBILITY AND TREATMENT
- ALL RANDOMIZED PATIENTS
PROTOCOL 157

POPULATION	TREATMENT GROUP	NUMBER OF PATIENTS EXAC.-FREE	EXACERBATION-FREE SURVIVAL AT 52 WEEKS PERCENT EXAC.-FREE	95% CI	P-VALUE
NON-REVERSIBLE	PLACEBO	312	70.1%	(65.5%, 74.8%)	.
	SB 207499	316	68.4%	(63.4%, 73.4%)	0.545
REVERSIBLE	PLACEBO	6	62.5%	(29.0%, 96.0%)	.
	SB 207499	12	72.2%	(45.1%, 99.2%)	0.770

1. EXACERBATION-FREE SURVIVAL IS ESTIMATED USING KAPLAN-MEIER ESTIMATE OF TIME-TO-FIRST EXACERBATION
2. P-VALUE IS BASED ON LOG-RANK TEST

CONFIDENTIAL

SB 207499

TABLE 14.7Y

SUMMARY OF EXACERBATION-FREE SURVIVAL BY REVERSIBILITY AND TREATMENT
- ALL RANDOMIZED PATIENTS
PROTOCOL 157

POPULATION	TREATMENT GROUP	NUMBER OF PATIENTS EXAC.-FREE	EXACERBATION-FREE SURVIVAL AT 52 WEEKS PERCENT EXAC.-FREE	95% CI	P-VALUE
NON-REVERSIBLE	PLACEBO	236	51.1%	(46.0%, 56.2%)	.
	SB 207499	252	51.2%	(45.8%, 56.5%)	0.850
REVERSIBLE	PLACEBO	4	44.4%	(12.0%, 76.9%)	.
	SB 207499	10	53.5%	(23.1%, 83.8%)	0.719

1. EXACERBATION-FREE SURVIVAL IS ESTIMATED USING KAPLAN-MEIER ESTIMATE OF TIME-TO-FIRST EXACERBATION
2. P-VALUE IS BASED ON LOG-RANK TEST

CONFIDENTIAL

SB 207499

TABLE 14.8A

SUMMARY OF AVERAGE CHANGE FROM BASELINE OVER 52 WEEKS (REPEATED MEASURES ANALYSIS) IN BRONCHODILATOR EFFECT - ITT
PROTOCOL 157

		BASELINE		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
PLACEBO	411	0.094	0.005	0.050	0.005	0.041	0.059	.	.	.	
SB 207499	390	0.098	0.005	0.053	0.005	0.043	0.063	0.003	-0.009	0.015	0.599

1.MEANS ARE ADJUSTED FOR BASELINE VALUE, COUNTRY AND WEEK
2. STATISTICS ARE REPORTED BASED ON THE MAXIMUM OF THREE REPORTED VALUES OF FEV1 (L)
3. * SIGNIFICANTLY DIFFERENT FROM PLACEBO

CONFIDENTIAL

SB 207499

TABLE 14.8B

SUMMARY STATISTICS FOR BRONCHODILATOR EFFECT BY WEEK AND TREATMENT GROUP
- ITT
PROTOCOL 157

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	414	0.095	0.005	.	.	.	.	.	.	.	.
	SB 207499	397	0.099	0.005	.	.	.	.	.	.	.	.
WEEK 4	PLACEBO	392	0.135	0.008	0.054	0.008	0.038	0.069	.	.	.	.
	SB 207499	371	0.124	0.008	0.042	0.008	0.027	0.058	-0.011	-0.031	0.008	0.260
WEEK 8	PLACEBO	386	0.129	0.007	0.048	0.007	0.034	0.062	.	.	.	.
	SB 207499	365	0.135	0.007	0.054	0.007	0.039	0.069	0.006	-0.012	0.024	0.493
WEEK 12	PLACEBO	377	0.129	0.008	0.049	0.008	0.034	0.064	.	.	.	.
	SB 207499	344	0.136	0.008	0.055	0.008	0.040	0.071	0.006	-0.013	0.025	0.518
WEEK 20	PLACEBO	371	0.134	0.008	0.054	0.008	0.038	0.070	.	.	.	.
	SB 207499	328	0.130	0.009	0.050	0.009	0.033	0.067	-0.004	-0.024	0.016	0.695
WEEK 28	PLACEBO	359	0.138	0.009	0.058	0.009	0.039	0.076	.	.	.	.
	SB 207499	311	0.128	0.010	0.047	0.010	0.027	0.067	-0.011	-0.035	0.013	0.372
WEEK 36	PLACEBO	342	0.114	0.008	0.037	0.008	0.021	0.053	.	.	.	.
	SB 207499	298	0.133	0.009	0.056	0.009	0.038	0.073	0.019	-0.002	0.039	0.076
WEEK 44	PLACEBO	326	0.135	0.009	0.057	0.009	0.040	0.074	.	.	.	.
	SB 207499	284	0.145	0.009	0.067	0.009	0.049	0.085	0.010	-0.012	0.032	0.361
WEEK 52	PLACEBO	316	0.121	0.009	0.043	0.009	0.025	0.061	.	.	.	.
	SB 207499	269	0.126	0.010	0.048	0.010	0.029	0.068	0.005	-0.018	0.029	0.657
ENDPOINT	PLACEBO	414	0.122	0.008	0.040	0.008	0.025	0.055	.	.	.	.
	SB 207499	397	0.135	0.008	0.052	0.008	0.037	0.068	0.013	-0.006	0.032	0.193

1. MEANS ARE ADJUSTED FOR BASELINE VALUE AND COUNTRY
2. STATISTICS ARE REPORTED BASED ON THE VALUE CORRESPONDING TO THE MAXIMUM FEV1 (L)
3. BASELINE = VISIT 3; WEEK 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 5, 6, 7, 8, 9, 10, 11, 12; ENDPOINT = LOCF
4. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.8C

DESCRIPTIVE STATISTICS FOR BRONCHODILATOR EFFECT BY WEEK AND TREATMENT GROUP - ITT
PROTOCOL 157

WEEK	TREATMENT GROUP	N	BASELINE MEAN	BASELINE SD	WEEKLY ASSESSMENT MEAN	WEEKLY ASSESSMENT SD	WEEKLY ASSESSMENT MEDIAN	WEEKLY ASSESSMENT MIN	WEEKLY ASSESSMENT MAX
BASELINE	PLACEBO	414	0.081	0.103	0.081	0.103	0.086	-0.320	0.470
	SB 207499	397	0.085	0.090	0.085	0.090	0.080	-0.160	0.300
WEEK 4	PLACEBO	392	0.080	0.103	0.126	0.141	0.115	-0.590	0.760
	SB 207499	371	0.083	0.090	0.117	0.145	0.100	-0.620	0.530
WEEK 8	PLACEBO	386	0.080	0.104	0.121	0.136	0.110	-0.430	0.640
	SB 207499	365	0.082	0.089	0.127	0.128	0.120	-0.170	0.630
WEEK 12	PLACEBO	377	0.081	0.104	0.122	0.133	0.110	-0.440	0.570
	SB 207499	344	0.080	0.088	0.128	0.142	0.100	-0.440	0.640
WEEK 20	PLACEBO	371	0.079	0.105	0.127	0.154	0.110	-1.020	0.670
	SB 207499	328	0.080	0.089	0.125	0.125	0.110	-0.310	0.650
WEEK 28	PLACEBO	359	0.081	0.103	0.128	0.164	0.120	-0.450	1.750
	SB 207499	311	0.080	0.086	0.118	0.152	0.100	-0.280	1.580
WEEK 36	PLACEBO	342	0.076	0.104	0.108	0.136	0.100	-0.510	0.580
	SB 207499	298	0.079	0.088	0.128	0.135	0.115	-0.380	0.730
WEEK 44	PLACEBO	326	0.076	0.104	0.123	0.137	0.100	-0.460	0.640
	SB 207499	284	0.080	0.089	0.136	0.144	0.110	-0.370	0.600
WEEK 52	PLACEBO	316	0.076	0.104	0.112	0.134	0.090	-0.410	0.540
	SB 207499	269	0.080	0.091	0.116	0.160	0.100	-1.170	0.600
ENDPOINT	PLACEBO	414	0.081	0.103	0.112	0.132	0.095	-0.410	0.540
	SB 207499	397	0.085	0.090	0.125	0.154	0.110	-1.170	0.640

1. STATISTICS ARE REPORTED BASED ON THE VALUE CORRESPONDING TO THE MAXIMUM FEV1 (L)
2. MEAN VALUES ARE SAMPLE MEANS
3. BASELINE = VISIT 3; WEEK 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 5, 6, 7, 8, 9, 10, 11, 12; ENDPOINT = LOCF

CONFIDENTIAL

SB 207499

TABLE 14.9A

SUMMARY OF AVERAGE CHANGE FROM BASELINE OVER 52 WEEKS (REPEATED MEASURES ANALYSIS) IN TROUGH PEF(L/MIN) - ITT
PROTOCOL 157

		BASELINE		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
PLACEBO	416	208.61	3.966	-4.384	1.936	-8.184	-0.583	.	.	.	
SB 207499	395	198.12	4.084	1.116	1.995	-2.800	5.032	5.500	0.777	10.222	0.023*

1.MEANS ARE ADJUSTED FOR BASELINE VALUE, COUNTRY AND WEEK
2. STATISTICS ARE REPORTED BASED ON THE MAXIMUM OF THREE REPORTED VALUES OF FEV1 (L)
3. * SIGNIFICANTLY DIFFERENT FROM PLACEBO

CONFIDENTIAL

SB 207499

TABLE 14.9B

SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN TROUGH PEF (L/MIN) BY WEEK AND TREATMENT GROUP - ITT
PROTOCOL 157

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	420	207.928	3.909	.	.	.	.	.	.	.	.
	SB 207499	403	197.785	3.991	.	.	.	.	.	.	.	.
WEEK 4	PLACEBO	415	194.788	2.189	-2.724	2.189	-7.021	1.572	.	.	.	.
	SB 207499	391	200.148	2.251	2.637	2.251	-1.783	7.056	5.361	-0.105	10.826	0.055
WEEK 8	PLACEBO	400	196.839	2.357	-0.780	2.357	-5.407	3.847	.	.	.	.
	SB 207499	380	201.362	2.428	3.742	2.428	-1.023	8.508	4.522	-1.362	10.407	0.132
WEEK 12	PLACEBO	388	196.882	2.574	-1.566	2.574	-6.620	3.487	.	.	.	.
	SB 207499	356	203.194	2.658	4.746	2.658	-0.471	9.964	6.312	-0.091	12.716	0.053
WEEK 20	PLACEBO	377	194.129	2.666	-4.684	2.666	-9.919	0.551	.	.	.	.
	SB 207499	333	198.267	2.814	-0.546	2.814	-6.071	4.980	4.139	-2.537	10.814	0.224
WEEK 28	PLACEBO	366	193.675	2.940	-5.769	2.940	-11.543	0.004	.	.	.	.
	SB 207499	317	200.575	3.119	1.131	3.119	-4.994	7.256	6.900	-0.525	14.325	0.068
WEEK 36	PLACEBO	349	191.293	2.803	-8.341	2.803	-13.845	-2.836	.	.	.	.
	SB 207499	303	197.105	2.978	-2.528	2.978	-8.376	3.319	5.812	-1.259	12.884	0.107
WEEK 44	PLACEBO	334	193.045	3.012	-6.047	3.012	-11.961	-0.132	.	.	.	.
	SB 207499	291	201.077	3.198	1.986	3.198	-4.295	8.266	8.032	0.422	15.642	0.039
WEEK 52	PLACEBO	322	193.259	3.029	-5.278	3.029	-11.228	0.671	.	.	.	.
	SB 207499	275	201.926	3.214	3.388	3.214	-2.925	9.701	8.667	1.123	16.210	0.024
ENDPOINT	PLACEBO	420	190.143	2.481	-6.982	2.481	-11.853	-2.112	.	.	.	.
	SB 207499	403	198.984	2.521	1.858	2.521	-3.091	6.807	8.840	2.627	15.054	0.005

1. MEANS ARE ADJUSTED FOR BASELINE VALUE AND COUNTRY
2. STATISITCS ARE REPORTED BASED ON THE MAXIMUM OF THREE REPORTED VALUES OFTROUGH FVC (L)
3. BASELINE=VISIT 3; WEEK 4, 8, 12, 20, 28, 36, 44, 52 =VISIT 5, 6, 7, 8, 9, 10, 11,12; ENDPOINT=LOCF
4. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14.9C

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN TROUGH PEF(L/MIN) BY WEEK AND TREATMENT GROUP - ITT

PROTOCOL 157

WEEK	TREATMENT GROUP	N	BASELINE MEAN	BASELINE SD	WEEKLY ASSESSMENT MEAN	WEEKLY ASSESSMENT SD	WEEKLY ASSESSMENT MEDIAN	WEEKLY ASSESSMENT MIN	WEEKLY ASSESSMENT MAX	CHANGE FROM BASELINE MEAN	CHANGE FROM BASELINE SD	CHANGE FROM BASELINE MEDIAN	CHANGE FROM BASELINE MIN	CHANGE FROM BASELINE MAX
BASELINE	PLACEBO	420	201.479	72.991	201.479	72.991	193.000	52.000	432.000	.	.	.	.	.
	SB 207499	403	192.589	72.952	192.589	72.952	180.000	43.000	454.000	.	.	.	.	.
WEEK 4	PLACEBO	415	202.239	73.003	199.404	74.369	189.000	59.000	508.000	-2.835	41.722	-4.000	-271.00	160.000
	SB 207499	391	192.495	73.320	196.088	75.807	182.000	56.000	441.000	3.593	38.722	-1.000	-181.00	249.000
WEEK 8	PLACEBO	400	202.561	72.503	200.716	75.153	186.000	49.000	481.000	-1.845	44.081	-3.000	-287.00	243.000
	SB 207499	380	192.418	72.052	196.489	76.175	183.000	45.000	434.000	4.071	40.273	0.000	-144.00	181.000
WEEK 12	PLACEBO	388	202.890	72.598	199.710	76.675	184.500	49.000	522.000	-3.180	49.505	-4.000	-256.00	248.000
	SB 207499	356	193.607	73.260	198.452	78.452	187.000	61.000	469.000	4.845	39.427	0.000	-197.00	220.000
WEEK 20	PLACEBO	377	203.027	71.835	197.100	74.106	182.000	50.000	493.000	-5.927	50.071	-5.000	-277.00	243.000
	SB 207499	333	194.042	73.491	193.644	75.754	175.000	6.690	417.000	-0.398	42.928	1.000	-342.31	125.000
WEEK 28	PLACEBO	366	203.585	71.851	198.121	74.873	181.000	67.000	530.000	-5.464	48.842	-5.000	-276.00	249.000
	SB 207499	317	194.662	74.032	197.262	86.668	180.000	59.000	792.000	2.599	50.187	-1.000	-144.00	465.000
WEEK 36	PLACEBO	349	203.613	71.981	194.742	73.125	182.000	63.000	461.000	-8.871	50.563	-7.800	-255.00	183.000
	SB 207499	303	195.050	73.892	193.616	77.708	181.000	54.000	463.000	-1.434	42.852	-2.000	-140.00	178.000
WEEK 44	PLACEBO	334	203.054	72.187	196.449	77.573	181.900	58.000	522.000	-6.605	53.210	-8.500	-270.00	221.000
	SB 207499	291	194.543	73.701	197.344	78.818	187.000	59.000	510.000	2.801	45.394	0.000	-149.00	214.000
WEEK 52	PLACEBO	322	202.258	71.720	195.541	72.558	186.500	66.000	442.000	-6.717	48.671	-9.000	-269.00	169.000
	SB 207499	275	194.182	73.691	197.155	82.486	182.000	61.000	546.000	2.973	45.620	0.000	-152.00	250.000
ENDPOINT	PLACEBO	420	201.479	72.991	193.870	73.267	185.000	50.000	468.000	-7.609	46.944	-9.000	-269.00	169.000
	SB 207499	403	192.589	72.952	194.458	80.977	179.000	45.000	546.000	1.869	45.060	0.000	-153.00	250.000

1. STATISITCS ARE REPORTED BASED ON THE VALUE CORRESPONDING TO THE MAXIMUM FEV1 (L)
2. MEAN VALUES ARE SAMPLE MEANS
3. BASELINE = VISIT 3; WEEK 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 5, 6, 7, 8, 9, 10, 11,12; ENDPOINT = LOCF

CONFIDENTIAL

SB 207499

TABLE 14.10

SUMMARY OF TESTS OF SIGNIFICANCE FOR PROGNOSTIC FACTORS EFFECTING CHANGE FROM BASELINE IN TROUGH FEV1 (L)
- ITT
PROTOCOL 157

FACTOR	P-VALUE
BASELINE	0.0000
TREATMENT	0.0001
VIS_ID	0.0035
AGE	0.0010
GENDER	0.0042
% PREDICTED FEV1	0.0000
SMOKING STATUS	0.2980
COUNTRY	0.0002

1. STATISTICS ARE REPORTED BASED ON THE MAXIMUM OF THREE REPORTED VALUES OF FEV1 (L)
2. P-VALUES ARE BASED ON REPEATED MEASURES MODEL WITH ONLY THE DISPLAYED MAIN EFFECTS
3. BASELINE REFERS TO FEV1 AT VISIT 3.

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.10A

SUMMARY OF AVERAGE CHANGE FROM BASELINE OVER 52 WEEKS (REPEATED MEASURES ANALYSIS) IN DOMICILIARY PEF(L/MIN) BY SMOKING STATUS - ITT
PROTOCOL 157

	BASELINE		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
PLACEBO	418	255.82	4.683	2.948	1.394	0.211	5.684	.	.	.	
SB 207499	407	248.01	4.757	3.251	1.415	0.475	6.028	0.304	-2.490	3.097	0.831

1. MEANS ARE ADJUSTED FOR BASELINE VALUE, COUNTRY AND WEEK
2. STATISTICS ARE REPORTED BASED ON THE MAXIMUM OF THREE OBSERVED VALUES OF PEF (L/MIN)
3. * SIGNIFICANTLY DIFFERENT FROM PLACEBO

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.10B

SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN DOMICILIARY PEF (L/MIN) BY WEEK AND TREATMENT GROUP - ITT
PROTOCOL 157

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	420	255.873	4.675	.	.	.	.	.	.	.	.
	SB 207499	407	247.968	4.752	.	.	.	.	.	.	.	.
WEEK 2	PLACEBO	404	252.133	1.148	0.925	1.148	-1.329	3.178	.	.	.	.
	SB 207499	387	251.892	1.174	0.684	1.174	-1.620	2.988	-0.241	-3.126	2.644	0.870
WEEK 4	PLACEBO	390	254.078	1.426	1.050	1.426	-1.749	3.849	.	.	.	.
	SB 207499	365	255.347	1.488	2.319	1.488	-0.602	5.240	1.269	-2.317	4.854	0.488
WEEK 8	PLACEBO	390	255.594	1.822	2.168	1.822	-1.409	5.745	.	.	.	.
	SB 207499	360	256.750	1.912	3.324	1.912	-0.431	7.079	1.156	-3.406	5.718	0.619
WEEK 12	PLACEBO	374	255.201	2.064	2.503	2.064	-1.550	6.556	.	.	.	.
	SB 207499	335	256.144	2.172	3.446	2.172	-0.818	7.710	0.943	-4.248	6.134	0.721
WEEK 20	PLACEBO	353	254.658	2.314	-0.287	2.314	-4.832	4.258	.	.	.	.
	SB 207499	304	259.088	2.500	4.142	2.500	-0.768	9.052	4.429	-1.418	10.277	0.137
WEEK 28	PLACEBO	347	257.261	2.603	0.554	2.603	-4.557	5.666	.	.	.	.
	SB 207499	299	258.878	2.786	2.172	2.786	-3.300	7.643	1.617	-5.004	8.239	0.632
WEEK 36	PLACEBO	335	257.929	2.600	1.918	2.600	-3.187	7.024	.	.	.	.
	SB 207499	288	263.209	2.797	7.198	2.797	1.705	12.692	5.280	-1.344	11.904	0.118
WEEK 44	PLACEBO	310	255.892	2.714	1.376	2.714	-3.956	6.708	.	.	.	.
	SB 207499	274	263.421	2.897	8.905	2.897	3.215	14.595	7.529	0.686	14.372	0.031
WEEK 52	PLACEBO	300	258.975	3.136	5.282	3.136	-0.879	11.444	.	.	.	.
	SB 207499	261	265.926	3.257	12.233	3.257	5.835	18.631	6.951	-0.386	14.288	0.063
ENDPOINT	PLACEBO	420	252.689	2.411	2.030	2.411	-2.702	6.763	.	.	.	.
	SB 207499	407	257.674	2.449	7.015	2.449	2.207	11.823	4.985	-1.039	11.009	0.105

1. MEANS ARE ADJUSTED FOR BASELINE VALUE AND COUNTRY
2. STATISITCS ARE REPORTED BASED ON THE MAXIMUM OF THREE OBSERVED VALUES OF PEF (L/MIN)
3. BASELINE = VISIT 3; WEEK 2, 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 4, 5, 6, 7, 8, 9, 10, 11,12; ENDPOINT = LOCF
4. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14.10C

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN DOMICILIARY PEF(L/MIN) BY WEEK AND TREATMENT GROUP - ITT

PROTOCOL 157

WEEK	TREATMENT GROUP	N	BASELINE MEAN	BASELINE SD	WEEKLY ASSESSMENT MEAN	WEEKLY ASSESSMENT SD	WEEKLY ASSESSMENT MEDIAN	WEEKLY ASSESSMENT MIN	WEEKLY ASSESSMENT MAX	CHANGE FROM BASELINE MEAN	CHANGE FROM BASELINE SD	CHANGE FROM BASELINE MEDIAN	CHANGE FROM BASELINE MIN	CHANGE FROM BASELINE MAX
BASELINE	PLACEBO	420	253.842	87.885	253.842	87.885	245.857	60.000	544.231	.	.	.	.	.
	SB 207499	407	247.373	88.183	247.373	88.183	232.727	65.000	592.143	.	.	.	.	.
WEEK 2	PLACEBO	404	253.753	87.562	254.918	88.626	245.550	60.000	547.500	1.165	19.650	-0.082	-100.00	94.571
	SB 207499	387	248.552	87.731	249.552	90.291	237.143	17.077	563.077	1.000	21.124	1.071	-145.07	152.143
WEEK 4	PLACEBO	390	255.779	88.489	257.390	90.019	248.214	60.000	559.286	1.612	25.384	-0.308	-98.690	105.000
	SB 207499	365	250.089	86.629	253.031	87.816	241.071	79.231	512.857	2.941	24.284	1.895	-148.46	139.286
WEEK 8	PLACEBO	390	256.718	87.555	259.312	88.281	248.214	60.071	540.000	2.595	30.775	0.000	-103.57	117.857
	SB 207499	360	249.860	86.258	254.156	89.436	235.714	68.571	497.143	4.296	32.487	2.857	-177.86	122.857
WEEK 12	PLACEBO	374	255.121	87.309	257.895	90.201	248.571	60.000	574.286	2.774	35.206	-0.714	-95.165	235.824
	SB 207499	335	249.993	88.050	253.980	90.065	240.714	10.714	582.143	3.987	34.841	1.643	-156.26	129.286
WEEK 20	PLACEBO	353	257.565	87.983	258.554	90.316	249.286	75.000	565.385	0.989	39.725	0.000	-201.43	177.857
	SB 207499	304	251.904	85.571	257.839	89.530	241.484	0.000	575.000	5.935	35.900	5.714	-148.46	118.572
WEEK 28	PLACEBO	347	257.747	87.888	260.069	91.380	245.769	36.429	585.714	2.322	42.876	0.549	-202.14	240.714
	SB 207499	299	255.499	85.017	259.908	91.180	247.857	0.000	589.286	4.409	42.667	3.571	-348.00	123.571
WEEK 36	PLACEBO	335	258.231	86.798	261.332	92.371	247.857	65.714	613.571	3.102	43.178	0.000	-203.57	260.000
	SB 207499	288	253.428	88.353	261.782	94.252	246.429	0.000	572.143	8.354	39.968	4.862	-156.32	156.428
WEEK 44	PLACEBO	310	257.867	89.507	260.554	95.003	247.024	71.429	617.857	2.687	43.165	0.178	-221.43	242.143
	SB 207499	274	250.724	88.791	260.681	94.862	246.429	57.143	558.571	9.957	40.265	8.132	-151.54	149.285
WEEK 52	PLACEBO	300	255.643	89.396	261.713	95.632	247.143	72.857	581.429	6.071	42.888	2.143	-179.29	224.286
	SB 207499	261	251.452	89.184	264.037	100.139	249.286	79.286	920.000	12.585	44.768	8.681	-157.91	327.857
ENDPOINT	PLACEBO	420	253.842	87.885	256.542	93.576	244.643	60.000	581.429	2.700	44.373	0.278	-221.43	224.286
	SB 207499	407	247.373	88.183	254.758	96.982	237.857	58.571	920.000	7.385	43.847	5.000	-166.37	327.857

1. STATISITCS ARE REPORTED BASED ON THE MAXIMUM OF THREE OBSERVED VALUES OF PEF (L/MIN)
2. MEAN VALUES ARE SAMPLE MEANS
3. BASELINE = VISIT 3; WEEK 2, 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 4, 5, 6, 7, 8, 9, 10, 11, 12; ENDPOINT = LOCF

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.11B

SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN EQ-5D TARRIF HEALTH STATE BY WEEK AND TREATMENT GROUP - ITT
PROTOCOL 157

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	365	0.808	0.011	.	.	.	.	.	.	.	.
	SB 207499	320	0.811	0.011	.	.	.	.	.	.	.	.
WEEK 28	PLACEBO	335	0.834	0.011	0.028	0.011	0.006	0.050	.	.	.	.
	SB 207499	286	0.826	0.012	0.020	0.012	-0.004	0.044	-0.008	-0.036	0.021	0.603
WEEK 52	PLACEBO	288	0.812	0.012	0.005	0.012	-0.018	0.028	.	.	.	.
	SB 207499	254	0.824	0.012	0.016	0.012	-0.008	0.040	0.012	-0.018	0.041	0.440
ENDPOINT	PLACEBO	365	0.810	0.010	0.004	0.010	-0.016	0.025	.	.	.	.
	SB 207499	320	0.814	0.011	0.008	0.011	-0.014	0.030	0.004	-0.023	0.031	0.772

1. MEANS ARE ADJUSTED FOR BASELINE VALUE AND COUNTRY
2. BASELINE = VISIT 3; WEEK 28, 52 = VISIT 9, 12; ENDPOINT = LOCF
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.11C

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN EQ-5D TARRIF HEALTH STATE BY WEEK AND TREATMENT GROUP - ITT
PROTOCOL 157

			BASELINE		WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	365	0.801	0.197	0.801	0.197	0.814	0.020	1.000	.	.	.	.	.
	SB 207499	320	0.810	0.181	0.810	0.181	0.814	-0.170	1.000	.	.	.	.	.
WEEK 28	PLACEBO	335	0.801	0.196	0.816	0.219	0.848	-0.513	1.000	0.014	0.213	0.000	-1.513	0.876
	SB 207499	286	0.811	0.181	0.817	0.199	0.848	-0.077	1.000	0.005	0.185	0.000	-0.873	0.982
WEEK 52	PLACEBO	288	0.807	0.188	0.805	0.214	0.814	-0.513	1.000	-0.003	0.195	0.000	-1.396	0.807
	SB 207499	254	0.808	0.183	0.821	0.192	0.848	-0.016	1.000	0.013	0.187	0.000	-0.899	1.018
ENDPOINT	PLACEBO	365	0.801	0.197	0.799	0.214	0.814	-0.513	1.000	-0.003	0.199	0.000	-1.396	0.807
	SB 207499	320	0.810	0.181	0.811	0.201	0.814	-0.016	1.000	0.001	0.193	0.000	-0.899	1.018

1. MEAN VALUES ARE SAMPLE MEANS
2. BASELINE = VISIT 3; WEEK 28, 52 =VISIT 9, 12; ENDPOINT = LOCF

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.12B

SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN EQ-5D THERMOMETER HEALTH SCALE BY WEEK AND TREATMENT GROUP - ITT
PROTOCOL 157

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	358	63.562	1.035	.	.	.	.	.	.	.	.
	SB 207499	318	63.696	1.100	.	.	.	.	.	.	.	.
WEEK 28	PLACEBO	322	63.688	1.091	0.287	1.091	-1.856	2.430	.	.	.	.
	SB 207499	286	63.862	1.161	0.461	1.161	-1.820	2.742	0.174	-2.610	2.957	0.902
WEEK 52	PLACEBO	285	64.108	1.036	0.499	1.036	-1.535	2.534	.	.	.	.
	SB 207499	251	66.333	1.088	2.725	1.088	0.588	4.862	2.226	-0.379	4.830	0.094
ENDPOINT	PLACEBO	358	62.524	0.941	-0.598	0.941	-2.446	1.249	.	.	.	.
	SB 207499	318	65.012	1.000	1.889	1.000	-0.073	3.852	2.488	0.063	4.913	0.044

1. MEANS ARE ADJUSTED FOR BASELINE VALUE AND COUNTRY
2. BASELINE=VISIT 3; WEEK 28, 52 =VISIT 9, 12; ENDPOINT=LOCF
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.12C

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN EQ-5D THERMOMETER HEALTH SCALE BY WEEK AND TREATMENT GROUP - ITT
PROTOCOL 157

			BASELINE		WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	358	62.978	18.230	62.978	18.230	65.000	3.000	100.000	.	.	.	.	.
	SB 207499	318	63.286	17.638	63.286	17.638	65.000	4.000	100.000	.	.	.	.	.
WEEK 28	PLACEBO	322	63.435	18.303	63.371	20.017	65.000	4.000	100.000	-0.064	20.393	0.000	-75.000	82.000
	SB 207499	286	63.364	17.689	63.640	19.153	65.000	5.000	100.000	0.276	19.721	0.000	-82.000	75.000
WEEK 52	PLACEBO	285	63.112	17.904	64.270	17.664	65.000	0.000	100.000	1.158	17.623	0.000	-68.000	80.000
	SB 207499	251	64.171	17.341	67.070	17.719	70.000	7.000	100.000	2.898	17.676	0.000	-71.000	70.000
ENDPOINT	PLACEBO	358	62.978	18.230	62.620	18.566	60.000	0.000	100.000	-0.358	18.365	0.000	-75.000	80.000
	SB 207499	318	63.286	17.638	65.346	18.331	70.000	6.000	100.000	2.060	18.201	0.000	-71.000	70.000

1. STATISITCS ARE REPORTED BASED ON THE VALUE CORRESPONDING TO THE MAXIMUM FEV1 (L)
1. MEAN VALUES ARE SAMPLE MEANS
2. BASELINE = VISIT 3; WEEK 28, 52 =VISIT 9, 12; ENDPOINT = LOCF

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.14B

SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN CD4+/CD8+ RATIO BY WEEK AND TREATMENT GROUP - ITT
PROTOCOL 157

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	323	2.127	0.078	.	.	.	.	.	.	.	.
	SB 207499	285	2.142	0.082	.	.	.	.	.	.	.	.
WEEK 52	PLACEBO	295	2.153	0.040	0.013	0.040	-0.065	0.091	.	.	.	.
	SB 207499	253	2.123	0.042	-0.016	0.042	-0.099	0.067	-0.029	-0.129	0.071	0.566
ENDPOINT	PLACEBO	323	2.156	0.038	0.023	0.038	-0.051	0.098	.	.	.	.
	SB 207499	285	2.119	0.040	-0.014	0.040	-0.092	0.064	-0.037	-0.132	0.059	0.450

1. MEANS ARE ADJUSTED FOR BASELINE VALUE AND COUNTRY
2. BASELINE = VISIT 3; WEEK 52 = VISIT 12; ENDPOINT = LOCF
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14.14C

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN CD4+/CD8+ RATIO BY WEEK AND TREATMENT GROUP
- ITT
PROTOCOL 157

		BASELINE			WEEKLY ASSESSMENT				CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	323	2.138	1.278	2.138	1.278	1.830	0.290	7.330	.	.	.	.	.
	SB 207499	285	2.127	1.232	2.127	1.232	1.900	0.230	10.150	.	.	.	.	.
WEEK 52	PLACEBO	295	2.139	1.307	2.156	1.391	1.810	0.450	9.000	0.017	0.639	0.000	-3.530	6.070
	SB 207499	253	2.141	1.266	2.127	1.129	1.880	0.350	6.620	-0.014	0.584	0.010	-3.530	3.070
ENDPOINT	PLACEBO	323	2.138	1.278	2.157	1.393	1.810	0.450	9.000	0.020	0.652	0.000	-3.530	6.070
	SB 207499	285	2.127	1.232	2.108	1.114	1.860	0.350	6.620	-0.019	0.563	0.010	-3.530	3.070

1. MEAN VALUES ARE SAMPLE MEANS
2. BASELINE=VISIT 3; WEEK 52 =VISIT 12; ENDPOINT=LOCF

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.15B

SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN RESIDUAL VOLUME BY WEEK AND TREATMENT GROUP - ITT
PROTOCOL 157

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	23	3.987	0.330	.	.	.	.	.	.	.	.
	SB 207499	21	4.304	0.353	.	.	.	.	.	.	.	.
WEEK 28	PLACEBO	22	4.246	0.214	0.055	0.214	-0.378	0.488	.	.	.	.
	SB 207499	20	4.625	0.223	0.434	0.223	-0.018	0.887	0.379	-0.172	0.930	0.171
WEEK 52	PLACEBO	18	4.231	0.174	0.070	0.174	-0.285	0.425	.	.	.	.
	SB 207499	17	4.535	0.173	0.374	0.173	0.020	0.727	0.304	-0.174	0.782	0.204
ENDPOINT	PLACEBO	23	4.279	0.199	0.143	0.199	-0.259	0.545	.	.	.	.
	SB 207499	21	4.478	0.213	0.342	0.213	-0.088	0.772	0.199	-0.329	0.727	0.450

1. MEANS ARE ADJUSTED FOR BASELINE VALUE AND COUNTRY
2. STATISITCS ARE REPORTED BASED ON THE MAXIMUM OF THREE REPORTED VALUES OFTROUGH FEV1 (L)
3. BASELINE=VISIT 3; WEEK 28, 52 =VISIT 12; ENDPOINT=LOCF
4. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14.15C

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN RESIDUAL VOLUME BY WEEK AND TREATMENT GROUP - ITT
PROTOCOL 157

		BASELINE			WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	23	3.969	1.291	3.969	1.291	3.890	1.950	6.290	.	.	.	.	.
	SB 207499	21	4.319	1.494	4.319	1.494	4.010	1.380	7.630	.	.	.	.	.
WEEK 28	PLACEBO	22	4.039	1.276	4.076	1.088	3.950	2.560	6.560	0.037	0.785	0.055	-2.390	1.790
	SB 207499	20	4.358	1.522	4.749	1.961	4.245	1.880	9.810	0.392	0.902	0.145	-1.260	2.450
WEEK 52	PLACEBO	18	3.772	1.264	3.976	1.125	3.765	2.560	6.250	0.204	0.733	0.150	-0.780	1.800
	SB 207499	17	4.573	1.532	4.861	1.330	4.910	1.910	7.320	0.288	0.675	0.240	-1.190	1.340
ENDPOINT	PLACEBO	23	3.969	1.291	4.189	1.360	3.830	2.560	7.360	0.220	0.913	0.130	-1.010	2.860
	SB 207499	21	4.319	1.494	4.654	1.341	4.240	1.910	7.320	0.335	0.851	0.150	-1.190	2.800

1. STATISITCS ARE REPORTED BASED ON THE VALUE CORRESPONDING TO THE MAXIMUM FEV1 (L)
1. MEAN VALUES ARE SAMPLE MEANS
2. BASELINE=VISIT 3; WEEK 28, 52 =VISIT 9, 12; ENDPOINT=LOCF

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.16B

SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN SERUM C REACTIVE PROTEIN (MG) BY WEEK AND TREATMENT GROUP - ITT
PROTOCOL 157

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	38	0.018	0.005	.	.	.	.	.	.	.	.
	SB 207499	40	0.018	0.005	.	.	.	.	.	.	.	.
WEEK 52	PLACEBO	33	0.018	0.006	0.008	0.006	-0.005	0.020	.	.	.	.
	SB 207499	33	0.026	0.006	0.015	0.006	0.003	0.027	0.008	-0.007	0.023	0.315
ENDPOINT	PLACEBO	38	0.023	0.008	0.008	0.008	-0.007	0.023	.	.	.	.
	SB 207499	40	0.023	0.007	0.008	0.007	-0.006	0.022	0.000	-0.018	0.018	0.991

1. MEANS ARE ADJUSTED FOR BASELINE VALUE AND COUNTRY
2. BASELINE = VISIT 3; WEEK 52 = VISIT 12; ENDPOINT = LOCF
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14.16C

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN SERUM C REACTIVE PROTEIN (MG) BY WEEK AND TREATMENT GROUP - ITT
PROTOCOL 157

		BASELINE			WEEKLY ASSESSMENT				CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	38	0.012	0.017	0.012	0.017	0.006	0.004	0.079	.	.	.	.	.
	SB 207499	40	0.017	0.028	0.017	0.028	0.008	0.004	0.165	.	.	.	.	.
WEEK 52	PLACEBO	33	0.010	0.012	0.016	0.026	0.008	0.004	0.141	0.006	0.029	0.002	-0.052	0.133
	SB 207499	33	0.011	0.011	0.019	0.033	0.008	0.004	0.188	0.008	0.035	0.001	-0.031	0.183
ENDPOINT	PLACEBO	38	0.012	0.017	0.021	0.042	0.008	0.004	0.224	0.008	0.043	0.002	-0.074	0.189
	SB 207499	40	0.017	0.028	0.018	0.030	0.008	0.004	0.188	0.001	0.042	0.000	-0.157	0.183

1. STATISITCS ARE REPORTED BASED ON THE VALUE CORRESPONDING TO THE MAXIMUM FEV1 (L)
1. MEAN VALUES ARE SAMPLE MEANS
2. BASELINE=VISIT 3; WEEK 52 =VISIT 12; ENDPOINT=LOCF

CONFIDENTIAL

SB 207499

TABLE 14.21A

SUMMARY OF AVERAGE CHANGE FROM BASELINE OVER 52 WEEKS (REPEATED MEASURES ANALYSIS) IN ACTIVITY SCORE OF THE SGRQ - ITT
PROTOCOL 157

	BASELINE		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
PLACEBO	346	53.519	1.296	-1.454	0.962	-3.344	0.435	.	.	.	
SB 207499	299	53.925	1.387	-1.069	1.029	-3.089	0.951	0.385	-2.058	2.828	0.757

1.MEANS ARE ADJUSTED FOR BASELINE VALUE, COUNTRY AND WEEK
2. * SIGNIFICANTLY DIFFERENT FROM PLACEBO

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.21B

SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN ACTIVITY SCORE OF THE SGRQ BY WEEK AND TREATMENT GROUP - ITT
PROTOCOL 157

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	384	54.018	1.211	.	.	.	.	.	.	.	.
	SB 207499	360	54.675	1.255	.	.	.	.	.	.	.	.
WEEK 28	PLACEBO	336	52.539	1.052	-0.875	1.052	-2.942	1.191	.	.	.	.
	SB 207499	287	53.006	1.140	-0.408	1.140	-2.647	1.830	0.467	-2.205	3.139	0.731
WEEK 52	PLACEBO	290	51.265	1.181	-1.879	1.181	-4.200	0.441	.	.	.	.
	SB 207499	263	51.357	1.239	-1.787	1.239	-4.220	0.646	0.092	-2.871	3.056	0.951
ENDPOINT	PLACEBO	384	52.956	1.012	-1.461	1.012	-3.448	0.525	.	.	.	.
	SB 207499	360	53.512	1.048	-0.905	1.048	-2.963	1.153	0.556	-1.995	3.107	0.669

1. MEANS ARE ADJUSTED FOR BASELINE VALUE AND COUNTRY
2. BASELINE = VISIT 3; WEEK 28, 52 =VISIT 9, 12; ENDPOINT = LOCF
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.21C

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN ACTIVITY SCORE OF THE SGRQ BY WEEK AND TREATMENT GROUP - ITT
PROTOCOL 157

			BASELINE		WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	384	54.367	22.194	54.367	22.194	53.900	0.000	100.000	.	.	.	.	.
	SB 207499	360	54.471	21.855	54.471	21.855	53.618	0.000	100.000	.	.	.	.	.
WEEK 28	PLACEBO	336	53.811	21.972	52.735	23.038	53.618	0.000	100.000	-1.076	17.916	0.000	-75.023	52.758
	SB 207499	287	52.949	22.050	52.311	23.953	53.527	0.000	100.000	-0.638	17.508	0.000	-66.157	55.694
WEEK 52	PLACEBO	290	53.326	22.081	50.767	23.943	53.618	0.000	100.000	-2.559	19.808	0.000	-61.748	54.834
	SB 207499	263	52.944	21.856	50.357	23.689	53.536	0.000	100.000	-2.586	17.565	-0.331	-66.752	52.312
ENDPOINT	PLACEBO	384	54.367	22.194	52.441	24.557	53.618	0.000	100.000	-1.925	19.477	0.000	-61.748	54.834
	SB 207499	360	54.471	21.855	52.867	23.425	53.618	0.000	100.000	-1.603	18.021	0.000	-66.752	55.694

1. MEAN VALUES ARE SAMPLE MEANS
2. BASELINE = VISIT 3; WEEK 28, 52 =VISIT 9, 12; ENDPOINT = LOCF

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.22A

SUMMARY OF AVERAGE CHANGE FROM BASELINE OVER 52 WEEKS (REPEATED MEASURES ANALYSIS) IN IMPACT SCORE OF THE SGRQ - ITT
PROTOCOL 157

	BASELINE		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
PLACEBO	346	27.668	1.122	-1.164	0.802	-2.739	0.411	.	.	.	
SB 207499	299	27.851	1.201	-0.777	0.857	-2.461	0.907	0.387	-1.653	2.426	0.710

1.MEANS ARE ADJUSTED FOR BASELINE VALUE, COUNTRY AND WEEK
2. * SIGNIFICANTLY DIFFERENT FROM PLACEBO

CONFIDENTIAL

SB 207499

TABLE 14.22B

SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN IMPACT SCORE OF THE SGRQ BY WEEK AND TREATMENT GROUP - ITT
PROTOCOL 157

		WEEKLY ASSESSMENT			CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	384	28.504	1.053	.	.	.	.	.	.	.	.
	SB 207499	360	28.455	1.090	.	.	.	.	.	.	.	.
WEEK 28	PLACEBO	336	25.882	0.892	-2.234	0.892	-3.985	-0.483	.	.	.	.
	SB 207499	287	26.997	0.966	-1.118	0.966	-3.014	0.778	1.115	-1.148	3.379	0.334
WEEK 52	PLACEBO	290	27.572	0.967	-0.220	0.967	-2.120	1.679	.	.	.	.
	SB 207499	263	26.950	1.014	-0.842	1.014	-2.835	1.151	-0.621	-3.047	1.804	0.615
ENDPOINT	PLACEBO	384	29.050	0.858	0.272	0.858	-1.412	1.955	.	.	.	.
	SB 207499	360	28.003	0.888	-0.775	0.888	-2.519	0.969	-1.047	-3.208	1.115	0.342

1. MEANS ARE ADJUSTED FOR BASELINE VALUE AND COUNTRY
2. BASELINE = VISIT 3; WEEK 28, 52 = VISIT 9, 12; ENDPOINT = LOCF
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.22C

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN IMPACT SCORE OF THE SGRQ BY WEEK AND TREATMENT GROUP - ITT
PROTOCOL 157

			BASELINE		WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	384	28.758	19.120	28.758	19.120	25.109	0.000	92.672	.	.	.	.	.
	SB 207499	360	28.799	19.460	28.799	19.460	25.671	0.000	96.681	.	.	.	.	.
WEEK 28	PLACEBO	336	28.034	19.096	26.338	18.806	23.491	0.000	85.334	-1.696	14.510	-0.393	-53.598	44.546
	SB 207499	287	28.211	19.754	27.206	19.751	24.252	0.000	87.822	-1.005	17.056	0.000	-76.273	52.139
WEEK 52	PLACEBO	290	27.781	19.269	26.914	19.675	22.545	0.000	89.739	-0.867	15.493	0.000	-52.347	39.924
	SB 207499	263	27.804	19.452	26.061	19.782	21.537	0.000	91.142	-1.743	15.573	-1.903	-72.514	39.994
ENDPOINT	PLACEBO	384	28.758	19.120	28.851	20.189	25.087	0.000	89.739	0.093	15.614	0.574	-52.347	39.924
	SB 207499	360	28.799	19.460	27.566	19.913	23.829	0.000	91.142	-1.233	16.803	-0.321	-72.514	54.026

1. MEAN VALUES ARE SAMPLE MEANS
2. BASELINE = VISIT 3; WEEK 28, 52 =VISIT 9, 12; ENDPOINT = LOCF

CONFIDENTIAL

SB 207499

TABLE 14.23A

SUMMARY OF AVERAGE CHANGE FROM BASELINE OVER 52 WEEKS (REPEATED MEASURES ANALYSIS) IN SYMPTOMS SCORE OF THE SGRQ - ITT
PROTOCOL 157

		BASELINE		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
PLACEBO	356	45.365	1.257	-2.870	1.024	-4.880	-0.859	.	.	.	
SB 207499	306	46.421	1.342	-3.419	1.090	-5.559	-1.278	-0.549	-3.152	2.054	0.679

1.MEANS ARE ADJUSTED FOR BASELINE VALUE, COUNTRY AND WEEK
2. * SIGNIFICANTLY DIFFERENT FROM PLACEBO

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.23B

SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN SYMPTOMS SCORE OF THE SGRQ BY WEEK AND TREATMENT GROUP - ITT
PROTOCOL 157

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	395	45.960	1.196	.	.	.	.	.	.	.	.
	SB 207499	369	47.089	1.234	.	.	.	.	.	.	.	.
WEEK 28	PLACEBO	347	43.421	1.151	-2.585	1.151	-4.846	-0.325	.	.	.	.
	SB 207499	300	42.102	1.234	-3.905	1.234	-6.329	-1.481	-1.320	-4.269	1.629	0.380
WEEK 52	PLACEBO	303	41.848	1.267	-3.810	1.267	-6.299	-1.322	.	.	.	.
	SB 207499	271	42.307	1.328	-3.352	1.328	-5.960	-0.743	0.459	-2.722	3.639	0.777
ENDPOINT	PLACEBO	395	44.579	1.142	-2.133	1.142	-4.375	0.109	.	.	.	.
	SB 207499	369	43.899	1.178	-2.813	1.178	-5.126	-0.500	-0.680	-3.554	2.194	0.642

1. MEANS ARE ADJUSTED FOR BASELINE VALUE AND COUNTRY
2. BASELINE = VISIT 3; WEEK 28, 52 =VISIT 9, 12; ENDPOINT = LOCF
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.23C

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN SYMPTOMS SCORE OF THE SGRQ BY WEEK AND TREATMENT GROUP - ITT
PROTOCOL 157

			BASELINE		WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	395	46.486	23.064	46.486	23.064	47.577	0.000	100.000	.	.	.	.	.
	SB 207499	369	46.954	23.270	46.954	23.270	46.128	0.000	97.555	.	.	.	.	.
WEEK 28	PLACEBO	347	45.946	23.027	43.276	23.870	42.279	0.000	100.000	-2.670	21.650	-0.392	-68.060	61.374
	SB 207499	300	46.077	22.809	41.600	23.463	39.894	0.000	100.000	-4.477	20.237	-3.253	-69.645	50.355
WEEK 52	PLACEBO	303	45.767	23.185	41.431	23.540	40.317	0.000	100.000	-4.336	21.525	-4.423	-83.879	59.260
	SB 207499	271	45.537	22.592	41.591	24.063	40.951	0.000	98.008	-3.946	21.883	-4.377	-74.611	71.547
ENDPOINT	PLACEBO	395	46.486	23.064	44.531	24.953	43.502	0.000	100.000	-1.956	22.625	-1.660	-83.879	59.260
	SB 207499	369	46.954	23.270	43.879	24.266	44.181	0.000	100.000	-3.076	21.896	-3.925	-74.611	71.547

1. MEAN VALUES ARE SAMPLE MEANS
2. BASELINE = VISIT 3; WEEK 28, 52 =VISIT 9, 12; ENDPOINT = LOCF

CONFIDENTIAL

SB 207499

TABLE 14.24A

SUMMARY OF AVERAGE CHANGE FROM BASELINE OVER 52 WEEKS (REPEATED MEASURES ANALYSIS) IN TROUGH FEF25-75 (L/SEC) - ITT
PROTOCOL 157

		BASELINE		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
PLACEBO	416	0.591	0.020	-0.018	0.011	-0.040	0.003	.	.	.	
SB 207499	395	0.565	0.021	-0.028	0.011	-0.050	-0.006	-0.010	-0.037	0.017	0.468

1.MEANS ARE ADJUSTED FOR BASELINE VALUE, COUNTRY AND WEEK
2. STATISTICS ARE REPORTED BASED ON THE MAXIMUM OF THREE REPORTED VALUES OF FEV1 (L)
3. * SIGNIFICANTLY DIFFERENT FROM PLACEBO

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.24B

SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN TROUGH FEF25-75 (L/SEC) BY WEEK AND TREATMENT GROUP - ITT
PROTOCOL 157

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	420	0.587	0.020	.	.	.	.	.	.	.	.
	SB 207499	403	0.561	0.020	.	.	.	.	.	.	.	.
WEEK 4	PLACEBO	415	0.573	0.013	-0.014	0.013	-0.038	0.011	.	.	.	.
	SB 207499	391	0.562	0.013	-0.024	0.013	-0.050	0.002	-0.010	-0.042	0.021	0.524
WEEK 8	PLACEBO	400	0.579	0.013	-0.010	0.013	-0.035	0.015	.	.	.	.
	SB 207499	380	0.565	0.013	-0.024	0.013	-0.050	0.002	-0.014	-0.045	0.018	0.403
WEEK 12	PLACEBO	388	0.586	0.015	-0.005	0.015	-0.034	0.023	.	.	.	.
	SB 207499	356	0.572	0.015	-0.019	0.015	-0.049	0.010	-0.014	-0.050	0.023	0.453
WEEK 20	PLACEBO	377	0.583	0.015	-0.007	0.015	-0.036	0.022	.	.	.	.
	SB 207499	333	0.565	0.016	-0.024	0.016	-0.055	0.007	-0.017	-0.055	0.020	0.358
WEEK 28	PLACEBO	365	0.578	0.016	-0.015	0.016	-0.046	0.016	.	.	.	.
	SB 207499	317	0.559	0.017	-0.034	0.017	-0.067	-0.000	-0.019	-0.059	0.021	0.354
WEEK 36	PLACEBO	349	0.568	0.015	-0.027	0.015	-0.056	0.003	.	.	.	.
	SB 207499	303	0.571	0.016	-0.024	0.016	-0.055	0.008	0.003	-0.035	0.041	0.889
WEEK 44	PLACEBO	334	0.559	0.015	-0.038	0.015	-0.067	-0.009	.	.	.	.
	SB 207499	290	0.572	0.016	-0.025	0.016	-0.056	0.006	0.012	-0.025	0.050	0.519
WEEK 52	PLACEBO	323	0.574	0.015	-0.027	0.015	-0.057	0.003	.	.	.	.
	SB 207499	273	0.562	0.016	-0.038	0.016	-0.070	-0.007	-0.012	-0.049	0.026	0.550
ENDPOINT	PLACEBO	420	0.557	0.012	-0.028	0.012	-0.052	-0.005	.	.	.	.
	SB 207499	403	0.552	0.012	-0.033	0.012	-0.057	-0.009	-0.005	-0.035	0.025	0.762

1. MEANS ARE ADJUSTED FOR BASELINE VALUE AND COUNTRY
2. STATISITCS ARE REPORTED BASED ON THE MAXIMUM OF THREE REPORTED VALUES OFTROUGH FEV1 (L)
3. BASELINE = VISIT 3; WEEK 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 5, 6, 7, 8, 9, 10, 11,12; ENDPOINT = LOCF
4. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.24C

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN TROUGH FEF25-75 (L/SEC) BY WEEK AND TREATMENT GROUP - ITT
PROTOCOL 157

			BASELINE		WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	420	0.598	0.317	0.598	0.317	0.520	0.130	2.800	.	.	.	.	.
	SB 207499	403	0.572	0.414	0.572	0.414	0.480	0.100	5.620	.	.	.	.	.
WEEK 4	PLACEBO	415	0.599	0.318	0.598	0.344	0.500	0.170	2.760	-0.001	0.217	-0.010	-2.190	1.810
	SB 207499	391	0.573	0.419	0.569	0.336	0.490	0.160	2.890	-0.004	0.305	0.000	-4.400	1.370
WEEK 8	PLACEBO	400	0.601	0.320	0.601	0.322	0.520	0.044	2.220	0.000	0.201	-0.010	-2.150	1.130
	SB 207499	380	0.576	0.423	0.575	0.314	0.485	0.130	2.050	-0.002	0.335	0.010	-4.600	1.050
WEEK 12	PLACEBO	388	0.602	0.321	0.606	0.354	0.530	0.170	3.250	0.003	0.244	-0.010	-2.200	2.440
	SB 207499	356	0.579	0.433	0.579	0.332	0.480	0.019	2.810	0.000	0.344	0.010	-4.280	1.950
WEEK 20	PLACEBO	377	0.596	0.320	0.597	0.358	0.520	0.150	3.220	0.001	0.265	-0.020	-2.270	2.360
	SB 207499	333	0.581	0.432	0.572	0.319	0.490	0.068	1.910	-0.009	0.344	0.000	-4.230	1.020
WEEK 28	PLACEBO	365	0.598	0.320	0.603	0.369	0.510	0.180	3.040	0.005	0.265	-0.010	-2.210	2.530
	SB 207499	317	0.586	0.439	0.581	0.322	0.490	0.036	1.910	-0.005	0.359	0.010	-4.310	0.980
WEEK 36	PLACEBO	349	0.598	0.322	0.590	0.326	0.530	0.150	2.150	-0.008	0.215	-0.010	-2.170	0.890
	SB 207499	303	0.591	0.447	0.592	0.344	0.480	0.160	2.370	0.001	0.369	0.010	-4.230	1.670
WEEK 44	PLACEBO	334	0.603	0.326	0.587	0.335	0.495	0.150	1.930	-0.016	0.212	-0.020	-2.230	1.110
	SB 207499	290	0.591	0.451	0.595	0.328	0.510	0.140	1.950	0.004	0.368	0.020	-4.380	0.900
WEEK 52	PLACEBO	323	0.602	0.324	0.594	0.328	0.520	0.024	1.990	-0.008	0.214	-0.020	-2.330	0.650
	SB 207499	273	0.599	0.460	0.585	0.312	0.510	0.160	1.860	-0.014	0.379	0.000	-4.510	0.920
ENDPOINT	PLACEBO	420	0.598	0.317	0.581	0.317	0.510	0.024	1.990	-0.016	0.200	-0.020	-2.330	0.650
	SB 207499	403	0.572	0.414	0.562	0.302	0.480	0.130	1.860	-0.010	0.328	0.000	-4.510	0.920

1. STATISITCS ARE REPORTED BASED ON THE VALUE CORRESPONDING TO THE MAXIMUM FEV1 (L)
2. MEAN VALUES ARE SAMPLE MEANS
3. BASELINE=VISIT 3; WEEK 4, 8, 12, 20, 28, 36, 44, 52 =VISIT 5, 6, 7, 8, 9, 10, 11,12; ENDPOINT=LOCF

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.25A

SUMMARY OF AVERAGE CHANGE FROM BASELINE OVER 52 WEEKS (REPEATED MEASURES ANALYSIS) IN DOMICILIARY COUGH - ITT
PROTOCOL 157

		BASELINE		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
PLACEBO	418	1.305	0.045	-0.090	0.024	-0.137	-0.043	.	.	.	
SB 207499	405	1.339	0.046	-0.073	0.025	-0.121	-0.024	0.018	-0.038	0.073	0.531

1.MEANS ARE ADJUSTED FOR BASELINE VALUE, COUNTRY AND WEEK
2. * SIGNIFICANTLY DIFFERENT FROM PLACEBO

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.25B

SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN DOMICILIARY COUGH BY WEEK AND TREATMENT GROUP - ITT
PROTOCOL 157

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	419	1.306	0.045	.	.	.	.	.	.	.	.
	SB 207499	405	1.338	0.046	.	.	.	.	.	.	.	.
WEEK 2	PLACEBO	404	1.362	0.025	-0.006	0.025	-0.055	0.043	.	.	.	.
	SB 207499	382	1.406	0.026	0.038	0.026	-0.012	0.088	0.044	-0.019	0.107	0.167
WEEK 4	PLACEBO	388	1.306	0.030	-0.047	0.030	-0.105	0.012	.	.	.	.
	SB 207499	362	1.334	0.031	-0.018	0.031	-0.079	0.043	0.029	-0.046	0.104	0.454
WEEK 8	PLACEBO	386	1.270	0.034	-0.094	0.034	-0.162	-0.027	.	.	.	.
	SB 207499	358	1.314	0.036	-0.050	0.036	-0.121	0.020	0.044	-0.042	0.130	0.315
WEEK 12	PLACEBO	372	1.254	0.035	-0.100	0.035	-0.169	-0.032	.	.	.	.
	SB 207499	331	1.284	0.037	-0.070	0.037	-0.142	0.002	0.030	-0.058	0.118	0.501
WEEK 20	PLACEBO	349	1.252	0.038	-0.103	0.038	-0.177	-0.028	.	.	.	.
	SB 207499	302	1.250	0.041	-0.105	0.041	-0.185	-0.025	-0.002	-0.097	0.093	0.963
WEEK 28	PLACEBO	345	1.220	0.040	-0.131	0.040	-0.210	-0.053	.	.	.	.
	SB 207499	300	1.228	0.043	-0.123	0.043	-0.207	-0.039	0.008	-0.093	0.110	0.875
WEEK 36	PLACEBO	331	1.268	0.039	-0.081	0.039	-0.158	-0.004	.	.	.	.
	SB 207499	285	1.186	0.042	-0.162	0.042	-0.245	-0.079	-0.081	-0.182	0.019	0.112
WEEK 44	PLACEBO	309	1.289	0.044	-0.071	0.044	-0.158	0.016	.	.	.	.
	SB 207499	269	1.218	0.047	-0.142	0.047	-0.234	-0.049	-0.071	-0.182	0.040	0.212
WEEK 52	PLACEBO	300	1.244	0.048	-0.098	0.048	-0.191	-0.004	.	.	.	.
	SB 207499	260	1.230	0.049	-0.111	0.049	-0.208	-0.014	-0.013	-0.125	0.098	0.815
ENDPOINT	PLACEBO	419	1.262	0.036	-0.097	0.036	-0.168	-0.026	.	.	.	.
	SB 207499	405	1.261	0.037	-0.098	0.037	-0.170	-0.026	-0.001	-0.091	0.089	0.983

1.MEANS ARE ADJUSTED FOR BASELINE VALUE AND COUNTRY
2. BASELINE = VISIT 3; WEEK 2, 4, 8, 12, 20, 28, 36, 44, 52 =VISIT 4, 5, 6, 7, 8, 9, 10, 11, 12; ENDPOINT = LOCF
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14.25C

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN DOMICILIARY COUGH BY WEEK AND TREATMENT GROUP - ITT
PROTOCOL 157

		BASELINE			WEEKLY ASSESSMENT				CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	419	1.348	0.856	1.348	0.856	1.300	0.000	3.000	.	.	.	.	.
	SB 207499	405	1.372	0.856	1.372	0.856	1.357	0.000	3.000	.	.	.	.	.
WEEK 2	PLACEBO	404	1.356	0.853	1.349	0.870	1.297	0.000	3.000	-0.007	0.482	0.000	-2.252	1.714
	SB 207499	382	1.381	0.849	1.413	0.828	1.500	0.000	3.000	0.032	0.441	0.000	-1.500	2.000
WEEK 4	PLACEBO	388	1.339	0.858	1.284	0.893	1.214	0.000	3.000	-0.055	0.531	0.000	-2.182	2.231
	SB 207499	362	1.367	0.855	1.332	0.819	1.286	0.000	3.000	-0.035	0.573	0.000	-2.750	2.143
WEEK 8	PLACEBO	386	1.356	0.833	1.265	0.828	1.286	0.000	3.000	-0.091	0.600	0.000	-3.000	1.643
	SB 207499	358	1.373	0.869	1.315	0.854	1.286	0.000	3.000	-0.058	0.682	0.000	-3.000	2.357
WEEK 12	PLACEBO	372	1.335	0.828	1.253	0.873	1.214	0.000	3.000	-0.082	0.587	0.000	-3.000	1.643
	SB 207499	331	1.376	0.865	1.313	0.825	1.286	0.000	3.000	-0.063	0.682	0.000	-3.000	2.143
WEEK 20	PLACEBO	349	1.341	0.828	1.253	0.854	1.154	0.000	3.000	-0.088	0.622	0.000	-2.182	2.000
	SB 207499	302	1.371	0.863	1.278	0.856	1.155	0.000	3.000	-0.094	0.706	0.000	-2.286	2.214
WEEK 28	PLACEBO	345	1.326	0.825	1.214	0.879	1.077	0.000	3.000	-0.112	0.672	0.000	-3.000	2.000
	SB 207499	300	1.380	0.850	1.252	0.853	1.143	0.000	3.000	-0.128	0.756	0.000	-2.571	3.000
WEEK 36	PLACEBO	331	1.312	0.827	1.236	0.853	1.083	0.000	3.000	-0.075	0.696	0.000	-2.370	2.572
	SB 207499	285	1.392	0.847	1.204	0.827	1.000	0.000	3.000	-0.188	0.683	-0.040	-2.769	2.000
WEEK 44	PLACEBO	309	1.321	0.829	1.238	0.913	1.071	0.000	3.000	-0.083	0.691	0.000	-2.214	2.143
	SB 207499	269	1.404	0.857	1.225	0.860	1.000	0.000	3.000	-0.179	0.763	0.000	-2.846	2.000
WEEK 52	PLACEBO	300	1.319	0.829	1.199	0.871	1.000	0.000	3.000	-0.119	0.664	0.000	-2.214	2.000
	SB 207499	260	1.368	0.848	1.220	0.830	1.143	0.000	3.000	-0.148	0.794	0.000	-3.000	2.286
ENDPOINT	PLACEBO	419	1.348	0.856	1.239	0.889	1.071	0.000	3.000	-0.108	0.686	0.000	-3.000	2.000
	SB 207499	405	1.372	0.856	1.258	0.837	1.214	0.000	3.000	-0.114	0.753	0.000	-3.000	2.600

1. MEAN VALUES ARE SAMPLE MEANS
2. BASELINE = VISIT 3; WEEK 2, 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 4, 5, 6, 7, 8, 9, 10, 11,12; ENDPOINT = LOCF

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.26A

SUMMARY OF AVERAGE CHANGE FROM BASELINE OVER 52 WEEKS (REPEATED MEASURES ANALYSIS) IN DOMICILIARY SPUTUM - ITT
PROTOCOL 157

		BASELINE		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
PLACEBO	417	1.222	0.047	-0.043	0.023	-0.088	0.001	.	.	.	
SB 207499	404	1.205	0.048	-0.020	0.023	-0.065	0.026	0.023	-0.028	0.074	0.371

1.MEANS ARE ADJUSTED FOR BASELINE VALUE, COUNTRY AND WEEK
2. * SIGNIFICANTLY DIFFERENT FROM PLACEBO

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.26B

SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN DOMICILIARY SPUTUM BY WEEK AND TREATMENT GROUP - ITT
PROTOCOL 157

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	418	1.224	0.047	.	.	.	.	.	.	.	.
	SB 207499	404	1.205	0.048	.	.	.	.	.	.	.	.
WEEK 2	PLACEBO	403	1.240	0.022	-0.005	0.022	-0.048	0.039	.	.	.	.
	SB 207499	377	1.269	0.023	0.024	0.023	-0.021	0.069	0.029	-0.027	0.085	0.310
WEEK 4	PLACEBO	383	1.237	0.029	-0.002	0.029	-0.058	0.054	.	.	.	.
	SB 207499	361	1.251	0.030	0.012	0.030	-0.046	0.070	0.014	-0.057	0.085	0.703
WEEK 8	PLACEBO	384	1.207	0.033	-0.036	0.033	-0.102	0.029	.	.	.	.
	SB 207499	353	1.261	0.035	0.017	0.035	-0.051	0.086	0.053	-0.030	0.137	0.210
WEEK 12	PLACEBO	368	1.220	0.035	-0.010	0.035	-0.079	0.059	.	.	.	.
	SB 207499	327	1.255	0.037	0.025	0.037	-0.047	0.098	0.035	-0.053	0.123	0.434
WEEK 20	PLACEBO	345	1.198	0.037	-0.049	0.037	-0.121	0.024	.	.	.	.
	SB 207499	300	1.225	0.040	-0.022	0.040	-0.100	0.056	0.027	-0.067	0.120	0.575
WEEK 28	PLACEBO	343	1.212	0.039	-0.033	0.039	-0.109	0.044	.	.	.	.
	SB 207499	299	1.182	0.042	-0.063	0.042	-0.145	0.019	-0.030	-0.129	0.069	0.550
WEEK 36	PLACEBO	325	1.185	0.039	-0.054	0.039	-0.131	0.022	.	.	.	.
	SB 207499	285	1.198	0.042	-0.042	0.042	-0.123	0.040	0.013	-0.086	0.111	0.803
WEEK 44	PLACEBO	306	1.225	0.044	-0.028	0.044	-0.116	0.059	.	.	.	.
	SB 207499	265	1.200	0.048	-0.053	0.048	-0.147	0.040	-0.025	-0.137	0.087	0.661
WEEK 52	PLACEBO	298	1.150	0.046	-0.082	0.046	-0.173	0.008	.	.	.	.
	SB 207499	255	1.168	0.048	-0.065	0.048	-0.159	0.030	0.018	-0.091	0.126	0.747
ENDPOINT	PLACEBO	418	1.170	0.035	-0.071	0.035	-0.141	-0.002	.	.	.	.
	SB 207499	404	1.206	0.036	-0.035	0.036	-0.106	0.035	0.036	-0.052	0.124	0.422

1.MEANS ARE ADJUSTED FOR BASELINE VALUE AND COUNTRY
2. BASELINE = VISIT 3; WEEK 2, 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 4, 5, 6, 7, 8, 9, 10, 11, 12; ENDPOINT = LOCF
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14.26C

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN DOMICILIARY SPUTUM BY WEEK AND TREATMENT GROUP - ITT
PROTOCOL 157

		BASELINE		WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	418	1.252	0.869	1.252	0.869	1.214	0.000	3.000	.	.	.	.	.
	SB 207499	404	1.230	0.870	1.230	0.870	1.143	0.000	3.000	.	.	.	.	.
WEEK 2	PLACEBO	403	1.252	0.865	1.236	0.899	1.200	0.000	3.000	-0.016	0.384	0.000	-1.786	1.357
	SB 207499	377	1.237	0.864	1.251	0.849	1.214	0.000	3.000	0.014	0.426	0.000	-2.000	1.500
WEEK 4	PLACEBO	383	1.247	0.881	1.215	0.926	1.143	0.000	3.000	-0.032	0.481	0.000	-2.060	1.643
	SB 207499	361	1.231	0.862	1.210	0.828	1.077	0.000	3.000	-0.021	0.545	0.000	-2.769	1.977
WEEK 8	PLACEBO	384	1.245	0.861	1.184	0.869	1.071	0.000	3.000	-0.061	0.605	0.000	-2.615	2.857
	SB 207499	353	1.242	0.875	1.236	0.843	1.071	0.000	3.000	-0.005	0.630	0.000	-3.000	2.071
WEEK 12	PLACEBO	368	1.231	0.850	1.193	0.869	1.179	0.000	3.000	-0.038	0.610	0.000	-3.000	1.932
	SB 207499	327	1.229	0.872	1.230	0.859	1.214	0.000	3.000	0.002	0.657	0.000	-3.000	2.308
WEEK 20	PLACEBO	345	1.244	0.856	1.182	0.883	1.071	0.000	3.000	-0.061	0.620	0.000	-2.929	2.083
	SB 207499	300	1.250	0.874	1.215	0.863	1.071	0.000	3.000	-0.034	0.685	0.000	-2.000	2.000
WEEK 28	PLACEBO	343	1.238	0.849	1.194	0.903	1.143	0.000	3.000	-0.043	0.672	0.000	-3.000	2.000
	SB 207499	299	1.252	0.862	1.171	0.871	1.000	0.000	3.000	-0.081	0.703	0.000	-2.006	2.071
WEEK 36	PLACEBO	325	1.227	0.847	1.149	0.860	1.000	0.000	3.000	-0.079	0.663	0.000	-2.286	2.215
	SB 207499	285	1.254	0.864	1.175	0.874	1.000	0.000	3.000	-0.079	0.670	0.000	-2.615	2.000
WEEK 44	PLACEBO	306	1.240	0.849	1.172	0.933	1.000	0.000	3.000	-0.068	0.688	0.000	-2.286	2.000
	SB 207499	265	1.269	0.865	1.172	0.901	1.000	0.000	3.000	-0.097	0.762	0.000	-2.615	3.000
WEEK 52	PLACEBO	298	1.231	0.864	1.137	0.906	1.000	0.000	3.000	-0.095	0.658	0.000	-2.692	2.000
	SB 207499	255	1.234	0.858	1.164	0.861	1.000	0.000	3.000	-0.070	0.724	0.000	-2.385	2.071
ENDPOINT	PLACEBO	418	1.252	0.869	1.168	0.910	1.000	0.000	3.000	-0.084	0.682	0.000	-3.000	2.083
	SB 207499	404	1.230	0.870	1.190	0.865	1.036	0.000	3.000	-0.040	0.700	0.000	-2.615	2.071

1. MEAN VALUES ARE SAMPLE MEANS
2. BASELINE = VISIT 3; WEEK 2, 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 4, 5, 6, 7, 8, 9, 10, 11,12; ENDPOINT = LOCF

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.27A

SUMMARY OF AVERAGE CHANGE FROM BASELINE OVER 52 WEEKS (REPEATED MEASURES ANALYSIS) IN DOMICILIARY BREATHLESSNESS - ITT
PROTOCOL 157

		BASELINE		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
PLACEBO	415	1.356	0.049	0.049	0.027	-0.005	0.102	.	.	.	
SB 207499	404	1.387	0.049	0.007	0.028	-0.048	0.062	-0.042	-0.105	0.022	0.199

1.MEANS ARE ADJUSTED FOR BASELINE VALUE, COUNTRY AND WEEK
2. * SIGNIFICANTLY DIFFERENT FROM PLACEBO

CONFIDENTIAL

SB 207499

TABLE 14.27B

SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN DOMICILIARY BREATHLESSNESS BY WEEK AND TREATMENT GROUP - ITT
PROTOCOL 157

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	MEAN	SEM	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	416	1.354	0.049	.	.	.	.	.	.	.	.
	SB 207499	404	1.387	0.049	.	.	.	.	.	.	.	.
WEEK 2	PLACEBO	401	1.426	0.028	0.049	0.028	-0.006	0.104	.	.	.	.
	SB 207499	382	1.396	0.028	0.018	0.028	-0.038	0.074	-0.031	-0.101	0.039	0.389
WEEK 4	PLACEBO	386	1.419	0.032	0.051	0.032	-0.013	0.114	.	.	.	.
	SB 207499	360	1.376	0.034	0.008	0.034	-0.058	0.074	-0.043	-0.123	0.038	0.303
WEEK 8	PLACEBO	382	1.431	0.037	0.058	0.037	-0.014	0.131	.	.	.	.
	SB 207499	357	1.358	0.039	-0.015	0.039	-0.090	0.061	-0.073	-0.165	0.019	0.122
WEEK 12	PLACEBO	369	1.416	0.037	0.063	0.037	-0.011	0.136	.	.	.	.
	SB 207499	331	1.349	0.039	-0.003	0.039	-0.081	0.074	-0.066	-0.160	0.027	0.165
WEEK 20	PLACEBO	346	1.398	0.043	0.044	0.043	-0.041	0.129	.	.	.	.
	SB 207499	302	1.342	0.046	-0.011	0.046	-0.103	0.080	-0.055	-0.164	0.053	0.318
WEEK 28	PLACEBO	340	1.387	0.042	0.042	0.042	-0.039	0.124	.	.	.	.
	SB 207499	298	1.359	0.044	0.014	0.044	-0.073	0.101	-0.029	-0.134	0.077	0.593
WEEK 36	PLACEBO	329	1.386	0.043	0.037	0.043	-0.048	0.123	.	.	.	.
	SB 207499	285	1.327	0.047	-0.021	0.047	-0.113	0.071	-0.058	-0.169	0.053	0.303
WEEK 44	PLACEBO	304	1.407	0.045	0.049	0.045	-0.039	0.136	.	.	.	.
	SB 207499	270	1.374	0.047	0.015	0.047	-0.078	0.108	-0.033	-0.145	0.079	0.558
WEEK 52	PLACEBO	296	1.322	0.052	-0.020	0.052	-0.121	0.082	.	.	.	.
	SB 207499	261	1.307	0.053	-0.034	0.053	-0.139	0.071	-0.015	-0.135	0.106	0.811
ENDPOINT	PLACEBO	416	1.404	0.039	0.028	0.039	-0.048	0.104	.	.	.	.
	SB 207499	404	1.384	0.039	0.007	0.039	-0.070	0.085	-0.020	-0.118	0.077	0.679

1.MEANS ARE ADJUSTED FOR BASELINE VALUE AND COUNTRY
2. BASELINE = VISIT 3; WEEK 2, 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 4, 5, 6, 7, 8, 9, 10, 11, 12; ENDPOINT = LOCF
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14.27C

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN DOMICILIARY BREATHLESSNESS BY WEEK AND TREATMENT GROUP - ITT PROTOCOL 157

			BASELINE		WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	416	1.373	0.943	1.373	0.943	1.080	0.000	4.000	.	.	.	.	.
	SB 207499	404	1.381	0.983	1.381	0.983	1.214	0.000	4.000	.	.	.	.	.
WEEK 2	PLACEBO	401	1.376	0.934	1.403	0.960	1.143	0.000	4.000	0.027	0.491	0.000	-2.631	3.000
	SB 207499	382	1.380	0.984	1.373	0.964	1.214	0.000	4.000	-0.007	0.533	0.000	-2.143	1.714
WEEK 4	PLACEBO	386	1.364	0.941	1.392	0.973	1.143	0.000	4.000	0.029	0.575	0.000	-2.917	3.000
	SB 207499	360	1.373	0.973	1.352	0.951	1.143	0.000	4.000	-0.021	0.596	0.000	-2.615	1.835
WEEK 8	PLACEBO	382	1.374	0.926	1.420	0.981	1.143	0.000	4.000	0.046	0.665	0.000	-2.917	3.000
	SB 207499	357	1.371	0.970	1.339	0.936	1.071	0.000	4.000	-0.033	0.686	0.000	-3.000	2.857
WEEK 12	PLACEBO	369	1.355	0.914	1.400	0.974	1.000	0.000	4.000	0.045	0.662	0.000	-2.917	3.000
	SB 207499	331	1.350	0.971	1.323	0.936	1.071	0.000	4.000	-0.028	0.670	0.000	-3.000	2.500
WEEK 20	PLACEBO	346	1.347	0.917	1.369	0.964	1.071	0.000	4.000	0.022	0.711	0.000	-2.917	3.154
	SB 207499	302	1.362	0.968	1.313	0.948	1.000	0.000	4.000	-0.049	0.796	0.000	-3.000	2.643
WEEK 28	PLACEBO	340	1.334	0.901	1.335	0.942	1.000	0.000	4.000	0.001	0.698	0.000	-2.917	2.214
	SB 207499	298	1.357	0.954	1.315	0.954	1.000	0.000	4.000	-0.042	0.756	0.000	-3.000	2.857
WEEK 36	PLACEBO	329	1.351	0.912	1.365	0.934	1.000	0.000	4.000	0.014	0.757	0.000	-2.917	3.000
	SB 207499	285	1.346	0.941	1.292	0.954	1.000	0.000	4.000	-0.054	0.739	0.000	-2.357	2.143
WEEK 44	PLACEBO	304	1.342	0.908	1.342	0.911	1.000	0.000	4.000	0.000	0.733	0.000	-2.917	2.786
	SB 207499	270	1.377	0.977	1.321	0.938	1.000	0.000	4.000	-0.056	0.774	0.000	-3.000	2.879
WEEK 52	PLACEBO	296	1.334	0.892	1.308	0.932	1.000	0.000	4.000	-0.025	0.746	0.000	-3.071	3.000
	SB 207499	261	1.350	0.958	1.298	0.952	1.000	0.000	4.000	-0.053	0.822	0.000	-3.500	3.500
ENDPOINT	PLACEBO	416	1.373	0.943	1.375	0.991	1.000	0.000	4.000	0.002	0.725	0.000	-3.071	3.000
	SB 207499	404	1.381	0.983	1.359	0.981	1.143	0.000	4.000	-0.022	0.794	0.000	-3.500	3.500

1. MEAN VALUES ARE SAMPLE MEANS
2. BASELINE = VISIT 3; WEEK 2, 4, 8, 12, 20, 28, 36, 44, 52 = VISIT 4, 5, 6, 7, 8, 9, 10, 11,12; ENDPOINT = LOCF

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.30

AVERAGE DAILY INHALER USE BY TREATMENT GROUP
- ITT
PROTOCOL 157

WEEK	TREATMENT GROUP	N	WEEKLY ASSESSMENT MEAN	MIN	MEDIAN	MAX	CHANGE FROM BASELINE MEAN	MIN	MEDIAN	MAX	COMPARISON WITH PLACEBO MEAN	P-VALUE
BASELINE	PLACEBO	408	2.07	0.00	1.79	42.18	.	.	.	.	.	.
	SB 207499	392	2.68	0.00	1.89	196.25	.	.	.	.	.	.
WEEK 2	PLACEBO	393	2.60	0.00	1.93	217.14	0.52	-40.75	0.00	216.93	.	.
	SB 207499	359	2.63	0.00	2.00	175.86	-0.07	-20.39	0.00	6.20	-0.59	0.068
WEEK 4	PLACEBO	374	2.16	0.00	2.00	24.00	0.06	-40.47	0.00	23.64	.	.
	SB 207499	348	2.60	0.00	1.77	185.71	-0.06	-30.00	0.00	7.14	-0.11	0.232
WEEK 8	PLACEBO	377	2.21	0.00	2.00	29.93	0.12	-40.54	0.00	29.93	.	.
	SB 207499	334	2.77	0.00	1.86	162.43	0.08	-33.82	0.00	25.50	-0.04	0.149
WEEK 12	PLACEBO	360	2.18	0.00	2.00	21.21	0.21	-6.29	0.00	18.45	.	.
	SB 207499	313	2.74	0.00	1.79	175.00	0.08	-21.25	0.00	11.86	-0.13	0.105
WEEK 20	PLACEBO	336	2.25	0.00	2.00	31.57	0.16	-42.18	0.00	26.00	.	.
	SB 207499	287	2.88	0.00	1.79	219.29	0.27	-5.40	0.00	23.04	0.11	0.118
WEEK 28	PLACEBO	332	2.15	0.00	2.00	19.00	0.13	-42.18	0.00	16.29	.	.
	SB 207499	281	2.79	0.00	1.79	195.86	0.08	-28.14	0.00	11.14	-0.05	0.522
WEEK 36	PLACEBO	322	2.33	0.00	2.00	20.07	0.25	-42.18	0.00	7.85	.	.
	SB 207499	270	2.84	0.00	1.71	224.29	0.09	-28.71	0.00	28.04	-0.16	0.009
WEEK 44	PLACEBO	298	2.19	0.00	1.96	19.71	0.11	-41.97	0.00	8.23	.	.
	SB 207499	256	2.15	0.00	1.85	11.50	0.04	-29.00	0.00	6.08	-0.07	0.318
WEEK 52	PLACEBO	289	2.24	0.00	2.00	20.00	0.14	-42.18	0.00	7.23	.	.
	SB 207499	243	2.12	0.00	1.86	11.54	0.05	-28.57	0.00	6.39	-0.10	0.166
ENDPOINT	PLACEBO	408	2.80	0.00	2.00	217.14	0.73	-42.18	0.00	216.93	.	.
	SB 207499	392	2.85	0.00	1.97	224.29	0.18	-28.57	0.00	28.04	-0.55	0.144

1. P-VALUE IS OF WILCOXON RANK SUM STATISTIC
2. ANALYZED VALUES ARE THE NUMBER OF DAILY INHALER USES AVERAGED OVER THE 14 DAYS IMMEDIATELY PRIOR TO THE VISIT.

CONFIDENTIAL

SB 207499

TABLE 14.31

PERCENT OF DAYS WHITOUT SALBUTAMOL BY TREATMENT GROUP
- ITT
PROTOCOL 157

			WEEKLY ASSESSMENT				CHANGE FROM BASELINE				COMPARISON WITH PLACEBO	
WEEK	TREATMENT GROUP	N	MEAN	MIN	MEDIAN	MAX	MEAN	MIN	MEDIAN	MAX	MEAN	P-VALUE
BASELINE	PLACEBO	408	30.40	0.00	0.00	100.00	.	.	.	.	.	.
	SB 207499	392	32.01	0.00	0.00	100.00	.	.	.	.	.	.
WEEK 2	PLACEBO	393	28.72	0.00	0.00	100.00	-1.31	-100.0	0.00	80.00	.	.
	SB 207499	359	30.25	0.00	0.00	100.00	-1.00	-100.0	0.00	100.00	0.32	0.565
WEEK 4	PLACEBO	374	29.76	0.00	0.00	100.00	-0.60	-100.0	0.00	100.00	.	.
	SB 207499	348	32.92	0.00	0.00	100.00	-0.13	-100.0	0.00	100.00	0.47	0.961
WEEK 8	PLACEBO	377	28.49	0.00	0.00	100.00	-1.15	-100.0	0.00	100.00	.	.
	SB 207499	334	33.18	0.00	0.00	100.00	0.44	-100.0	0.00	100.00	1.59	0.387
WEEK 12	PLACEBO	360	29.54	0.00	0.00	100.00	-0.80	-100.0	0.00	100.00	.	.
	SB 207499	313	31.92	0.00	0.00	100.00	-1.54	-100.0	0.00	100.00	-0.74	0.994
WEEK 20	PLACEBO	336	28.89	0.00	0.00	100.00	-1.33	-100.0	0.00	100.00	.	.
	SB 207499	287	33.82	0.00	0.00	100.00	-1.71	-100.0	0.00	100.00	-0.38	0.896
WEEK 28	PLACEBO	332	30.05	0.00	0.00	100.00	-1.34	-100.0	0.00	100.00	.	.
	SB 207499	281	34.30	0.00	0.00	100.00	-0.37	-100.0	0.00	100.00	0.97	0.801
WEEK 36	PLACEBO	322	28.33	0.00	0.00	100.00	-2.08	-100.0	0.00	100.00	.	.
	SB 207499	270	34.67	0.00	0.00	100.00	0.57	-100.0	0.00	100.00	2.65	0.491
WEEK 44	PLACEBO	298	30.09	0.00	0.00	100.00	-1.07	-100.0	0.00	100.00	.	.
	SB 207499	256	30.94	0.00	0.00	100.00	-2.07	-100.0	0.00	100.00	-1.00	0.881
WEEK 52	PLACEBO	289	30.77	0.00	0.00	100.00	-0.65	-100.0	0.00	100.00	.	.
	SB 207499	243	34.05	0.00	0.00	100.00	-0.31	-100.0	0.00	100.00	0.34	0.841
ENDPOINT	PLACEBO	408	30.09	0.00	0.00	100.00	-0.31	-100.0	0.00	100.00	.	.
	SB 207499	392	31.71	0.00	0.00	100.00	-0.31	-100.0	0.00	100.00	0.00	0.971

1. P-VALUE IS OF WILCOXON RANK SUM STATISTIC
2. ANALYZED VALUES ARE THE PERCENT OF THE LAST 14 DAYS IMMEDIATELY PRIOR TO THE VISIT WITHOUT INHALER USE.

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.32

AVERAGE NUMBER OF NIGHTTIME AWAKENINGS BY TREATMENT GROUP
- ITT
PROTOCOL 157

			WEEKLY ASSESSMENT				CHANGE FROM BASELINE				COMPARISON WITH PLACEBO	
WEEK	TREATMENT GROUP	N	MEAN	MIN	MEDIAN	MAX	MEAN	MIN	MEDIAN	MAX	MEAN	P-VALUE
BASELINE	PLACEBO	391	0.38	0.00	0.00	3.50	.	.	.	.	.	.
	SB 207499	371	0.47	0.00	0.00	5.67	.	.	.	.	.	.
WEEK 2	PLACEBO	368	0.96	0.00	0.00	211.43	0.58	-2.00	0.00	211.43	.	.
	SB 207499	334	0.49	0.00	0.00	6.69	0.02	-4.50	0.00	5.76	-0.56	0.407
WEEK 4	PLACEBO	347	0.37	0.00	0.00	3.79	-0.02	-2.00	0.00	1.68	.	.
	SB 207499	312	0.41	0.00	0.00	3.57	-0.02	-4.50	0.00	2.43	-0.00	0.452
WEEK 8	PLACEBO	339	0.37	0.00	0.00	4.00	-0.02	-3.14	0.00	2.43	.	.
	SB 207499	307	0.45	0.00	0.00	6.50	-0.01	-4.50	0.00	3.96	0.01	0.903
WEEK 12	PLACEBO	329	0.36	0.00	0.00	4.43	-0.02	-1.92	0.00	3.50	.	.
	SB 207499	280	0.43	0.00	0.00	4.93	-0.01	-4.50	0.00	2.57	0.00	0.403
WEEK 20	PLACEBO	305	0.33	0.00	0.00	4.00	-0.05	-2.50	0.00	2.43	.	.
	SB 207499	265	0.37	0.00	0.00	3.07	-0.04	-2.71	0.00	3.00	0.01	0.379
WEEK 28	PLACEBO	303	0.31	0.00	0.00	3.93	-0.06	-2.50	0.00	2.55	.	.
	SB 207499	257	0.39	0.00	0.00	4.23	-0.01	-2.64	0.00	2.00	0.05	0.173
WEEK 36	PLACEBO	293	0.32	0.00	0.00	3.69	-0.07	-2.50	0.00	2.00	.	.
	SB 207499	251	0.38	0.00	0.00	6.50	-0.01	-2.71	0.00	3.73	0.06	0.890
WEEK 44	PLACEBO	277	0.35	0.00	0.00	3.71	-0.03	-2.50	0.00	2.31	.	.
	SB 207499	234	0.42	0.00	0.00	7.00	-0.01	-2.45	0.00	5.09	0.02	0.692
WEEK 52	PLACEBO	268	0.36	0.00	0.00	4.57	-0.01	-2.50	0.00	3.21	.	.
	SB 207499	224	0.42	0.00	0.00	4.50	0.01	-2.43	0.00	3.20	0.02	0.583
ENDPOINT	PLACEBO	391	0.92	0.00	0.00	211.43	0.54	-2.50	0.00	211.43	.	.
	SB 207499	371	0.45	0.00	0.00	4.50	-0.02	-4.00	0.00	3.20	-0.56	0.908

1. P-VALUE IS OF WILCOXON RANK SUM STATISTIC
2. ANALYZED VALUES ARE THE NUMBER OF NIGHTTIME AWAKENINGS AVERAGED OVER THE 14 DAYS IMMEDIATELY PRIOR TO THE VISIT.

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.33

AVERAGE DAILY BREATHLESSNESS SCORE BY TREATMENT GROUP
- ITT
PROTOCOL 157

WEEK	TREATMENT GROUP	N	WEEKLY ASSESSMENT MEAN	MIN	MEDIAN	MAX	CHANGE FROM BASELINE MEAN	MIN	MEDIAN	MAX	COMPARISON WITH PLACEBO MEAN	P-VALUE
BASELINE	PLACEBO	416	1.37	0.00	1.08	4.00	.	.	.	.	.	.
	SB 207499	404	1.38	0.00	1.21	4.00	.	.	.	.	.	.
WEEK 2	PLACEBO	401	1.40	0.00	1.14	4.00	0.03	-2.63	0.00	3.00	.	.
	SB 207499	382	1.37	0.00	1.21	4.00	-0.01	-2.14	0.00	1.71	-0.03	0.306
WEEK 4	PLACEBO	386	1.39	0.00	1.14	4.00	0.03	-2.92	0.00	3.00	.	.
	SB 207499	360	1.35	0.00	1.14	4.00	-0.02	-2.62	0.00	1.84	-0.05	0.282
WEEK 8	PLACEBO	382	1.42	0.00	1.14	4.00	0.05	-2.92	0.00	3.00	.	.
	SB 207499	357	1.34	0.00	1.07	4.00	-0.03	-3.00	0.00	2.86	-0.08	0.129
WEEK 12	PLACEBO	369	1.40	0.00	1.00	4.00	0.04	-2.92	0.00	3.00	.	.
	SB 207499	331	1.32	0.00	1.07	4.00	-0.03	-3.00	0.00	2.50	-0.07	0.219
WEEK 20	PLACEBO	346	1.37	0.00	1.07	4.00	0.02	-2.92	0.00	3.15	.	.
	SB 207499	302	1.31	0.00	1.00	4.00	-0.05	-3.00	0.00	2.64	-0.07	0.297
WEEK 28	PLACEBO	340	1.34	0.00	1.00	4.00	0.00	-2.92	0.00	2.21	.	.
	SB 207499	298	1.31	0.00	1.00	4.00	-0.04	-3.00	0.00	2.86	-0.04	0.444
WEEK 36	PLACEBO	329	1.37	0.00	1.00	4.00	0.01	-2.92	0.00	3.00	.	.
	SB 207499	285	1.29	0.00	1.00	4.00	-0.05	-2.36	0.00	2.14	-0.07	0.113
WEEK 44	PLACEBO	304	1.34	0.00	1.00	4.00	0.00	-2.92	0.00	2.79	.	.
	SB 207499	270	1.32	0.00	1.00	4.00	-0.06	-3.00	0.00	2.88	-0.06	0.282
WEEK 52	PLACEBO	296	1.31	0.00	1.00	4.00	-0.03	-3.07	0.00	3.00	.	.
	SB 207499	261	1.30	0.00	1.00	4.00	-0.05	-3.50	0.00	3.50	-0.03	0.692
ENDPOINT	PLACEBO	416	1.37	0.00	1.00	4.00	0.00	-3.07	0.00	3.00	.	.
	SB 207499	404	1.36	0.00	1.14	4.00	-0.02	-3.50	0.00	3.50	-0.02	0.879

1. P-VALUE IS OF WILCOXON RANK SUM STATISTIC
2. ANALYZED VALUES ARE DAILY SCORES AVERAGED OVER THE 14 DAYS IMMEDIATELY PRIOR TO THE VISIT.
3. DAILY BREATHLESSNESS SCORE: 0/1/2/3/4 (0=NO SYMPTOMS, 4=WORST SYMPTOMS)

CONFIDENTIAL

SB 207499

TABLE 14.34

AVERAGE DAILY COUGHING SCORE BY TREATMENT GROUP
- ITT
PROTOCOL 157

WEEK	TREATMENT GROUP	N	WEEKLY ASSESSMENT MEAN	MIN	MEDIAN	MAX	CHANGE FROM BASELINE MEAN	MIN	MEDIAN	MAX	COMPARISON WITH PLACEBO MEAN	P-VALUE
BASELINE	PLACEBO	419	1.35	0.00	1.30	3.00	.	.	.	.	.	.
	SB 207499	405	1.37	0.00	1.36	3.00	.	.	.	.	.	.
WEEK 2	PLACEBO	404	1.35	0.00	1.30	3.00	-0.01	-2.25	0.00	1.71	.	.
	SB 207499	382	1.41	0.00	1.50	3.00	0.03	-1.50	0.00	2.00	0.04	0.142
WEEK 4	PLACEBO	388	1.28	0.00	1.21	3.00	-0.05	-2.18	0.00	2.23	.	.
	SB 207499	362	1.33	0.00	1.29	3.00	-0.03	-2.75	0.00	2.14	0.02	0.351
WEEK 8	PLACEBO	386	1.26	0.00	1.29	3.00	-0.09	-3.00	0.00	1.64	.	.
	SB 207499	358	1.32	0.00	1.29	3.00	-0.06	-3.00	0.00	2.36	0.03	0.679
WEEK 12	PLACEBO	372	1.25	0.00	1.21	3.00	-0.08	-3.00	0.00	1.64	.	.
	SB 207499	331	1.31	0.00	1.29	3.00	-0.06	-3.00	0.00	2.14	0.02	0.990
WEEK 20	PLACEBO	349	1.25	0.00	1.15	3.00	-0.09	-2.18	0.00	2.00	.	.
	SB 207499	302	1.28	0.00	1.16	3.00	-0.09	-2.29	0.00	2.21	-0.01	0.606
WEEK 28	PLACEBO	345	1.21	0.00	1.08	3.00	-0.11	-3.00	0.00	2.00	.	.
	SB 207499	300	1.25	0.00	1.14	3.00	-0.13	-2.57	0.00	3.00	-0.02	0.632
WEEK 36	PLACEBO	331	1.24	0.00	1.08	3.00	-0.08	-2.37	0.00	2.57	.	.
	SB 207499	285	1.20	0.00	1.00	3.00	-0.19	-2.77	-0.04	2.00	-0.11	0.053
WEEK 44	PLACEBO	309	1.24	0.00	1.07	3.00	-0.08	-2.21	0.00	2.14	.	.
	SB 207499	269	1.22	0.00	1.00	3.00	-0.18	-2.85	0.00	2.00	-0.10	0.106
WEEK 52	PLACEBO	300	1.20	0.00	1.00	3.00	-0.12	-2.21	0.00	2.00	.	.
	SB 207499	260	1.22	0.00	1.14	3.00	-0.15	-3.00	0.00	2.29	-0.03	0.595
ENDPOINT	PLACEBO	419	1.24	0.00	1.07	3.00	-0.11	-3.00	0.00	2.00	.	.
	SB 207499	405	1.26	0.00	1.21	3.00	-0.11	-3.00	0.00	2.60	-0.01	0.771

1. P-VALUE IS OF WILCOXON RANK SUM STATISTIC
2. ANALYZED VALUES ARE DAILY SCORES AVERAGED OVER THE 14 DAYS IMMEDIATELY PRIOR TO THE VISIT.
3. DAILY COUGHING SCORE: 0/1/2/3 (0=NO SYMPTOMS, 3=WORST SYMPTOMS)

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.35

AVERAGE DAILY SPUTUM QUANTITY BY TREATMENT GROUP
- ITT
PROTOCOL 157

WEEK	TREATMENT GROUP	N	WEEKLY ASSESSMENT MEAN	MIN	MEDIAN	MAX	CHANGE FROM BASELINE MEAN	MIN	MEDIAN	MAX	COMPARISON WITH PLACEBO MEAN	P-VALUE
BASELINE	PLACEBO	418	1.25	0.00	1.21	3.00	.	.	.	.	.	.
	SB 207499	404	1.23	0.00	1.14	3.00	.	.	.	.	.	.
WEEK 2	PLACEBO	403	1.24	0.00	1.20	3.00	-0.02	-1.79	0.00	1.36	.	.
	SB 207499	377	1.25	0.00	1.21	3.00	0.01	-2.00	0.00	1.50	0.03	0.413
WEEK 4	PLACEBO	383	1.22	0.00	1.14	3.00	-0.03	-2.06	0.00	1.64	.	.
	SB 207499	361	1.21	0.00	1.08	3.00	-0.02	-2.77	0.00	1.98	0.01	0.589
WEEK 8	PLACEBO	384	1.18	0.00	1.07	3.00	-0.06	-2.62	0.00	2.86	.	.
	SB 207499	353	1.24	0.00	1.07	3.00	-0.01	-3.00	0.00	2.07	0.06	0.324
WEEK 12	PLACEBO	368	1.19	0.00	1.18	3.00	-0.04	-3.00	0.00	1.93	.	.
	SB 207499	327	1.23	0.00	1.21	3.00	0.00	-3.00	0.00	2.31	0.04	0.389
WEEK 20	PLACEBO	345	1.18	0.00	1.07	3.00	-0.06	-2.93	0.00	2.08	.	.
	SB 207499	300	1.22	0.00	1.07	3.00	-0.03	-2.00	0.00	2.00	0.03	0.616
WEEK 28	PLACEBO	343	1.19	0.00	1.14	3.00	-0.04	-3.00	0.00	2.00	.	.
	SB 207499	299	1.17	0.00	1.00	3.00	-0.08	-2.01	0.00	2.07	-0.04	0.374
WEEK 36	PLACEBO	325	1.15	0.00	1.00	3.00	-0.08	-2.29	0.00	2.22	.	.
	SB 207499	285	1.17	0.00	1.00	3.00	-0.08	-2.62	0.00	2.00	-0.00	0.870
WEEK 44	PLACEBO	306	1.17	0.00	1.00	3.00	-0.07	-2.29	0.00	2.00	.	.
	SB 207499	265	1.17	0.00	1.00	3.00	-0.10	-2.62	0.00	3.00	-0.03	0.780
WEEK 52	PLACEBO	298	1.14	0.00	1.00	3.00	-0.09	-2.69	0.00	2.00	.	.
	SB 207499	255	1.16	0.00	1.00	3.00	-0.07	-2.39	0.00	2.07	0.02	0.676
ENDPOINT	PLACEBO	418	1.17	0.00	1.00	3.00	-0.08	-3.00	0.00	2.08	.	.
	SB 207499	404	1.19	0.00	1.04	3.00	-0.04	-2.62	0.00	2.07	0.04	0.312

1. P-VALUE IS OF WILCOXON RANK SUM STATISTIC
2. ANALYZED VALUES ARE DAILY SCORES AVERAGED OVER THE 14 DAYS IMMEDIATELY PRIOR TO THE VISIT.
3. DAILY SPUTUM QUANTITY SCORE: 0/1/2/3 (0=NO SYMPTOMS, 3=WORST SYMPTOMS)

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 14.36

AVERAGE DAILY SPUTUM COLOUR BY TREATMENT GROUP
- ITT
PROTOCOL 157

WEEK	TREATMENT GROUP	N	WEEKLY ASSESSMENT MEAN	MIN	MEDIAN	MAX	CHANGE FROM BASELINE MEAN	MIN	MEDIAN	MAX	COMPARISON WITH PLACEBO MEAN	P-VALUE
BASELINE	PLACEBO	416	1.22	0.00	1.09	4.00	.	.	.	.	.	.
	SB 207499	404	1.18	0.00	1.07	4.00	.	.	.	.	.	.
WEEK 2	PLACEBO	396	1.20	0.00	1.04	4.00	-0.03	-2.00	0.00	1.61	.	.
	SB 207499	375	1.20	0.00	1.08	3.43	0.02	-2.23	0.00	2.01	0.05	0.228
WEEK 4	PLACEBO	381	1.16	0.00	1.00	4.00	-0.03	-2.00	0.00	1.92	.	.
	SB 207499	355	1.15	0.00	1.00	3.00	-0.04	-2.23	0.00	2.00	-0.00	0.643
WEEK 8	PLACEBO	380	1.20	0.00	1.14	4.00	-0.03	-2.21	0.00	2.46	.	.
	SB 207499	348	1.19	0.00	1.00	3.43	-0.00	-3.00	0.00	2.29	0.03	0.593
WEEK 12	PLACEBO	366	1.18	0.00	1.00	4.00	-0.05	-2.21	0.00	2.19	.	.
	SB 207499	325	1.18	0.00	1.00	3.36	0.02	-2.79	0.00	3.00	0.06	0.095
WEEK 20	PLACEBO	341	1.21	0.00	1.14	4.00	-0.03	-2.07	0.00	2.79	.	.
	SB 207499	299	1.16	0.00	1.00	3.00	-0.01	-3.00	0.00	2.34	0.02	0.486
WEEK 28	PLACEBO	339	1.19	0.00	1.00	4.00	-0.05	-2.22	0.00	2.00	.	.
	SB 207499	294	1.12	0.00	1.00	3.00	-0.08	-3.00	0.00	2.00	-0.03	0.932
WEEK 36	PLACEBO	330	1.19	0.00	1.00	4.00	-0.07	-2.29	0.00	2.00	.	.
	SB 207499	281	1.12	0.00	1.00	3.00	-0.08	-3.00	0.00	2.00	-0.02	0.872
WEEK 44	PLACEBO	305	1.13	0.00	1.00	4.00	-0.12	-2.36	0.00	2.00	.	.
	SB 207499	266	1.13	0.00	1.00	3.29	-0.08	-3.00	0.00	2.00	0.04	0.145
WEEK 52	PLACEBO	297	1.13	0.00	1.00	4.00	-0.11	-2.64	0.00	2.00	.	.
	SB 207499	252	1.14	0.00	1.00	3.43	-0.07	-3.00	0.00	2.00	0.04	0.376
ENDPOINT	PLACEBO	416	1.14	0.00	1.00	4.00	-0.08	-2.64	0.00	2.79	.	.
	SB 207499	404	1.15	0.00	1.00	3.43	-0.03	-3.00	0.00	2.29	0.04	0.249

1. P-VALUE IS OF WILCOXON RANK SUM STATISTIC
2. ANALYZED VALUES ARE DAILY SCORES AVERAGED OVER THE 14 DAYS IMMEDIATELY PRIOR TO THE VISIT.
3. DAILY SPUTUM COLOUR SCORE: 0/1/2/3/4 (0=NO SYMPTOMS, 4=WORST SYMPTOMS)

CONFIDENTIAL

SB 207499

TABLE 14.37

AVERAGE DAILY MISSED TIME FROM WORK OR USUAL ACTIVITIES BY TREATMENT GROUP - ITT
PROTOCOL 157

WEEK	TREATMENT GROUP	N	WEEKLY ASSESSMENT MEAN	MIN	MEDIAN	MAX	CHANGE FROM BASELINE MEAN	MIN	MEDIAN	MAX	COMPARISON WITH PLACEBO MEAN	P-VALUE
BASELINE	PLACEBO	406	0.06	0.00	0.00	2.00	.	.	.	.	.	.
	SB 207499	390	0.06	0.00	0.00	2.00	.	.	.	.	.	.
WEEK 2	PLACEBO	389	0.06	0.00	0.00	2.00	0.00	-1.00	0.00	0.93	.	.
	SB 207499	367	0.06	0.00	0.00	2.00	0.00	-1.00	0.00	1.20	0.00	0.870
WEEK 4	PLACEBO	376	0.06	0.00	0.00	2.00	-0.00	-1.67	0.00	2.00	.	.
	SB 207499	346	0.05	0.00	0.00	2.00	-0.01	-1.00	0.00	1.29	-0.01	0.688
WEEK 8	PLACEBO	371	0.06	0.00	0.00	2.00	-0.01	-1.00	0.00	0.92	.	.
	SB 207499	346	0.05	0.00	0.00	2.00	-0.00	-1.76	0.00	1.85	0.00	0.563
WEEK 12	PLACEBO	360	0.07	0.00	0.00	2.00	0.01	-1.00	0.00	1.43	.	.
	SB 207499	313	0.06	0.00	0.00	2.00	0.01	-1.00	0.00	1.64	0.00	0.900
WEEK 20	PLACEBO	338	0.06	0.00	0.00	2.00	0.00	-1.00	0.00	2.00	.	.
	SB 207499	292	0.04	0.00	0.00	1.29	-0.01	-2.00	0.00	1.14	-0.01	0.613
WEEK 28	PLACEBO	331	0.06	0.00	0.00	2.00	0.00	-1.00	0.00	2.00	.	.
	SB 207499	288	0.05	0.00	0.00	2.00	0.00	-2.00	0.00	1.86	-0.00	0.939
WEEK 36	PLACEBO	316	0.06	0.00	0.00	2.00	-0.00	-1.00	0.00	2.00	.	.
	SB 207499	273	0.04	0.00	0.00	1.86	-0.01	-2.00	0.00	1.29	-0.01	0.594
WEEK 44	PLACEBO	298	0.08	0.00	0.00	2.00	0.02	-1.00	0.00	2.00	.	.
	SB 207499	257	0.04	0.00	0.00	2.00	0.00	-1.00	0.00	1.29	-0.02	0.907
WEEK 52	PLACEBO	289	0.07	0.00	0.00	2.00	0.01	-1.00	0.00	2.00	.	.
	SB 207499	248	0.04	0.00	0.00	2.00	0.00	-1.00	0.00	1.29	-0.01	0.704
ENDPOINT	PLACEBO	406	0.08	0.00	0.00	2.00	0.02	-1.67	0.00	2.00	.	.
	SB 207499	390	0.06	0.00	0.00	2.00	0.00	-2.00	0.00	1.67	-0.02	0.579

1. P-VALUE IS OF WILCOXON RANK SUM STATISTIC
2. ANALYZED VALUES ARE DAILY SCORES AVERAGED OVER THE 14 DAYS IMMEDIATELY PRIOR TO THE VISIT.
3. DAILY MISSED TIME SCORE: 0/1/2 = NONE/HALF DAY/FULL DAY

CONFIDENTIAL

SB 207499

TABLE 14.38

AVERAGE DAILY CAREGIVER ASSISTANCE BY TREATMENT GROUP
- ITT
PROTOCOL 157

WEEK	TREATMENT GROUP	N	WEEKLY ASSESSMENT MEAN	MIN	MEDIAN	MAX	CHANGE FROM BASELINE MEAN	MIN	MEDIAN	MAX	COMPARISON WITH PLACEBO MEAN	P-VALUE
BASELINE	PLACEBO	408	0.02	0.00	0.00	2.00	.	.	.	.	.	.
	SB 207499	395	0.02	0.00	0.00	1.10	.	.	.	.	.	.
WEEK 2	PLACEBO	392	0.02	0.00	0.00	2.00	0.00	-0.29	0.00	0.69	.	.
	SB 207499	367	0.02	0.00	0.00	1.23	0.01	-1.00	0.00	1.07	0.00	0.962
WEEK 4	PLACEBO	372	0.01	0.00	0.00	2.00	-0.00	-0.50	0.00	0.71	.	.
	SB 207499	347	0.02	0.00	0.00	1.50	0.01	-1.00	0.00	1.50	0.01	0.812
WEEK 8	PLACEBO	373	0.02	0.00	0.00	2.00	-0.00	-1.00	0.00	0.48	.	.
	SB 207499	349	0.02	0.00	0.00	1.43	0.00	-1.00	0.00	1.43	0.00	0.837
WEEK 12	PLACEBO	361	0.03	0.00	0.00	2.00	0.01	-0.29	0.00	1.08	.	.
	SB 207499	317	0.03	0.00	0.00	1.50	0.01	-0.31	0.00	1.50	0.00	0.197
WEEK 20	PLACEBO	332	0.03	0.00	0.00	2.00	0.01	-0.71	0.00	1.77	.	.
	SB 207499	293	0.02	0.00	0.00	1.00	0.00	-0.31	0.00	1.00	-0.00	0.437
WEEK 28	PLACEBO	328	0.02	0.00	0.00	2.00	0.00	-1.21	0.00	1.64	.	.
	SB 207499	291	0.02	0.00	0.00	1.08	0.00	-0.21	0.00	0.57	0.00	0.995
WEEK 36	PLACEBO	314	0.01	0.00	0.00	2.00	-0.00	-1.21	0.00	0.15	.	.
	SB 207499	278	0.02	0.00	0.00	1.07	0.01	-0.31	0.00	1.07	0.01	0.639
WEEK 44	PLACEBO	295	0.03	0.00	0.00	2.00	0.00	-1.21	0.00	1.23	.	.
	SB 207499	261	0.01	0.00	0.00	1.00	0.01	-0.31	0.00	1.00	0.00	0.660
WEEK 52	PLACEBO	288	0.02	0.00	0.00	2.00	-0.00	-1.21	0.00	0.36	.	.
	SB 207499	250	0.02	0.00	0.00	1.17	0.01	-0.31	0.00	1.17	0.01	0.805
ENDPOINT	PLACEBO	408	0.03	0.00	0.00	2.00	0.00	-1.21	0.00	1.77	.	.
	SB 207499	395	0.03	0.00	0.00	1.17	0.01	-1.00	0.00	1.17	0.00	0.898

1. P-VALUE IS OF WILCOXON RANK SUM STATISTIC
2. ANALYZED VALUES ARE DAILY SCORES AVERAGED OVER THE 14 DAYS IMMEDIATELY PRIOR TO THE VISIT.
3. DAILY CAREGIVER SCORE: 0/1/2 = NONE/HALF DAY/FULL DAY

CONFIDENTIAL

SB 207499

TABLE 14.41

INVESTIGATOR GLOBAL ASSESSMENTS BY TREATMENT GROUP
- ITT
PROTOCOL 157

WEEK	TREATMENT GROUP	N	INVESTIGATOR GLOBAL ASSESSMENT: NOT ASSESSED	VERY MUCH IMPROVED (1)	MUCH IMPROVED (2)	IMPROVED (3)	NO CHANGE (4)	WORSE (5)	MUCH WORSE (6)	VERY MUCH WORSE (7)	AT LEAST IMPROVED	P-Value
WEEK 28	PLACEBO	365	7 (1.9)	5 (1.4)	42 (11.5)	108 (29.6)	172 (47.1)	26 (7.1)	5 (1.4)	0 (0.0)	155 (42.5)	.
	SB 207499	321	5 (1.6)	7 (2.2)	41 (12.8)	108 (33.6)	131 (40.8)	25 (7.8)	3 (0.9)	1 (0.3)	156 (48.6)	0.1146
WEEK 52	PLACEBO	324	8 (2.5)	5 (1.5)	53 (16.4)	94 (29.0)	136 (42.0)	22 (6.8)	6 (1.9)	0 (0.0)	152 (46.9)	.
	SB 207499	279	3 (1.1)	9 (3.2)	50 (17.9)	104 (37.3)	94 (33.7)	15 (5.4)	4 (1.4)	0 (0.0)	163 (58.4)	0.0077
ENDPOINT	PLACEBO	390	9 (2.3)	5 (1.3)	56 (14.4)	106 (27.2)	160 (41.0)	36 (9.2)	16 (4.1)	2 (0.5)	167 (42.8)	.
	SB 207499	356	5 (1.4)	10 (2.8)	52 (14.6)	119 (33.4)	129 (36.2)	27 (7.6)	12 (3.4)	2 (0.6)	181 (50.8)	0.0363

1. P-VALUE IS OF CHI-SQUARD STATISTIC WHICH ANALYSES AT LEAST IMPROVED V. NO BETTER
2. 'NOT ASSESSED' IS TREATED AS MISSING

CONFIDENTIAL

SB 207499

TABLE 14.42

PATIENT GLOBAL ASSESSMENTS BY TREATMENT GROUP
- ITT
PROTOCOL 157

WEEK	TREATMENT GROUP	N	PATIENT GLOBAL ASSESSMENT: NOT ASSESSED	VERY MUCH IMPROVED (1)	MUCH IMPROVED (2)	IMPROVED (3)	NO CHANGE (4)	WORSE (5)	MUCH WORSE (6)	VERY MUCH WORSE (7)	AT LEAST IMPROVED	P-Value
WEEK 28	PLACEBO	364	3 (0.8)	14 (3.8)	63 (17.3)	103 (28.3)	143 (39.3)	28 (7.7)	9 (2.5)	1 (0.3)	180 (49.5)	.
	SB 207499	321	0 (0.0)	18 (5.6)	53 (16.5)	107 (33.3)	112 (34.9)	25 (7.8)	5 (1.6)	1 (0.3)	178 (55.5)	0.1445
WEEK 52	PLACEBO	323	5 (1.5)	14 (4.3)	79 (24.5)	85 (26.3)	117 (36.2)	16 (5.0)	6 (1.9)	1 (0.3)	178 (55.1)	.
	SB 207499	279	2 (0.7)	19 (6.8)	66 (23.7)	91 (32.6)	79 (28.3)	17 (6.1)	5 (1.8)	0 (0.0)	176 (63.1)	0.0609
ENDPOINT	PLACEBO	390	6 (1.5)	16 (4.1)	85 (21.8)	94 (24.1)	138 (35.4)	27 (6.9)	20 (5.1)	4 (1.0)	195 (50.0)	.
	SB 207499	355	4 (1.1)	20 (5.6)	71 (20.0)	103 (29.0)	115 (32.4)	25 (7.0)	14 (3.9)	3 (0.8)	194 (54.6)	0.2232

1. P-VALUE IS OF CHI-SQUARD STATISTIC WHICH ANALYSES AT LEAST IMPROVED V. NO BETTER
2. 'NOT ASSESSED' IS TREATED AS MISSING

CONFIDENTIAL

SB 207499

TABLE 14.1O2

SUMMARY OF ANALYSES OF CONTINUOUS PROGNOSTIC FACTORS AFFECTING CHANGE FROM BASELINE IN TROUGH FEV1 (L) - ITT
PROTOCOL 157

FACTOR	UNIT	P-VALUE	ESTIMATE	95% CI LOWER	95% CI UPPER
AGE	YEAR	0.6424	-0.0003	-0.0015	0.0010
BASELINE FEV1	LITRE	0.0001	-0.0494	-0.0741	-0.0246
% PREDICTED FEV1	PERCENTAGE	0.6842	-0.0002	-0.0012	0.0008

1. EACH FACTOR WAS ANALYZED SEPARATELY IN A REPEATED MEASURES MODEL WITH COVARIATES VISIT, TREATMENT AND THE FACTOR.
2. EACH ESTIMATE IS OF THE CHANGE IN LITRES (OF FEV1 CHANGE FROM BASELINE) PER UNIT INCREASE IN THE FACTOR.

CONFIDENTIAL

SB 207499

TABLE 14.103

SUMMARY OF ANALYSES OF CATEGORICAL PROGNOSTIC FACTORS AFFECTING CHANGE FROM BASELINE IN TROUGH FEV1 (L) - ITT
PROTOCOL 157

FACTOR	LEVEL 0 / LEVEL 1	P-VALUE	ESTIMATE	95% CI LOWER	95% CI UPPER
SEX	MALE / FEMALE	0.0941	0.0227	-0.0039	0.0493
BASELINE SMOKING STATUS	YES / NO	0.8863	-0.0016	-0.0240	0.0207

1. EACH FACTOR WAS ANALYZED SEPARATELY IN A REPEATED MEASURES MODEL WITH COVARIATES VISIT, TREATMENT AND THE FACTOR.
2. EACH ESTIMATE IS OF THE CHANGE IN LITRES (OF FEV1 CHANGE FROM BASELINE) AS THE FACTOR CHANGED FROM LEVEL 0 TO LEVEL 1.

CONFIDENTIAL

15. Safety Data Source Tables

Page

TABLE 15.1A SUMMARY OF STUDY MEDICATION EXPOSURE (DAYS) BY TREATMENT GROUP 497

TABLE 15.1B DESCRIPTIVE STATISTICS FOR STUDY MEDICATION EXPOSURE (DAYS) BY TREATMENT GROUP 498

TABLE 15.2A INCIDENCE OF ALL ON-THERAPY ADVERSE EXPERIENCES BY MEDDRA PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND TREATMENT GROUP 499

TABLE 15.2B INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP 526

TABLE 15.3 INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT, MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP 543

TABLE 15.4 INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY, MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP 569

TABLE 15.5 INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES (>= 2%) BY INITIAL TIME OF ONSET, MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP 594

TABLE 15.6 ON-THERAPY ADVERSE EXPERIENCES THAT LED TO INTERRUPTION BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP 600

TABLE 15.7 ON-THERAPY ADVERSE EXPERIENCES THAT REQUIRED CORRECTIVE THERAPY BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP 603

TABLE 15.8A INCIDENCE OF RUN-IN SERIOUS ADVERSE EXPERIENCES BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP 615

TABLE 15.8B ON-THERAPY SERIOUS ADVERSE EXPERIENCES BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP 616

TABLE 15.8C POST-THERAPY SERIOUS ADVERSE EXPERIENCES BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP 620

TABLE 15.9A INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES LEADING TO PATIENT WITHDRAWAL BY MEDDRA PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND TREATMENT GROUP 622

TABLE 15.9B ON-THERAPY ADVERSE EXPERIENCES LEADING TO PATIENT WITHDRAWAL BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP 626

TABLE 15.10 ALL POST-THERAPY ADVERSE EXPERIENCES BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP 630

TABLE 15.11A GASTROINTESTINAL ADVERSE EXPERIENCES OF CONCERN BY MEDDRA PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND TREATMENT GROUP 635

TABLE 15.11B GASTROINTESTINAL ADVERSE EXPERIENCES OF CONCERN THAT LED TO PATIENT WITHDRAWAL BY MEDDRA PREFERRED TERM, DESCENDING FREQUENCY OF OCC AND TREATMENT GROUP 637

TABLE 15.11C INCIDENCE OF ON-THERAPY GASTROINTESTINAL ADVERSE EXPERIENCES OF CONCERN BY TREATMENT GROUP, MEDDRA PREFERRED TERM, INVESTIGATOR-DETERMINED INTENSITY AND DESCENDING FREQUENCY OF OCCURRENCE 638

TABLE 15.12A TRANSITIONS FROM BASELINE IN FOB RESULTS FOR PATIENTS WITH GI AES OF CONCERN DURING DOUBLE-BLIND PERIOD . 640

TABLE 15.12B TRANSITIONS FROM BASELINE IN FOB RESULTS FOR ALL PATIENTS DURING DOUBLE-BLIND PERIOD 641

TABLE 15.13A TRANSITIONS FROM BASELINE IN ORTHOSTATIC VITAL SIGNS FOR PATIENTS WITH GASTROINTESTINAL ADVERSE EXPERIENCES OF CONCERN 642

TABLE 15.13B TRANSITIONS FROM BASELINE IN ORTHOSTATIC VITAL SIGNS 648

TABLE 15.14 DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND TREATMENT GROUP 654

TABLE 15.15 TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE 671

TABLE 15.16 DESCRIPTIVE STATISTICS FOR STANDARD VITAL SIGNS BY VISIT/WEEK AND TREATMENT GROUP 711

TABLE 15.17 TRANSITIONS FROM BASELINE IN SITTING VITAL SIGNS 713

TABLE 15.18 DESCRIPTIVE STATISTICS FOR ECGS BY VISIT/WEEK AND TREATMENT GROUP 719

TABLE 15.19A TRANSITIONS FROM BASELINE IN ECG PARAMETERS 724

TABLE 15.19B CHANGE FROM BASELINE IN QTC 790

TABLE 15.20 INCIDENCE OF NEW-ONSET ON-THERAPY ECG ABNORMALITIES BY TREATMENT GROUP 801

SB 207499

TABLE 15.1A

SUMMARY OF STUDY MEDICATION EXPOSURE (DAYS) BY TREATMENT GROUP

PROTOCOL 157

EXPOSURE	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
<= 14 Days	14 (3.1%)	22 (4.8%)
15 - 28 Days	8 (1.8%)	21 (4.6%)
29 - 56 Days	14 (3.1%)	20 (4.4%)
57 - 84 Days	12 (2.7%)	24 (5.3%)
85 - 140 Days	13 (2.9%)	22 (4.8%)
141 - 196 Days	14 (3.1%)	22 (4.8%)
197 - 252 Days	17 (3.8%)	8 (1.8%)
253 - 308 Days	14 (3.1%)	17 (3.7%)
309 - 364 Days	181 (40.0%)	144 (31.6%)
> 364 Days	165 (36.5%)	155 (34.1%)

1. EXPOSURE=(DATE OF LAST DOUBLE BLIND STUDY MEDICATION - DATE OF FIRST DOUBLE BLIND STUDY MEDICATION)+1
2. NO ADJUSTMENTS ARE MADE FOR DOSE INTERRUPTIONS

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.1B

DESCRIPTIVE STATISTICS FOR STUDY MEDICATION EXPOSURE (DAYS) BY TREATMENT GROUP

PROTOCOL 157

Statistic	PLACEBO	SB 207499
N	452	455
MEAN	309.53	275.37
STD	112.48	137.56
MEDIAN	364	363
MIN	1	1
MAX	426	433

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.2A

INCIDENCE OF ALL ON-THERAPY ADVERSE EXPERIENCES BY MEDDRA PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND TREATMENT GROUP
PROTOCOL 157

MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
TOTAL	343 (75.9%)	351 (77.1%)
CHRONIC OBSTRUCTIVE AIRWAYS DISEASE EXACERBATED	209 (46.2%)	191 (42.0%)
NAUSEA	14 (3.1%)	44 (9.7%)
NASOPHARYNGITIS	54 (11.9%)	43 (9.5%)
HEADACHE	22 (4.9%)	35 (7.7%)
DIARRHOEA	13 (2.9%)	33 (7.3%)
VOMITING	8 (1.8%)	21 (4.6%)
ANOREXIA	1 (0.2%)	18 (4.0%)
DYSPEPSIA	6 (1.3%)	18 (4.0%)
COUGH	11 (2.4%)	14 (3.1%)
INFLUENZA	17 (3.8%)	14 (3.1%)
ABDOMINAL PAIN UPPER	5 (1.1%)	13 (2.9%)
DIZZINESS	5 (1.1%)	13 (2.9%)
HYPERTENSION	18 (4.0%)	13 (2.9%)
RHINITIS	11 (2.4%)	12 (2.6%)
UPPER RESPIRATORY TRACT INFECTION	11 (2.4%)	12 (2.6%)
ABDOMINAL PAIN	5 (1.1%)	9 (2.0%)
FATIGUE	2 (0.4%)	8 (1.8%)
ANXIETY	1 (0.2%)	7 (1.5%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AT LEAST ONE ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
4. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO SB 207499 TREATMENT GROUP

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.2A

INCIDENCE OF ALL ON-THERAPY ADVERSE EXPERIENCES BY MEDDRA PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND TREATMENT GROUP
PROTOCOL 157

MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
DEPRESSION	7 (1.5%)	7 (1.5%)
DYSPNOEA EXACERBATED	1 (0.2%)	7 (1.5%)
LOOSE STOOLS	2 (0.4%)	7 (1.5%)
BACK PAIN	20 (4.4%)	6 (1.3%)
BRONCHITIS	6 (1.3%)	6 (1.3%)
HYPERGLYCAEMIA	6 (1.3%)	6 (1.3%)
LOWER RESPIRATORY TRACT INFECTION	4 (0.9%)	6 (1.3%)
PHARYNGITIS	2 (0.4%)	6 (1.3%)
PHARYNGOLARYNGEAL PAIN	16 (3.5%)	6 (1.3%)
ARTHRALGIA	7 (1.5%)	5 (1.1%)
CHEST DISCOMFORT	4 (0.9%)	5 (1.1%)
CHEST PAIN	13 (2.9%)	5 (1.1%)
CONSTIPATION	4 (0.9%)	5 (1.1%)
PAIN IN EXTREMITY	7 (1.5%)	5 (1.1%)
PNEUMONIA	3 (0.7%)	5 (1.1%)
RESPIRATORY TRACT INFECTION	4 (0.9%)	5 (1.1%)
WEIGHT DECREASED	1 (0.2%)	5 (1.1%)
ATRIAL FIBRILLATION	2 (0.4%)	4 (0.9%)
BLOOD GLUCOSE INCREASED	2 (0.4%)	4 (0.9%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AT LEAST ONE ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
4. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO SB 207499 TREATMENT GROUP

CONFIDENTIAL

SB 207499

TABLE 15.2A

INCIDENCE OF ALL ON-THERAPY ADVERSE EXPERIENCES BY MEDDRA PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND TREATMENT GROUP
PROTOCOL 157

MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
EPISTAXIS	5 (1.1%)	4 (0.9%)
GOUT	0 .	4 (0.9%)
HERPES ZOSTER	2 (0.4%)	4 (0.9%)
INGUINAL HERNIA	1 (0.2%)	4 (0.9%)
JOINT INJURY	0 .	4 (0.9%)
LEUKOCYTOSIS	3 (0.7%)	4 (0.9%)
PROTEINURIA	3 (0.7%)	4 (0.9%)
PRURITUS	4 (0.9%)	4 (0.9%)
RHINITIS ALLERGIC	3 (0.7%)	4 (0.9%)
SINUS TACHYCARDIA	2 (0.4%)	4 (0.9%)
SINUSITIS	7 (1.5%)	4 (0.9%)
SLEEP DISORDER	1 (0.2%)	4 (0.9%)
URTICARIA	3 (0.7%)	4 (0.9%)
BLOOD IN STOOL	1 (0.2%)	3 (0.7%)
BURSITIS	1 (0.2%)	3 (0.7%)
CHOLELITHIASIS	2 (0.4%)	3 (0.7%)
CONTUSION	2 (0.4%)	3 (0.7%)
CORONARY ARTERY DISEASE	1 (0.2%)	3 (0.7%)
DIABETES MELLITUS	6 (1.3%)	3 (0.7%)
DIVERTICULUM	0 .	3 (0.7%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AT LEAST ONE ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
4. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO SB 207499 TREATMENT GROUP

CONFIDENTIAL

SB 207499

TABLE 15.2A

INCIDENCE OF ALL ON-THERAPY ADVERSE EXPERIENCES BY MEDDRA PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND TREATMENT GROUP
PROTOCOL 157

MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
DYSPNOEA	9 (2.0%)	3 (0.7%)
EAR INFECTION	5 (1.1%)	3 (0.7%)
FREQUENT BOWEL MOVEMENTS	4 (0.9%)	3 (0.7%)
FUNGAL INFECTION	1 (0.2%)	3 (0.7%)
GAMMA-GLUTAMYLTRANSFERASE INCREASED	9 (2.0%)	3 (0.7%)
GASTRITIS	3 (0.7%)	3 (0.7%)
GASTROENTERITIS	7 (1.5%)	3 (0.7%)
GASTROENTERITIS VIRAL	3 (0.7%)	3 (0.7%)
GASTROOESOPHAGEAL REFLUX DISEASE	2 (0.4%)	3 (0.7%)
HAEMATURIA	4 (0.9%)	3 (0.7%)
HEPATIC STEATOSIS	3 (0.7%)	3 (0.7%)
INFLUENZA LIKE ILLNESS	1 (0.2%)	3 (0.7%)
MYALGIA	2 (0.4%)	3 (0.7%)
OEDEMA PERIPHERAL	8 (1.8%)	3 (0.7%)
OSTEOARTHRITIS	3 (0.7%)	3 (0.7%)
PALPITATIONS	1 (0.2%)	3 (0.7%)
SUPRAVENTRICULAR EXTRASYSTOLES	3 (0.7%)	3 (0.7%)
VERTIGO	6 (1.3%)	3 (0.7%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AT LEAST ONE ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
4. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO SB 207499 TREATMENT GROUP

CONFIDENTIAL

SB 207499

TABLE 15.2A

INCIDENCE OF ALL ON-THERAPY ADVERSE EXPERIENCES BY MEDDRA PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND TREATMENT GROUP
PROTOCOL 157

MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
ABDOMINAL DISCOMFORT	1 (0.2%)	2 (0.4%)
ABDOMINAL DISTENSION	2 (0.4%)	2 (0.4%)
ANAEMIA	2 (0.4%)	2 (0.4%)
ANGINA PECTORIS	2 (0.4%)	2 (0.4%)
ARRHYTHMIA	1 (0.2%)	2 (0.4%)
ASTHENIA	2 (0.4%)	2 (0.4%)
ATRIAL FLUTTER	1 (0.2%)	2 (0.4%)
BLISTER	2 (0.4%)	2 (0.4%)
BLOOD PRESSURE INCREASED	2 (0.4%)	2 (0.4%)
BODY TEMPERATURE INCREASED	0 .	2 (0.4%)
C-REACTIVE PROTEIN INCREASED	2 (0.4%)	2 (0.4%)
CARDIAC FAILURE CONGESTIVE	0 .	2 (0.4%)
CATARACT	2 (0.4%)	2 (0.4%)
CHEST INJURY	0 .	2 (0.4%)
CONJUNCTIVITIS	4 (0.9%)	2 (0.4%)
CYSTITIS	2 (0.4%)	2 (0.4%)
DECREASED APPETITE	1 (0.2%)	2 (0.4%)
DRY MOUTH	1 (0.2%)	2 (0.4%)
DUODENAL ULCER	1 (0.2%)	2 (0.4%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AT LEAST ONE ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
4. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO SB 207499 TREATMENT GROUP

CONFIDENTIAL

SB 207499

TABLE 15.2A

INCIDENCE OF ALL ON-THERAPY ADVERSE EXPERIENCES BY MEDDRA PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND TREATMENT GROUP
PROTOCOL 157

MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
ECZEMA	3 (0.7%)	2 (0.4%)
EPIGASTRIC DISCOMFORT	0 .	2 (0.4%)
EYE INFECTION	0 .	2 (0.4%)
FACIAL PALSY	0 .	2 (0.4%)
FLATULENCE	2 (0.4%)	2 (0.4%)
GASTROINTESTINAL DISORDER	0 .	2 (0.4%)
HEART RATE INCREASED	0 .	2 (0.4%)
HEPATIC ENZYME INCREASED	1 (0.2%)	2 (0.4%)
HYPOKALAEMIA	0 .	2 (0.4%)
HYPOTENSION	1 (0.2%)	2 (0.4%)
INSOMNIA	5 (1.1%)	2 (0.4%)
LIMB INJURY	1 (0.2%)	2 (0.4%)
MALAISE	1 (0.2%)	2 (0.4%)
MUSCLE RIGIDITY	0 .	2 (0.4%)
MUSCLE STRAIN	1 (0.2%)	2 (0.4%)
MYOCARDIAL ISCHAEMIA	4 (0.9%)	2 (0.4%)
NASAL CONGESTION	1 (0.2%)	2 (0.4%)
PAIN	1 (0.2%)	2 (0.4%)
PERIARTHRITIS	0 .	2 (0.4%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AT LEAST ONE ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
4. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO SB 207499 TREATMENT GROUP

CONFIDENTIAL

SB 207499

TABLE 15.2A

INCIDENCE OF ALL ON-THERAPY ADVERSE EXPERIENCES BY MEDDRA PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND TREATMENT GROUP
PROTOCOL 157

MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
POSTNASAL DRIP	2 (0.4%)	2 (0.4%)
PYREXIA	2 (0.4%)	2 (0.4%)
REFLUX OESOPHAGITIS	1 (0.2%)	2 (0.4%)
RENAL COLIC	1 (0.2%)	2 (0.4%)
RHINORRHOEA	4 (0.9%)	2 (0.4%)
RIB FRACTURE	1 (0.2%)	2 (0.4%)
SKIN LACERATION	1 (0.2%)	2 (0.4%)
SPINAL DISORDER	3 (0.7%)	2 (0.4%)
SPUTUM INCREASED	0 .	2 (0.4%)
SUPRAVENTRICULAR TACHYCARDIA	0 .	2 (0.4%)
SYNCOPE	2 (0.4%)	2 (0.4%)
THROAT IRRITATION	1 (0.2%)	2 (0.4%)
TOOTHACHE	3 (0.7%)	2 (0.4%)
TREMOR	0 .	2 (0.4%)
URINARY TRACT INFECTION	12 (2.7%)	2 (0.4%)
VIRAL UPPER RESPIRATORY TRACT INFECTION	1 (0.2%)	2 (0.4%)
VITAMIN B12 DEFICIENCY	0 .	2 (0.4%)
WHEEZING	3 (0.7%)	2 (0.4%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AT LEAST ONE ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
4. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO SB 207499 TREATMENT GROUP

CONFIDENTIAL

SB 207499

TABLE 15.2A

INCIDENCE OF ALL ON-THERAPY ADVERSE EXPERIENCES BY MEDDRA PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND TREATMENT GROUP
PROTOCOL 157

MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
ABDOMINAL OBESITY	0 .	1 (0.2%)
ABNORMAL FAECES	0 .	1 (0.2%)
ACUTE MYOCARDIAL INFARCTION	0 .	1 (0.2%)
ACUTE RESPIRATORY FAILURE	0 .	1 (0.2%)
AFFECT LABILITY	1 (0.2%)	1 (0.2%)
AGE INDETERMINATE MYOCARDIAL INFARCTION	0 .	1 (0.2%)
ALANINE AMINOTRANSFERASE INCREASED	4 (0.9%)	1 (0.2%)
ALCOHOL USE	0 .	1 (0.2%)
ANIMAL BITE	1 (0.2%)	1 (0.2%)
AORTIC ANEURYSM	0 .	1 (0.2%)
AORTIC DISSECTION	0 .	1 (0.2%)
AORTIC VALVE CALCIFICATION	0 .	1 (0.2%)
ASPARTATE AMINOTRANSFERASE INCREASED	4 (0.9%)	1 (0.2%)
BACK INJURY	1 (0.2%)	1 (0.2%)
BENIGN PROSTATIC HYPERPLASIA	0 .	1 (0.2%)
BILIARY COLIC	0 .	1 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AT LEAST ONE ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
4. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO SB 207499 TREATMENT GROUP

CONFIDENTIAL

SB 207499

TABLE 15.2A

INCIDENCE OF ALL ON-THERAPY ADVERSE EXPERIENCES BY MEDDRA PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND TREATMENT GROUP
PROTOCOL 157

MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
BLADDER CANCER	0 .	1 (0.2%)
BLADDER INFECTION	0 .	1 (0.2%)
BLOOD ALKALINE PHOSPHATASE INCREASED	4 (0.9%)	1 (0.2%)
BLOOD BILIRUBIN INCREASED	4 (0.9%)	1 (0.2%)
BLOOD HOMOCYSTEINE DECREASED	0 .	1 (0.2%)
BLOOD SODIUM DECREASED	0 .	1 (0.2%)
BONE PAIN	0 .	1 (0.2%)
BRADYARRHYTHMIA	0 .	1 (0.2%)
BRONCHITIS ACUTE	2 (0.4%)	1 (0.2%)
BRONCHITIS ACUTE VIRAL	0 .	1 (0.2%)
BRONCHITIS VIRAL	0 .	1 (0.2%)
BRONCHOPNEUMONIA	3 (0.7%)	1 (0.2%)
BUNDLE BRANCH BLOCK LEFT	2 (0.4%)	1 (0.2%)
CANDIDIASIS	1 (0.2%)	1 (0.2%)
CARDIAC FAILURE	1 (0.2%)	1 (0.2%)
CARDIAC FAILURE ACUTE	0 .	1 (0.2%)
CATARRH	0 .	1 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AT LEAST ONE ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
4. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO SB 207499 TREATMENT GROUP

CONFIDENTIAL

SB 207499

TABLE 15.2A

INCIDENCE OF ALL ON-THERAPY ADVERSE EXPERIENCES BY MEDDRA PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND TREATMENT GROUP
PROTOCOL 157

MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
CEREBROVASCULAR ACCIDENT	1 (0.2%)	1 (0.2%)
CEREBROVASCULAR DISORDER	1 (0.2%)	1 (0.2%)
CHALAZION	0 .	1 (0.2%)
CHOLECYSTITIS CHRONIC	0 .	1 (0.2%)
CHRONIC HEPATITIS	0 .	1 (0.2%)
CHRONIC SINUSITIS	0 .	1 (0.2%)
CIRCULATORY COLLAPSE	1 (0.2%)	1 (0.2%)
COLONIC HAEMORRHAGE	0 .	1 (0.2%)
COLONIC POLYP	1 (0.2%)	1 (0.2%)
CONJUNCTIVAL HAEMORRHAGE	0 .	1 (0.2%)
CONTRAST MEDIA REACTION	0 .	1 (0.2%)
CONVULSION	0 .	1 (0.2%)
CORONARY ARTERY INSUFFICIENCY	0 .	1 (0.2%)
CYSTITIS ACUTE	0 .	1 (0.2%)
DERMATITIS CONTACT	0 .	1 (0.2%)
DIASTOLIC HYPERTENSION	0 .	1 (0.2%)
DISTURBANCE IN ATTENTION	0 .	1 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AT LEAST ONE ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
4. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO SB 207499 TREATMENT GROUP

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.2A

INCIDENCE OF ALL ON-THERAPY ADVERSE EXPERIENCES BY MEDDRA PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND TREATMENT GROUP
PROTOCOL 157

MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
DIVERTICULITIS	1 (0.2%)	1 (0.2%)
DIZZINESS POSTURAL	1 (0.2%)	1 (0.2%)
DRY SKIN	1 (0.2%)	1 (0.2%)
DYSGEUSIA	1 (0.2%)	1 (0.2%)
DYSPHONIA	0 .	1 (0.2%)
EAR DISORDER	0 .	1 (0.2%)
EAR PAIN	1 (0.2%)	1 (0.2%)
ECG SIGNS OF MYOCARDIAL ISCHAEMIA	0 .	1 (0.2%)
EJECTION FRACTION DECREASED	0 .	1 (0.2%)
ELECTROCARDIOGRAM T WAVE INVERSION	0 .	1 (0.2%)
EMOTIONAL DISTRESS	0 .	1 (0.2%)
EPICONDYLITIS	1 (0.2%)	1 (0.2%)
EPIDIDYMITIS	0 .	1 (0.2%)
FAECES DISCOLOURED	1 (0.2%)	1 (0.2%)
FAECES HARD	0 .	1 (0.2%)
FALL	2 (0.4%)	1 (0.2%)
FASCIITIS	0 .	1 (0.2%)
FEELING ABNORMAL	0 .	1 (0.2%)
FOOD POISONING	0 .	1 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AT LEAST ONE ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
4. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO SB 207499 TREATMENT GROUP

CONFIDENTIAL

SB 207499

TABLE 15.2A

INCIDENCE OF ALL ON-THERAPY ADVERSE EXPERIENCES BY MEDDRA PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND TREATMENT GROUP
PROTOCOL 157

MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
FURUNCLE	0 .	1 (0.2%)
GASTRIC DISORDER	0 .	1 (0.2%)
GASTRIC INFECTION	0 .	1 (0.2%)
GASTRIC ULCER	1 (0.2%)	1 (0.2%)
GASTRODUODENITIS	0 .	1 (0.2%)
GASTROINTESTINAL UPSET	0 .	1 (0.2%)
GLOSSITIS	0 .	1 (0.2%)
GYNAECOMASTIA	0 .	1 (0.2%)
HAEMATOMA	0 .	1 (0.2%)
HAEMORRHOIDAL HAEMORRHAGE	0 .	1 (0.2%)
HELICOBACTER GASTRITIS	0 .	1 (0.2%)
HELICOBACTER INFECTION	0 .	1 (0.2%)
HERPES SIMPLEX	1 (0.2%)	1 (0.2%)
HORDEOLUM	0 .	1 (0.2%)
HOT FLUSH	3 (0.7%)	1 (0.2%)
HYPERCHOLESTEROLAEMIA	2 (0.4%)	1 (0.2%)
HYPERHIDROSIS	1 (0.2%)	1 (0.2%)
HYPERLIPIDAEMIA	0 .	1 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AT LEAST ONE ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
4. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO SB 207499 TREATMENT GROUP

CONFIDENTIAL

SB 207499

TABLE 15.2A

INCIDENCE OF ALL ON-THERAPY ADVERSE EXPERIENCES BY MEDDRA PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND TREATMENT GROUP
PROTOCOL 157

MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
HYPERSENSITIVITY	1 (0.2%)	1 (0.2%)
HYPERTONIC BLADDER	0 .	1 (0.2%)
HYPERURICAEMIA	1 (0.2%)	1 (0.2%)
HYPOAESTHESIA	0 .	1 (0.2%)
ILEUS	1 (0.2%)	1 (0.2%)
INCREASED BRONCHIAL SECRETION	0 .	1 (0.2%)
INFECTED SEBACEOUS CYST	0 .	1 (0.2%)
JOINT ABSCESS	0 .	1 (0.2%)
JOINT EFFUSION	0 .	1 (0.2%)
JOINT SWELLING	2 (0.4%)	1 (0.2%)
KERATOCONJUNCTIVITIS SICCA	0 .	1 (0.2%)
KIDNEY HYPERMOBILITY	0 .	1 (0.2%)
LETHARGY	2 (0.4%)	1 (0.2%)
LOBAR PNEUMONIA	1 (0.2%)	1 (0.2%)
LUMBAR SPINAL STENOSIS	0 .	1 (0.2%)
LUNG NEOPLASM MALIGNANT	1 (0.2%)	1 (0.2%)
LYMPHADENOPATHY	1 (0.2%)	1 (0.2%)
MIDDLE INSOMNIA	0 .	1 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AT LEAST ONE ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
4. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO SB 207499 TREATMENT GROUP

CONFIDENTIAL

SB 207499

TABLE 15.2A

INCIDENCE OF ALL ON-THERAPY ADVERSE EXPERIENCES BY MEDDRA PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND TREATMENT GROUP
PROTOCOL 157

MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
MONOARTHRITIS	1 (0.2%)	1 (0.2%)
MUSCLE CRAMP	3 (0.7%)	1 (0.2%)
MUSCLE TIGHTNESS	0 .	1 (0.2%)
MUSCULOSKELETAL PAIN	0 .	1 (0.2%)
MYOCARDIAL INFARCTION	1 (0.2%)	1 (0.2%)
NASAL SEPTUM DEVIATION	1 (0.2%)	1 (0.2%)
NEPHROLITHIASIS	1 (0.2%)	1 (0.2%)
NEURODERMATITIS	0 .	1 (0.2%)
NEUTROPENIA	0 .	1 (0.2%)
NOCTURIA	0 .	1 (0.2%)
OESOPHAGITIS	2 (0.4%)	1 (0.2%)
ONYCHOMYCOSIS	1 (0.2%)	1 (0.2%)
ORAL CANDIDIASIS	1 (0.2%)	1 (0.2%)
ORAL FUNGAL INFECTION	0 .	1 (0.2%)
ORTHOSTATIC HYPOTENSION	0 .	1 (0.2%)
OSTEOPOROSIS	1 (0.2%)	1 (0.2%)
OTITIS EXTERNA	0 .	1 (0.2%)
PANCREATITIS	1 (0.2%)	1 (0.2%)
PANIC ATTACK	1 (0.2%)	1 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AT LEAST ONE ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
4. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO SB 207499 TREATMENT GROUP

CONFIDENTIAL

SB 207499

TABLE 15.2A

INCIDENCE OF ALL ON-THERAPY ADVERSE EXPERIENCES BY MEDDRA PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND TREATMENT GROUP
PROTOCOL 157

MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
PARKINSON'S DISEASE	0 .	1 (0.2%)
PEPTIC ULCER	0 .	1 (0.2%)
PHLEBITIS	0 .	1 (0.2%)
PLATELET COUNT INCREASED	0 .	1 (0.2%)
PLEURISY	0 .	1 (0.2%)
PNEUMONIA CHLAMYDIAL	0 .	1 (0.2%)
POLYCYTHAEMIA	0 .	1 (0.2%)
POST PROCEDURAL PAIN	0 .	1 (0.2%)
PROSTATIC HYPERTROPHY	0 .	1 (0.2%)
PROSTATISM	0 .	1 (0.2%)
PROSTATITIS	1 (0.2%)	1 (0.2%)
QRS AXIS ABNORMAL	0 .	1 (0.2%)
RADIATION ASSOCIATED PAIN	0 .	1 (0.2%)
RADIUS FRACTURE	0 .	1 (0.2%)
RASH	2 (0.4%)	1 (0.2%)
RASH PRURITIC	0 .	1 (0.2%)
RECTAL HAEMORRHAGE	1 (0.2%)	1 (0.2%)
RENAL IMPAIRMENT	0 .	1 (0.2%)
RESPIRATORY ALKALOSIS	0 .	1 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AT LEAST ONE ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
4. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO SB 207499 TREATMENT GROUP

CONFIDENTIAL

SB 207499

TABLE 15.2A

INCIDENCE OF ALL ON-THERAPY ADVERSE EXPERIENCES BY MEDDRA PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND TREATMENT GROUP
PROTOCOL 157

MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
RHEUMATOID ARTHRITIS	0 .	1 (0.2%)
RHINITIS INFECTIVE	0 .	1 (0.2%)
ROAD TRAFFIC ACCIDENT	0 .	1 (0.2%)
SALPINGITIS	0 .	1 (0.2%)
SEASONAL ALLERGY	1 (0.2%)	1 (0.2%)
SEXUAL DYSFUNCTION	0 .	1 (0.2%)
SINUS BRADYCARDIA	1 (0.2%)	1 (0.2%)
SKIN ATROPHY	0 .	1 (0.2%)
SKIN BURNING SENSATION	0 .	1 (0.2%)
SKIN HYPERTROPHY	0 .	1 (0.2%)
SKIN INFECTION	0 .	1 (0.2%)
SKIN LESION	1 (0.2%)	1 (0.2%)
SKIN PAPILLOMA	0 .	1 (0.2%)
SPINAL COLUMN STENOSIS	0 .	1 (0.2%)
SPUTUM TEST	0 .	1 (0.2%)
SQUAMOUS CELL CARCINOMA	0 .	1 (0.2%)
STRANGURY	0 .	1 (0.2%)
TACHYCARDIA	2 (0.4%)	1 (0.2%)
TENDON INJURY	0 .	1 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AT LEAST ONE ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
4. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO SB 207499 TREATMENT GROUP

CONFIDENTIAL

SB 207499

TABLE 15.2A

INCIDENCE OF ALL ON-THERAPY ADVERSE EXPERIENCES BY MEDDRA PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND TREATMENT GROUP
PROTOCOL 157

MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
THIRST	2 (0.4%)	1 (0.2%)
TINEA PEDIS	0 .	1 (0.2%)
TOOTH ABSCESS	2 (0.4%)	1 (0.2%)
TOOTH DISORDER	0 .	1 (0.2%)
TOOTH EXTRACTION	0 .	1 (0.2%)
TOOTH INFECTION	1 (0.2%)	1 (0.2%)
TOOTH INJURY	0 .	1 (0.2%)
TRANSIENT ISCHAEMIC ATTACK	0 .	1 (0.2%)
UMBILICAL HERNIA	0 .	1 (0.2%)
URINARY OCCULT BLOOD POSITIVE	1 (0.2%)	1 (0.2%)
URINARY RETENTION	0 .	1 (0.2%)
URINE KETONE BODY PRESENT	0 .	1 (0.2%)
URTICARIA PAPULAR	0 .	1 (0.2%)
VAGINAL HAEMORRHAGE	0 .	1 (0.2%)
VARICOSE VEIN	0 .	1 (0.2%)
VASCULAR SKIN DISORDER	0 .	1 (0.2%)
VENTRICULAR EXTRASYSTOLES	1 (0.2%)	1 (0.2%)
VENTRICULAR HYPERTROPHY	0 .	1 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AT LEAST ONE ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
4. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO SB 207499 TREATMENT GROUP

CONFIDENTIAL

SB 207499

TABLE 15.2A

INCIDENCE OF ALL ON-THERAPY ADVERSE EXPERIENCES BY MEDDRA PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND TREATMENT GROUP
PROTOCOL 157

MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
VENTRICULAR TACHYCARDIA	1 (0.2%)	1 (0.2%)
VERTEBRAL ARTERY OCCLUSION	0 .	1 (0.2%)
VULVITIS	0 .	1 (0.2%)
ABDOMINAL PAIN LOWER	1 (0.2%)	0 .
ABDOMINAL SYMPTOM	1 (0.2%)	0 .
ABNORMAL DREAMS	1 (0.2%)	0 .
ABSTAINS FROM ALCOHOL	1 (0.2%)	0 .
ALCOHOL POISONING	1 (0.2%)	0 .
ALCOHOLIC LIVER DISEASE	1 (0.2%)	0 .
ALCOHOLISM	2 (0.4%)	0 .
ANAPHYLACTIC SHOCK	1 (0.2%)	0 .
ANGINA UNSTABLE	1 (0.2%)	0 .
ARTHRITIS	1 (0.2%)	0 .
ARTHROPOD BITE	1 (0.2%)	0 .
ARTHROPOD STING	1 (0.2%)	0 .
AXILLARY PAIN	1 (0.2%)	0 .
BACTERIAL INFECTION	1 (0.2%)	0 .
BASAL CELL CARCINOMA	1 (0.2%)	0 .
BEREAVEMENT REACTION	1 (0.2%)	0 .

1. EACH PATIENT COUNTED ONCE PER MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AT LEAST ONE ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
4. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO SB 207499 TREATMENT GROUP

CONFIDENTIAL

SB 207499

TABLE 15.2A

INCIDENCE OF ALL ON-THERAPY ADVERSE EXPERIENCES BY MEDDRA PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND TREATMENT GROUP
PROTOCOL 157

MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
BLOOD CREATININE INCREASED	2 (0.4%)	0 .
BLOOD URIC ACID DECREASED	1 (0.2%)	0 .
BLOOD URINE	1 (0.2%)	0 .
BLOOD URINE PRESENT	4 (0.9%)	0 .
BRONCHOSPASM	1 (0.2%)	0 .
BUNDLE BRANCH BLOCK RIGHT	1 (0.2%)	0 .
CALCULUS BLADDER	1 (0.2%)	0 .
CARDIOVASCULAR DISORDER	1 (0.2%)	0 .
CARPAL TUNNEL SYNDROME	1 (0.2%)	0 .
CATARACT EXTRACTION	2 (0.4%)	0 .
CEREBRAL INFARCTION	1 (0.2%)	0 .
CEREBRAL THROMBOSIS	1 (0.2%)	0 .
CERUMEN IMPACTION	2 (0.4%)	0 .
CYSTITIS CHRONIC	1 (0.2%)	0 .
DEAFNESS	1 (0.2%)	0 .
DECUBITUS ULCER	1 (0.2%)	0 .
DENTAL CARIES	1 (0.2%)	0 .
DERMATITIS	1 (0.2%)	0 .

1. EACH PATIENT COUNTED ONCE PER MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AT LEAST ONE ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
4. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO SB 207499 TREATMENT GROUP

CONFIDENTIAL

SB 207499

TABLE 15.2A

INCIDENCE OF ALL ON-THERAPY ADVERSE EXPERIENCES BY MEDDRA PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND TREATMENT GROUP
PROTOCOL 157

MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
DERMATITIS ALLERGIC	1 (0.2%)	0 .
DERMATITIS MEDICAMENTOSA	1 (0.2%)	0 .
DIARRHOEA HAEMORRHAGIC	1 (0.2%)	0 .
DIVERTICULUM INTESTINAL	3 (0.7%)	0 .
DRY THROAT	1 (0.2%)	0 .
DYSPHAGIA	1 (0.2%)	0 .
DYSURIA	1 (0.2%)	0 .
EAR LOBE INFECTION	1 (0.2%)	0 .
EAR PRURITUS	1 (0.2%)	0 .
ELECTROCARDIOGRAM P WAVE ABNORMAL	1 (0.2%)	0 .
ELECTROCARDIOGRAM ST SEGMENT DEPRESSION	1 (0.2%)	0 .
ENCEPHALOPATHY	1 (0.2%)	0 .
ENTRAPMENT NEUROPATHY	1 (0.2%)	0 .
EOSINOPHILIA	1 (0.2%)	0 .
ERYSIPELAS	1 (0.2%)	0 .
EYE ALLERGY	1 (0.2%)	0 .
EYE INFLAMMATION	2 (0.4%)	0 .

1. EACH PATIENT COUNTED ONCE PER MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AT LEAST ONE ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
4. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO SB 207499 TREATMENT GROUP

CONFIDENTIAL

SB 207499

TABLE 15.2A

INCIDENCE OF ALL ON-THERAPY ADVERSE EXPERIENCES BY MEDDRA PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND TREATMENT GROUP
PROTOCOL 157

MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
EYELID OEDEMA	1 (0.2%)	0 .
FAECAL OCCULT BLOOD POSITIVE	2 (0.4%)	0 .
FAECALOMA	1 (0.2%)	0 .
FAECES PALE	1 (0.2%)	0 .
FEELING HOT	1 (0.2%)	0 .
FIBROMYALGIA	1 (0.2%)	0 .
FOLLICULITIS	1 (0.2%)	0 .
FOOT FRACTURE	1 (0.2%)	0 .
FORCED EXPIRATORY VOLUME DECREASED	1 (0.2%)	0 .
GASTRIC CANCER	1 (0.2%)	0 .
GASTROINTESTINAL OBSTRUCTION	1 (0.2%)	0 .
GENITAL RASH	1 (0.2%)	0 .
GINGIVITIS	1 (0.2%)	0 .
GLAUCOMA	1 (0.2%)	0 .
GLUCOSE TOLERANCE IMPAIRED	1 (0.2%)	0 .
GLYCOSURIA	1 (0.2%)	0 .
HAEMOPTYSIS	1 (0.2%)	0 .
HAEMORRHOIDS	1 (0.2%)	0 .
HAND FRACTURE	1 (0.2%)	0 .

1. EACH PATIENT COUNTED ONCE PER MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AT LEAST ONE ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
4. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO SB 207499 TREATMENT GROUP

CONFIDENTIAL

SB 207499

TABLE 15.2A

INCIDENCE OF ALL ON-THERAPY ADVERSE EXPERIENCES BY MEDDRA PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND TREATMENT GROUP
PROTOCOL 157

MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
HEART INJURY	1 (0.2%)	0 .
HEAT RASH	1 (0.2%)	0 .
HIATUS HERNIA	2 (0.4%)	0 .
HIP FRACTURE	1 (0.2%)	0 .
HOARSENESS	1 (0.2%)	0 .
HUMERUS FRACTURE	1 (0.2%)	0 .
HYPERTENSIVE CRISIS	1 (0.2%)	0 .
HYPERTENSIVE HEART DISEASE	1 (0.2%)	0 .
HYPOACUSIS	1 (0.2%)	0 .
HYPOGLYCAEMIA	1 (0.2%)	0 .
HYPONATRAEMIA	1 (0.2%)	0 .
HYPOXIA	1 (0.2%)	0 .
INFECTED INSECT BITE	1 (0.2%)	0 .
INFECTED SKIN ULCER	1 (0.2%)	0 .
INFECTION	1 (0.2%)	0 .
INTESTINAL OBSTRUCTION	1 (0.2%)	0 .
INTESTINAL PERFORATION	1 (0.2%)	0 .
INTESTINAL POLYP	2 (0.4%)	0 .
IRON DEFICIENCY ANAEMIA	1 (0.2%)	0 .

1. EACH PATIENT COUNTED ONCE PER MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AT LEAST ONE ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
4. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO SB 207499 TREATMENT GROUP

CONFIDENTIAL

SB 207499

TABLE 15.2A

INCIDENCE OF ALL ON-THERAPY ADVERSE EXPERIENCES BY MEDDRA PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND TREATMENT GROUP
PROTOCOL 157

MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
JOINT SPRAIN	1 (0.2%)	0 .
LEUKOPENIA	2 (0.4%)	0 .
LICHEN PLANUS	1 (0.2%)	0 .
LOCAL SWELLING	1 (0.2%)	0 .
LOCALISED INFECTION	2 (0.4%)	0 .
LOCALISED OSTEOARTHRITIS	2 (0.4%)	0 .
LUNG DISORDER	2 (0.4%)	0 .
LUNG NODULE	1 (0.2%)	0 .
MANIA	1 (0.2%)	0 .
METASTASIS	1 (0.2%)	0 .
MOTION SICKNESS	1 (0.2%)	0 .
MOTOR DYSFUNCTION	1 (0.2%)	0 .
MOUTH ULCERATION	4 (0.9%)	0 .
MUSCLE INJURY	1 (0.2%)	0 .
MUSCULOSKELETAL CHEST PAIN	1 (0.2%)	0 .
MUSCULOSKELETAL DISCOMFORT	1 (0.2%)	0 .
NASAL CYST	1 (0.2%)	0 .
NASAL MUCOSAL DISORDER	1 (0.2%)	0 .
NASAL POLYPS	1 (0.2%)	0 .

1. EACH PATIENT COUNTED ONCE PER MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AT LEAST ONE ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
4. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO SB 207499 TREATMENT GROUP

CONFIDENTIAL

SB 207499

TABLE 15.2A

INCIDENCE OF ALL ON-THERAPY ADVERSE EXPERIENCES BY MEDDRA PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND TREATMENT GROUP
PROTOCOL 157

MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
NEUROPATHY	1 (0.2%)	0 .
NEUROSIS	1 (0.2%)	0 .
NEUTROPHILIA	1 (0.2%)	0 .
OEDEMA	1 (0.2%)	0 .
OROPHARYNGITIS FUNGAL	1 (0.2%)	0 .
PALLOR	1 (0.2%)	0 .
PARAESTHESIA	2 (0.4%)	0 .
PERIPHERAL COLDNESS	1 (0.2%)	0 .
PHARYNGEAL ERYTHEMA	1 (0.2%)	0 .
PLEURITIC PAIN	1 (0.2%)	0 .
PNEUMONIA BACTERIAL	1 (0.2%)	0 .
PNEUMOTHORAX	1 (0.2%)	0 .
POLLAKIURIA	2 (0.4%)	0 .
PRODUCTIVE COUGH	1 (0.2%)	0 .
PROSTATE CANCER	1 (0.2%)	0 .
PROTEIN URINE PRESENT	1 (0.2%)	0 .
PSORIASIS	1 (0.2%)	0 .
PULMONARY FIBROSIS	1 (0.2%)	0 .
PULPITIS DENTAL	1 (0.2%)	0 .

1. EACH PATIENT COUNTED ONCE PER MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AT LEAST ONE ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
4. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO SB 207499 TREATMENT GROUP

CONFIDENTIAL

SB 207499

TABLE 15.2A

INCIDENCE OF ALL ON-THERAPY ADVERSE EXPERIENCES BY MEDDRA PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND TREATMENT GROUP
PROTOCOL 157

MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
RADICULITIS LUMBOSACRAL	1 (0.2%)	0 .
RENAL CELL CARCINOMA STAGE UNSPECIFIED	1 (0.2%)	0 .
RENAL CYST	1 (0.2%)	0 .
RENAL INSUFFICIENCY	1 (0.2%)	0 .
RETINAL ARTERY THROMBOSIS	1 (0.2%)	0 .
RHINITIS SEASONAL	1 (0.2%)	0 .
SEBORRHOEIC DERMATITIS	1 (0.2%)	0 .
SEBORRHOEIC KERATOSIS	1 (0.2%)	0 .
SECONDARY ANAEMIA	1 (0.2%)	0 .
SHOULDER BLADE PAIN	1 (0.2%)	0 .
SJOGREN'S SYNDROME	1 (0.2%)	0 .
SKELETAL INJURY	1 (0.2%)	0 .
SKIN ULCER	1 (0.2%)	0 .
SQUAMOUS CELL CARCINOMA OF SKIN	2 (0.4%)	0 .
STAPHYLOCOCCAL INFECTION	1 (0.2%)	0 .
STASIS DERMATITIS	1 (0.2%)	0 .
SYNCOPE VASOVAGAL	1 (0.2%)	0 .

1. EACH PATIENT COUNTED ONCE PER MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AT LEAST ONE ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
4. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO SB 207499 TREATMENT GROUP

CONFIDENTIAL

SB 207499

TABLE 15.2A

INCIDENCE OF ALL ON-THERAPY ADVERSE EXPERIENCES BY MEDDRA PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND TREATMENT GROUP
PROTOCOL 157

MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
TENDONITIS	1 (0.2%)	0 .
TESTICULAR PAIN	1 (0.2%)	0 .
TESTICULAR SWELLING	1 (0.2%)	0 .
THERMAL BURN	1 (0.2%)	0 .
THROMBOCYTHAEMIA	1 (0.2%)	0 .
THROMBOPHLEBITIS	1 (0.2%)	0 .
THYROID GLAND CANCER	1 (0.2%)	0 .
TINEA INFECTION	1 (0.2%)	0 .
TINNITUS	1 (0.2%)	0 .
TONSILLITIS	2 (0.4%)	0 .
TORTICOLLIS	1 (0.2%)	0 .
URINARY TRACT OBSTRUCTION	1 (0.2%)	0 .
VACCINATION COMPLICATION	1 (0.2%)	0 .
VAGINAL MYCOSIS	1 (0.2%)	0 .
VARICOSE ULCERATION	1 (0.2%)	0 .
VIRAL INFECTION	1 (0.2%)	0 .
VIRAL LABYRINTHITIS	1 (0.2%)	0 .
WANDERING PACEMAKER	1 (0.2%)	0 .
WEIGHT INCREASED	1 (0.2%)	0 .

1. EACH PATIENT COUNTED ONCE PER MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AT LEAST ONE ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
4. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO SB 207499 TREATMENT GROUP

CONFIDENTIAL

SB 207499

TABLE 15.2A

INCIDENCE OF ALL ON-THERAPY ADVERSE EXPERIENCES BY MEDDRA PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND TREATMENT GROUP
PROTOCOL 157

MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
WHITE BLOOD CELL COUNT INCREASED	1 (0.2%)	0 .
WOUND	1 (0.2%)	0 .
WRIST FRACTURE	2 (0.4%)	0 .

1. EACH PATIENT COUNTED ONCE PER MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AT LEAST ONE ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
4. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO SB 207499 TREATMENT GROUP

CONFIDENTIAL

SB 207499

TABLE 15.2B

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP

PROTOCOL 157

MEDDRA BODY SYSTEM	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
TOTAL	TOTAL	343 (75.9%)	351 (77.1%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	TOTAL	13 (2.9%)	9 (2.0%)
	ANAEMIA	2 (0.4%)	2 (0.4%)
	EOSINOPHILIA	1 (0.2%)	0 .
	IRON DEFICIENCY ANAEMIA	1 (0.2%)	0 .
	LEUKOCYTOSIS	3 (0.7%)	4 (0.9%)
	LEUKOPENIA	2 (0.4%)	0 .
	LYMPHADENOPATHY	1 (0.2%)	1 (0.2%)
	NEUTROPENIA	0 .	1 (0.2%)
	NEUTROPHILIA	1 (0.2%)	0 .
	POLYCYTHAEMIA	0 .	1 (0.2%)
	SECONDARY ANAEMIA	1 (0.2%)	0 .
	THROMBOCYTHAEMIA	1 (0.2%)	0 .
CARDIAC DISORDERS	TOTAL	25 (5.5%)	38 (8.4%)
	ACUTE MYOCARDIAL INFARCTION	0 .	1 (0.2%)
	AGE INDETERMINATE MYOCARDIAL INFARCTION	0 .	1 (0.2%)
	ANGINA PECTORIS	2 (0.4%)	2 (0.4%)
	ANGINA UNSTABLE	1 (0.2%)	0 .
	AORTIC VALVE CALCIFICATION	0 .	1 (0.2%)
	ARRHYTHMIA	1 (0.2%)	2 (0.4%)
	ATRIAL FIBRILLATION	2 (0.4%)	4 (0.9%)
	ATRIAL FLUTTER	1 (0.2%)	2 (0.4%)
	BRADYARRHYTHMIA	0 .	1 (0.2%)
	BUNDLE BRANCH BLOCK LEFT	2 (0.4%)	1 (0.2%)
	BUNDLE BRANCH BLOCK RIGHT	1 (0.2%)	0 .
	CARDIAC FAILURE	1 (0.2%)	1 (0.2%)
	CARDIAC FAILURE ACUTE	0 .	1 (0.2%)
	CARDIAC FAILURE CONGESTIVE	0 .	2 (0.4%)
	CARDIOVASCULAR DISORDER	1 (0.2%)	0 .

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.2B

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP

PROTOCOL 157

MEDDRA BODY SYSTEM	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
CARDIAC DISORDERS	CORONARY ARTERY DISEASE	1 (0.2%)	3 (0.7%)
	CORONARY ARTERY INSUFFICIENCY	0 .	1 (0.2%)
	HYPERTENSIVE HEART DISEASE	1 (0.2%)	0 .
	MYOCARDIAL INFARCTION	1 (0.2%)	1 (0.2%)
	MYOCARDIAL ISCHAEMIA	4 (0.9%)	2 (0.4%)
	PALPITATIONS	1 (0.2%)	3 (0.7%)
	SINUS BRADYCARDIA	1 (0.2%)	1 (0.2%)
	SINUS TACHYCARDIA	2 (0.4%)	4 (0.9%)
	SUPRAVENTRICULAR EXTRASYSTOLES	3 (0.7%)	3 (0.7%)
	SUPRAVENTRICULAR TACHYCARDIA	0 .	2 (0.4%)
	TACHYCARDIA	2 (0.4%)	1 (0.2%)
	VENTRICULAR EXTRASYSTOLES	1 (0.2%)	1 (0.2%)
	VENTRICULAR HYPERTROPHY	0 .	1 (0.2%)
	VENTRICULAR TACHYCARDIA	1 (0.2%)	1 (0.2%)
	WANDERING PACEMAKER	1 (0.2%)	0 .
EAR AND LABYRINTH DISORDERS	TOTAL	13 (2.9%)	5 (1.1%)
	CERUMEN IMPACTION	2 (0.4%)	0 .
	DEAFNESS	1 (0.2%)	0 .
	EAR DISORDER	0 .	1 (0.2%)
	EAR PAIN	1 (0.2%)	1 (0.2%)
	EAR PRURITUS	1 (0.2%)	0 .
	HYPOACUSIS	1 (0.2%)	0 .
	MOTION SICKNESS	1 (0.2%)	0 .
	TINNITUS	1 (0.2%)	0 .
	VERTIGO	6 (1.3%)	3 (0.7%)
EYE DISORDERS	TOTAL	12 (2.7%)	7 (1.5%)
	CATARACT	2 (0.4%)	2 (0.4%)
	CHALAZION	0 .	1 (0.2%)
	CONJUNCTIVAL HAEMORRHAGE	0 .	1 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED

CONFIDENTIAL

SB 207499

TABLE 15.2B

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP

PROTOCOL 157

MEDDRA BODY SYSTEM	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
EYE DISORDERS	CONJUNCTIVITIS	4 (0.9%)	2 (0.4%)
	EYE ALLERGY	1 (0.2%)	0 .
	EYE INFLAMMATION	2 (0.4%)	0 .
	EYELID OEDEMA	1 (0.2%)	0 .
	GLAUCOMA	1 (0.2%)	0 .
	KERATOCONJUNCTIVITIS SICCA	0 .	1 (0.2%)
	RETINAL ARTERY THROMBOSIS	1 (0.2%)	0 .
GASTROINTESTINAL DISORDERS	TOTAL	67 (14.8%)	128 (28.1%)
	ABDOMINAL DISCOMFORT	1 (0.2%)	2 (0.4%)
	ABDOMINAL DISTENSION	2 (0.4%)	2 (0.4%)
	ABDOMINAL PAIN	5 (1.1%)	9 (2.0%)
	ABDOMINAL PAIN LOWER	1 (0.2%)	0 .
	ABDOMINAL PAIN UPPER	5 (1.1%)	13 (2.9%)
	ABDOMINAL SYMPTOM	1 (0.2%)	0 .
	ABNORMAL FAECES	0 .	1 (0.2%)
	COLONIC HAEMORRHAGE	0 .	1 (0.2%)
	COLONIC POLYP	1 (0.2%)	1 (0.2%)
	CONSTIPATION	4 (0.9%)	5 (1.1%)
	DIARRHOEA	13 (2.9%)	33 (7.3%)
	DIARRHOEA HAEMORRHAGIC	1 (0.2%)	0 .
	DIVERTICULITIS	1 (0.2%)	1 (0.2%)
	DIVERTICULUM	0 .	3 (0.7%)
	DIVERTICULUM INTESTINAL	3 (0.7%)	0 .
	DRY MOUTH	1 (0.2%)	2 (0.4%)
	DUODENAL ULCER	1 (0.2%)	2 (0.4%)
	DYSPEPSIA	6 (1.3%)	18 (4.0%)
	DYSPHAGIA	1 (0.2%)	0 .
	EPIGASTRIC DISCOMFORT	0 .	2 (0.4%)
	FAECALOMA	1 (0.2%)	0 .
	FAECES DISCOLOURED	1 (0.2%)	1 (0.2%)
	FAECES HARD	0 .	1 (0.2%)
	FAECES PALE	1 (0.2%)	0 .
	FLATULENCE	2 (0.4%)	2 (0.4%)
	FOOD POISONING	0 .	1 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED

CONFIDENTIAL

SB 207499

TABLE 15.2B

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP

PROTOCOL 157

MEDDRA BODY SYSTEM	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
GASTROINTESTINAL DISORDERS	FREQUENT BOWEL MOVEMENTS	4 (0.9%)	3 (0.7%)
	GASTRIC DISORDER	0 .	1 (0.2%)
	GASTRIC ULCER	1 (0.2%)	1 (0.2%)
	GASTRITIS	3 (0.7%)	3 (0.7%)
	GASTRODUODENITIS	0 .	1 (0.2%)
	GASTROINTESTINAL DISORDER	0 .	2 (0.4%)
	GASTROINTESTINAL OBSTRUCTION	1 (0.2%)	0 .
	GASTROINTESTINAL UPSET	0 .	1 (0.2%)
	GASTROOESOPHAGEAL REFLUX DISEASE	2 (0.4%)	3 (0.7%)
	GINGIVITIS	1 (0.2%)	0 .
	GLOSSITIS	0 .	1 (0.2%)
	HAEMORRHOIDAL HAEMORRHAGE	0 .	1 (0.2%)
	HAEMORRHOIDS	1 (0.2%)	0 .
	HIATUS HERNIA	2 (0.4%)	0 .
	ILEUS	1 (0.2%)	1 (0.2%)
	INGUINAL HERNIA	1 (0.2%)	4 (0.9%)
	INTESTINAL OBSTRUCTION	1 (0.2%)	0 .
	INTESTINAL PERFORATION	1 (0.2%)	0 .
	INTESTINAL POLYP	2 (0.4%)	0 .
	LOOSE STOOLS	2 (0.4%)	7 (1.5%)
	MOUTH ULCERATION	4 (0.9%)	0 .
	NAUSEA	14 (3.1%)	44 (9.7%)
	OESOPHAGITIS	2 (0.4%)	1 (0.2%)
	PANCREATITIS	1 (0.2%)	1 (0.2%)
	PEPTIC ULCER	0 .	1 (0.2%)
	RECTAL HAEMORRHAGE	1 (0.2%)	1 (0.2%)
	REFLUX OESOPHAGITIS	1 (0.2%)	2 (0.4%)
	TOOTH DISORDER	0 .	1 (0.2%)
	TOOTHACHE	3 (0.7%)	2 (0.4%)
	UMBILICAL HERNIA	0 .	1 (0.2%)
	VOMITING	8 (1.8%)	21 (4.6%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED

CONFIDENTIAL

SB 207499

TABLE 15.2B

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP

PROTOCOL 157

MEDDRA BODY SYSTEM	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	TOTAL	34 (7.5%)	32 (7.0%)
	ASTHENIA	2 (0.4%)	2 (0.4%)
	AXILLARY PAIN	1 (0.2%)	0 .
	CHEST DISCOMFORT	4 (0.9%)	5 (1.1%)
	CHEST PAIN	13 (2.9%)	5 (1.1%)
	FATIGUE	2 (0.4%)	8 (1.8%)
	FEELING ABNORMAL	0 .	1 (0.2%)
	FEELING HOT	1 (0.2%)	0 .
	INFLUENZA LIKE ILLNESS	1 (0.2%)	3 (0.7%)
	LETHARGY	2 (0.4%)	1 (0.2%)
	MALAISE	1 (0.2%)	2 (0.4%)
	OEDEMA	1 (0.2%)	0 .
	OEDEMA PERIPHERAL	8 (1.8%)	3 (0.7%)
	PAIN	1 (0.2%)	2 (0.4%)
	PYREXIA	2 (0.4%)	2 (0.4%)
	THIRST	2 (0.4%)	1 (0.2%)
HEPATOBILIARY DISORDERS	TOTAL	6 (1.3%)	8 (1.8%)
	ALCOHOLIC LIVER DISEASE	1 (0.2%)	0 .
	BILIARY COLIC	0 .	1 (0.2%)
	CHOLECYSTITIS CHRONIC	0 .	1 (0.2%)
	CHOLELITHIASIS	2 (0.4%)	3 (0.7%)
	CHRONIC HEPATITIS	0 .	1 (0.2%)
	HEPATIC STEATOSIS	3 (0.7%)	3 (0.7%)
IMMUNE SYSTEM DISORDERS	TOTAL	3 (0.7%)	2 (0.4%)
	ANAPHYLACTIC SHOCK	1 (0.2%)	0 .
	HYPERSENSITIVITY	1 (0.2%)	1 (0.2%)
	SEASONAL ALLERGY	1 (0.2%)	1 (0.2%)
INFECTIONS AND INFESTATIONS	TOTAL	133 (29.4%)	126 (27.7%)
	BACTERIAL INFECTION	1 (0.2%)	0 .
	BLADDER INFECTION	0 .	1 (0.2%)
	BRONCHITIS	6 (1.3%)	6 (1.3%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED

CONFIDENTIAL

SB 207499

TABLE 15.2B

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP

PROTOCOL 157

MEDDRA BODY SYSTEM	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
INFECTIONS AND INFESTATIONS	BRONCHITIS ACUTE	2 (0.4%)	1 (0.2%)
	BRONCHITIS ACUTE VIRAL	0 .	1 (0.2%)
	BRONCHITIS VIRAL	0 .	1 (0.2%)
	BRONCHOPNEUMONIA	3 (0.7%)	1 (0.2%)
	CANDIDIASIS	1 (0.2%)	1 (0.2%)
	CHRONIC SINUSITIS	0 .	1 (0.2%)
	CYSTITIS	2 (0.4%)	2 (0.4%)
	CYSTITIS ACUTE	0 .	1 (0.2%)
	DENTAL CARIES	1 (0.2%)	0 .
	EAR INFECTION	5 (1.1%)	3 (0.7%)
	EAR LOBE INFECTION	1 (0.2%)	0 .
	ERYSIPELAS	1 (0.2%)	0 .
	EYE INFECTION	0 .	2 (0.4%)
	FOLLICULITIS	1 (0.2%)	0 .
	FUNGAL INFECTION	1 (0.2%)	3 (0.7%)
	FURUNCLE	0 .	1 (0.2%)
	GASTRIC INFECTION	0 .	1 (0.2%)
	GASTROENTERITIS	7 (1.5%)	3 (0.7%)
	GASTROENTERITIS VIRAL	3 (0.7%)	3 (0.7%)
	HELICOBACTER GASTRITIS	0 .	1 (0.2%)
	HELICOBACTER INFECTION	0 .	1 (0.2%)
	HERPES SIMPLEX	1 (0.2%)	1 (0.2%)
	HERPES ZOSTER	2 (0.4%)	4 (0.9%)
	HORDEOLUM	0 .	1 (0.2%)
	INFECTED INSECT BITE	1 (0.2%)	0 .
	INFECTED SEBACEOUS CYST	0 .	1 (0.2%)
	INFECTED SKIN ULCER	1 (0.2%)	0 .
	INFECTION	1 (0.2%)	0 .
	INFLUENZA	17 (3.8%)	14 (3.1%)
	JOINT ABSCESS	0 .	1 (0.2%)
	LOBAR PNEUMONIA	1 (0.2%)	1 (0.2%)
	LOCALISED INFECTION	2 (0.4%)	0 .
	LOWER RESPIRATORY TRACT INFECTION	4 (0.9%)	6 (1.3%)
	NASOPHARYNGITIS	54 (11.9%)	43 (9.5%)
	ONYCHOMYCOSIS	1 (0.2%)	1 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED

CONFIDENTIAL

SB 207499

TABLE 15.2B

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP

PROTOCOL 157

MEDDRA BODY SYSTEM	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
INFECTIONS AND INFESTATIONS	ORAL CANDIDIASIS	1 (0.2%)	1 (0.2%)
	ORAL FUNGAL INFECTION	0 .	1 (0.2%)
	OROPHARYNGITIS FUNGAL	1 (0.2%)	0 .
	OTITIS EXTERNA	0 .	1 (0.2%)
	PHARYNGITIS	2 (0.4%)	6 (1.3%)
	PNEUMONIA	3 (0.7%)	5 (1.1%)
	PNEUMONIA BACTERIAL	1 (0.2%)	0 .
	PNEUMONIA CHLAMYDIAL	0 .	1 (0.2%)
	PULPITIS DENTAL	1 (0.2%)	0 .
	RESPIRATORY TRACT INFECTION	4 (0.9%)	5 (1.1%)
	RHINITIS INFECTIVE	0 .	1 (0.2%)
	SALPINGITIS	0 .	1 (0.2%)
	SINUSITIS	7 (1.5%)	4 (0.9%)
	SKIN INFECTION	0 .	1 (0.2%)
	STAPHYLOCOCCAL INFECTION	1 (0.2%)	0 .
	TINEA INFECTION	1 (0.2%)	0 .
	TINEA PEDIS	0 .	1 (0.2%)
	TONSILLITIS	2 (0.4%)	0 .
	TOOTH ABSCESS	2 (0.4%)	1 (0.2%)
	TOOTH INFECTION	1 (0.2%)	1 (0.2%)
	UPPER RESPIRATORY TRACT INFECTION	11 (2.4%)	12 (2.6%)
	URINARY TRACT INFECTION	12 (2.7%)	2 (0.4%)
	VAGINAL MYCOSIS	1 (0.2%)	0 .
	VIRAL INFECTION	1 (0.2%)	0 .
	VIRAL LABYRINTHITIS	1 (0.2%)	0 .
	VIRAL UPPER RESPIRATORY TRACT INFECTION	1 (0.2%)	2 (0.4%)
	VULVITIS	0 .	1 (0.2%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	TOTAL	24 (5.3%)	24 (5.3%)
	ALCOHOL POISONING	1 (0.2%)	0 .
	ANIMAL BITE	1 (0.2%)	1 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED

CONFIDENTIAL

SB 207499

TABLE 15.2B

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP

PROTOCOL 157

MEDDRA BODY SYSTEM	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	ARTHROPOD BITE	1 (0.2%)	0 .
	ARTHROPOD STING	1 (0.2%)	0 .
	BACK INJURY	1 (0.2%)	1 (0.2%)
	BLISTER	2 (0.4%)	2 (0.4%)
	CHEST INJURY	0 .	2 (0.4%)
	CONTRAST MEDIA REACTION	0 .	1 (0.2%)
	CONTUSION	2 (0.4%)	3 (0.7%)
	EPICONDYLITIS	1 (0.2%)	1 (0.2%)
	FALL	2 (0.4%)	1 (0.2%)
	FOOT FRACTURE	1 (0.2%)	0 .
	HAND FRACTURE	1 (0.2%)	0 .
	HEART INJURY	1 (0.2%)	0 .
	HIP FRACTURE	1 (0.2%)	0 .
	HUMERUS FRACTURE	1 (0.2%)	0 .
	JOINT INJURY	0 .	4 (0.9%)
	JOINT SPRAIN	1 (0.2%)	0 .
	LIMB INJURY	1 (0.2%)	2 (0.4%)
	MUSCLE INJURY	1 (0.2%)	0 .
	MUSCLE STRAIN	1 (0.2%)	2 (0.4%)
	POST PROCEDURAL PAIN	0 .	1 (0.2%)
	RADIATION ASSOCIATED PAIN	0 .	1 (0.2%)
	RADIUS FRACTURE	0 .	1 (0.2%)
	RIB FRACTURE	1 (0.2%)	2 (0.4%)
	ROAD TRAFFIC ACCIDENT	0 .	1 (0.2%)
	SKELETAL INJURY	1 (0.2%)	0 .
	SKIN LACERATION	1 (0.2%)	2 (0.4%)
	TENDON INJURY	0 .	1 (0.2%)
	THERMAL BURN	1 (0.2%)	0 .
	TOOTH INJURY	0 .	1 (0.2%)
	VACCINATION COMPLICATION	1 (0.2%)	0 .
	WOUND	1 (0.2%)	0 .
	WRIST FRACTURE	2 (0.4%)	0 .
INVESTIGATIONS	TOTAL	36 (8.0%)	34 (7.5%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.2B

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP

PROTOCOL 157

MEDDRA BODY SYSTEM	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
INVESTIGATIONS	ALANINE AMINOTRANSFERASE INCREASED	4 (0.9%)	1 (0.2%)
	ASPARTATE AMINOTRANSFERASE INCREASED	4 (0.9%)	1 (0.2%)
	BLOOD ALKALINE PHOSPHATASE INCREASED	4 (0.9%)	1 (0.2%)
	BLOOD BILIRUBIN INCREASED	4 (0.9%)	1 (0.2%)
	BLOOD CREATININE INCREASED	2 (0.4%)	0 .
	BLOOD GLUCOSE INCREASED	2 (0.4%)	4 (0.9%)
	BLOOD HOMOCYSTEINE DECREASED	0 .	1 (0.2%)
	BLOOD IN STOOL	1 (0.2%)	3 (0.7%)
	BLOOD PRESSURE INCREASED	2 (0.4%)	2 (0.4%)
	BLOOD SODIUM DECREASED	0 .	1 (0.2%)
	BLOOD URIC ACID DECREASED	1 (0.2%)	0 .
	BLOOD URINE	1 (0.2%)	0 .
	BLOOD URINE PRESENT	4 (0.9%)	0 .
	BODY TEMPERATURE INCREASED	0 .	2 (0.4%)
	C-REACTIVE PROTEIN INCREASED	2 (0.4%)	2 (0.4%)
	ECG SIGNS OF MYOCARDIAL ISCHAEMIA	0 .	1 (0.2%)
	EJECTION FRACTION DECREASED	0 .	1 (0.2%)
	ELECTROCARDIOGRAM P WAVE ABNORMAL	1 (0.2%)	0 .
	ELECTROCARDIOGRAM ST SEGMENT DEPRESSION	1 (0.2%)	0 .
	ELECTROCARDIOGRAM T WAVE INVERSION	0 .	1 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.2B

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP

PROTOCOL 157

MEDDRA BODY SYSTEM	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
INVESTIGATIONS	FAECAL OCCULT BLOOD POSITIVE	2 (0.4%)	0 .
	FORCED EXPIRATORY VOLUME DECREASED	1 (0.2%)	0 .
	GAMMA-GLUTAMYLTRANSFERASE INCREASED	9 (2.0%)	3 (0.7%)
	HEART RATE INCREASED	0 .	2 (0.4%)
	HEPATIC ENZYME INCREASED	1 (0.2%)	2 (0.4%)
	PLATELET COUNT INCREASED	0 .	1 (0.2%)
	PROTEIN URINE PRESENT	1 (0.2%)	0 .
	QRS AXIS ABNORMAL	0 .	1 (0.2%)
	SPUTUM INCREASED	0 .	2 (0.4%)
	SPUTUM TEST	0 .	1 (0.2%)
	URINARY OCCULT BLOOD POSITIVE	1 (0.2%)	1 (0.2%)
	URINE KETONE BODY PRESENT	0 .	1 (0.2%)
	WEIGHT DECREASED	1 (0.2%)	5 (1.1%)
	WEIGHT INCREASED	1 (0.2%)	0 .
	WHITE BLOOD CELL COUNT INCREASED	1 (0.2%)	0 .
METABOLISM AND NUTRITION DISORDERS	TOTAL	17 (3.8%)	37 (8.1%)
	ABDOMINAL OBESITY	0 .	1 (0.2%)
	ANOREXIA	1 (0.2%)	18 (4.0%)
	DECREASED APPETITE	1 (0.2%)	2 (0.4%)
	DIABETES MELLITUS	6 (1.3%)	3 (0.7%)
	GLUCOSE TOLERANCE IMPAIRED	1 (0.2%)	0 .
	GOUT	0 .	4 (0.9%)
	HYPERCHOLESTEROLAEMIA	2 (0.4%)	1 (0.2%)
	HYPERGLYCAEMIA	6 (1.3%)	6 (1.3%)
	HYPERLIPIDAEMIA	0 .	1 (0.2%)
	HYPERURICAEMIA	1 (0.2%)	1 (0.2%)
	HYPOGLYCAEMIA	1 (0.2%)	0 .
	HYPOKALAEMIA	0 .	2 (0.4%)
	HYPONATRAEMIA	1 (0.2%)	0 .

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED

CONFIDENTIAL

SB 207499

TABLE 15.2B

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP

PROTOCOL 157

MEDDRA BODY SYSTEM	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
METABOLISM AND NUTRITION DISORDERS	VITAMIN B12 DEFICIENCY	0 .	2 (0.4%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	TOTAL	52 (11.5%)	36 (7.9%)
	ARTHRALGIA	7 (1.5%)	5 (1.1%)
	ARTHRITIS	1 (0.2%)	0 .
	BACK PAIN	20 (4.4%)	6 (1.3%)
	BONE PAIN	0 .	1 (0.2%)
	BURSITIS	1 (0.2%)	3 (0.7%)
	FASCIITIS	0 .	1 (0.2%)
	FIBROMYALGIA	1 (0.2%)	0 .
	JOINT EFFUSION	0 .	1 (0.2%)
	JOINT SWELLING	2 (0.4%)	1 (0.2%)
	LOCAL SWELLING	1 (0.2%)	0 .
	LOCALISED OSTEOARTHRITIS	2 (0.4%)	0 .
	MONOARTHRITIS	1 (0.2%)	1 (0.2%)
	MUSCLE CRAMP	3 (0.7%)	1 (0.2%)
	MUSCLE RIGIDITY	0 .	2 (0.4%)
	MUSCLE TIGHTNESS	0 .	1 (0.2%)
	MUSCULOSKELETAL CHEST PAIN	1 (0.2%)	0 .
	MUSCULOSKELETAL DISCOMFORT	1 (0.2%)	0 .
	MUSCULOSKELETAL PAIN	0 .	1 (0.2%)
	MYALGIA	2 (0.4%)	3 (0.7%)
	OSTEOARTHRITIS	3 (0.7%)	3 (0.7%)
	OSTEOPOROSIS	1 (0.2%)	1 (0.2%)
	PAIN IN EXTREMITY	7 (1.5%)	5 (1.1%)
	PERIARTHRITIS	0 .	2 (0.4%)
	RHEUMATOID ARTHRITIS	0 .	1 (0.2%)
	SHOULDER BLADE PAIN	1 (0.2%)	0 .
	SJOGREN'S SYNDROME	1 (0.2%)	0 .
	SPINAL DISORDER	3 (0.7%)	2 (0.4%)
	TENDONITIS	1 (0.2%)	0 .
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	TOTAL	9 (2.0%)	4 (0.9%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED

CONFIDENTIAL

SB 207499

TABLE 15.2B

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP

PROTOCOL 157

MEDDRA BODY SYSTEM	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	BASAL CELL CARCINOMA	1 (0.2%)	0 .
	BLADDER CANCER	0 .	1 (0.2%)
	GASTRIC CANCER	1 (0.2%)	0 .
	LUNG NEOPLASM MALIGNANT	1 (0.2%)	1 (0.2%)
	LUNG NODULE	1 (0.2%)	0 .
	METASTASIS	1 (0.2%)	0 .
	PROSTATE CANCER	1 (0.2%)	0 .
	RENAL CELL CARCINOMA STAGE UNSPECIFIED	1 (0.2%)	0 .
	SEBORRHOEIC KERATOSIS	1 (0.2%)	0 .
	SKIN PAPILLOMA	0 .	1 (0.2%)
	SQUAMOUS CELL CARCINOMA	0 .	1 (0.2%)
	SQUAMOUS CELL CARCINOMA OF SKIN	2 (0.4%)	0 .
	THYROID GLAND CANCER	1 (0.2%)	0 .
NERVOUS SYSTEM DISORDERS	TOTAL	37 (8.2%)	55 (12.1%)
	CARPAL TUNNEL SYNDROME	1 (0.2%)	0 .
	CEREBRAL INFARCTION	1 (0.2%)	0 .
	CEREBRAL THROMBOSIS	1 (0.2%)	0 .
	CEREBROVASCULAR ACCIDENT	1 (0.2%)	1 (0.2%)
	CEREBROVASCULAR DISORDER	1 (0.2%)	1 (0.2%)
	CONVULSION	0 .	1 (0.2%)
	DISTURBANCE IN ATTENTION	0 .	1 (0.2%)
	DIZZINESS	5 (1.1%)	13 (2.9%)
	DIZZINESS POSTURAL	1 (0.2%)	1 (0.2%)
	DYSGEUSIA	1 (0.2%)	1 (0.2%)
	ENCEPHALOPATHY	1 (0.2%)	0 .
	ENTRAPMENT NEUROPATHY	1 (0.2%)	0 .

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED

CONFIDENTIAL

SB 207499

TABLE 15.2B

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP

PROTOCOL 157

MEDDRA BODY SYSTEM	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
NERVOUS SYSTEM DISORDERS	FACIAL PALSY	0 .	2 (0.4%)
	HEADACHE	22 (4.9%)	35 (7.7%)
	HYPOAESTHESIA	0 .	1 (0.2%)
	LUMBAR SPINAL STENOSIS	0 .	1 (0.2%)
	MOTOR DYSFUNCTION	1 (0.2%)	0 .
	NEUROPATHY	1 (0.2%)	0 .
	PARAESTHESIA	2 (0.4%)	0 .
	PARKINSON'S DISEASE	0 .	1 (0.2%)
	RADICULITIS LUMBOSACRAL	1 (0.2%)	0 .
	SPINAL COLUMN STENOSIS	0 .	1 (0.2%)
	SYNCOPE	2 (0.4%)	2 (0.4%)
	SYNCOPE VASOVAGAL	1 (0.2%)	0 .
	TORTICOLLIS	1 (0.2%)	0 .
	TRANSIENT ISCHAEMIC ATTACK	0 .	1 (0.2%)
	TREMOR	0 .	2 (0.4%)
	VERTEBRAL ARTERY OCCLUSION	0 .	1 (0.2%)
PSYCHIATRIC DISORDERS	TOTAL	20 (4.4%)	23 (5.1%)
	ABNORMAL DREAMS	1 (0.2%)	0 .
	AFFECT LABILITY	1 (0.2%)	1 (0.2%)
	ALCOHOLISM	2 (0.4%)	0 .
	ANXIETY	1 (0.2%)	7 (1.5%)
	BEREAVEMENT REACTION	1 (0.2%)	0 .
	DEPRESSION	7 (1.5%)	7 (1.5%)
	EMOTIONAL DISTRESS	0 .	1 (0.2%)
	INSOMNIA	5 (1.1%)	2 (0.4%)
	MANIA	1 (0.2%)	0 .
	MIDDLE INSOMNIA	0 .	1 (0.2%)
	NEUROSIS	1 (0.2%)	0 .
	PANIC ATTACK	1 (0.2%)	1 (0.2%)
	SLEEP DISORDER	1 (0.2%)	4 (0.9%)
RENAL AND URINARY DISORDERS	TOTAL	17 (3.8%)	14 (3.1%)
	CALCULUS BLADDER	1 (0.2%)	0 .

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED

CONFIDENTIAL

SB 207499

TABLE 15.2B

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP

PROTOCOL 157

MEDDRA BODY SYSTEM	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
RENAL AND URINARY DISORDERS	CYSTITIS CHRONIC	1 (0.2%)	0 .
	DYSURIA	1 (0.2%)	0 .
	GLYCOSURIA	1 (0.2%)	0 .
	HAEMATURIA	4 (0.9%)	3 (0.7%)
	HYPERTONIC BLADDER	0 .	1 (0.2%)
	KIDNEY HYPERMOBILITY	0 .	1 (0.2%)
	NEPHROLITHIASIS	1 (0.2%)	1 (0.2%)
	NOCTURIA	0 .	1 (0.2%)
	POLLAKIURIA	2 (0.4%)	0 .
	PROTEINURIA	3 (0.7%)	4 (0.9%)
	RENAL COLIC	1 (0.2%)	2 (0.4%)
	RENAL CYST	1 (0.2%)	0 .
	RENAL IMPAIRMENT	0 .	1 (0.2%)
	RENAL INSUFFICIENCY	1 (0.2%)	0 .
	STRANGURY	0 .	1 (0.2%)
	URINARY RETENTION	0 .	1 (0.2%)
	URINARY TRACT OBSTRUCTION	1 (0.2%)	0 .
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	TOTAL	4 (0.9%)	8 (1.8%)
	BENIGN PROSTATIC HYPERPLASIA	0 .	1 (0.2%)
	EPIDIDYMITIS	0 .	1 (0.2%)
	GENITAL RASH	1 (0.2%)	0 .
	GYNAECOMASTIA	0 .	1 (0.2%)
	PROSTATIC HYPERTROPHY	0 .	1 (0.2%)
	PROSTATISM	0 .	1 (0.2%)
	PROSTATITIS	1 (0.2%)	1 (0.2%)
	SEXUAL DYSFUNCTION	0 .	1 (0.2%)
	TESTICULAR PAIN	1 (0.2%)	0 .
	TESTICULAR SWELLING	1 (0.2%)	0 .
	VAGINAL HAEMORRHAGE	0 .	1 (0.2%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	TOTAL	242 (53.5%)	220 (48.4%)
	ACUTE RESPIRATORY FAILURE	0 .	1 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED

CONFIDENTIAL

SB 207499

TABLE 15.2B

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP

PROTOCOL 157

MEDDRA BODY SYSTEM	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	BRONCHOSPASM	1 (0.2%)	0 .
	CATARRH	0 .	1 (0.2%)
	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE EXACERBATED	209 (46.2%)	191 (42.0%)
	COUGH	11 (2.4%)	14 (3.1%)
	DRY THROAT	1 (0.2%)	0 .
	DYSPHONIA	0 .	1 (0.2%)
	DYSPNOEA	9 (2.0%)	3 (0.7%)
	DYSPNOEA EXACERBATED	1 (0.2%)	7 (1.5%)
	EPISTAXIS	5 (1.1%)	4 (0.9%)
	HAEMOPTYSIS	1 (0.2%)	0 .
	HOARSENESS	1 (0.2%)	0 .
	HYPOXIA	1 (0.2%)	0 .
	INCREASED BRONCHIAL SECRETION	0 .	1 (0.2%)
	LUNG DISORDER	2 (0.4%)	0 .
	NASAL CONGESTION	1 (0.2%)	2 (0.4%)
	NASAL CYST	1 (0.2%)	0 .
	NASAL MUCOSAL DISORDER	1 (0.2%)	0 .
	NASAL POLYPS	1 (0.2%)	0 .
	NASAL SEPTUM DEVIATION	1 (0.2%)	1 (0.2%)
	PHARYNGEAL ERYTHEMA	1 (0.2%)	0 .
	PHARYNGOLARYNGEAL PAIN	16 (3.5%)	6 (1.3%)
	PLEURISY	0 .	1 (0.2%)
	PLEURITIC PAIN	1 (0.2%)	0 .
	PNEUMOTHORAX	1 (0.2%)	0 .
	POSTNASAL DRIP	2 (0.4%)	2 (0.4%)
	PRODUCTIVE COUGH	1 (0.2%)	0 .
	PULMONARY FIBROSIS	1 (0.2%)	0 .
	RESPIRATORY ALKALOSIS	0 .	1 (0.2%)
	RHINITIS	11 (2.4%)	12 (2.6%)
	RHINITIS ALLERGIC	3 (0.7%)	4 (0.9%)
	RHINITIS SEASONAL	1 (0.2%)	0 .
	RHINORRHOEA	4 (0.9%)	2 (0.4%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED

CONFIDENTIAL

SB 207499

TABLE 15.2B

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP

PROTOCOL 157

MEDDRA BODY SYSTEM	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	THROAT IRRITATION	1 (0.2%)	2 (0.4%)
	WHEEZING	3 (0.7%)	2 (0.4%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	TOTAL	19 (4.2%)	18 (4.0%)
	DECUBITUS ULCER	1 (0.2%)	0 .
	DERMATITIS	1 (0.2%)	0 .
	DERMATITIS ALLERGIC	1 (0.2%)	0 .
	DERMATITIS CONTACT	0 .	1 (0.2%)
	DERMATITIS MEDICAMENTOSA	1 (0.2%)	0 .
	DRY SKIN	1 (0.2%)	1 (0.2%)
	ECZEMA	3 (0.7%)	2 (0.4%)
	HEAT RASH	1 (0.2%)	0 .
	HYPERHIDROSIS	1 (0.2%)	1 (0.2%)
	LICHEN PLANUS	1 (0.2%)	0 .
	NEURODERMATITIS	0 .	1 (0.2%)
	PRURITUS	4 (0.9%)	4 (0.9%)
	PSORIASIS	1 (0.2%)	0 .
	RASH	2 (0.4%)	1 (0.2%)
	RASH PRURITIC	0 .	1 (0.2%)
	SEBORRHOEIC DERMATITIS	1 (0.2%)	0 .
	SKIN ATROPHY	0 .	1 (0.2%)
	SKIN BURNING SENSATION	0 .	1 (0.2%)
	SKIN HYPERTROPHY	0 .	1 (0.2%)
	SKIN LESION	1 (0.2%)	1 (0.2%)
	SKIN ULCER	1 (0.2%)	0 .
	STASIS DERMATITIS	1 (0.2%)	0 .
	URTICARIA	3 (0.7%)	4 (0.9%)
	URTICARIA PAPULAR	0 .	1 (0.2%)
	VASCULAR SKIN DISORDER	0 .	1 (0.2%)
SOCIAL CIRCUMSTANCES	TOTAL	1 (0.2%)	1 (0.2%)
	ABSTAINS FROM ALCOHOL	1 (0.2%)	0 .

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED

CONFIDENTIAL

SB 207499

TABLE 15.2B

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP

PROTOCOL 157

MEDDRA BODY SYSTEM	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
SOCIAL CIRCUMSTANCES	ALCOHOL USE	0 .	1 (0.2%)
SURGICAL AND MEDICAL PROCEDURES	TOTAL	2 (0.4%)	1 (0.2%)
	CATARACT EXTRACTION	2 (0.4%)	0 .
	TOOTH EXTRACTION	0 .	1 (0.2%)
VASCULAR DISORDERS	TOTAL	26 (5.8%)	22 (4.8%)
	AORTIC ANEURYSM	0 .	1 (0.2%)
	AORTIC DISSECTION	0 .	1 (0.2%)
	CIRCULATORY COLLAPSE	1 (0.2%)	1 (0.2%)
	DIASTOLIC HYPERTENSION	0 .	1 (0.2%)
	HAEMATOMA	0 .	1 (0.2%)
	HOT FLUSH	3 (0.7%)	1 (0.2%)
	HYPERTENSION	18 (4.0%)	13 (2.9%)
	HYPERTENSIVE CRISIS	1 (0.2%)	0 .
	HYPOTENSION	1 (0.2%)	2 (0.4%)
	ORTHOSTATIC HYPOTENSION	0 .	1 (0.2%)
	PALLOR	1 (0.2%)	0 .
	PERIPHERAL COLDNESS	1 (0.2%)	0 .
	PHLEBITIS	0 .	1 (0.2%)
	THROMBOPHLEBITIS	1 (0.2%)	0 .
	VARICOSE ULCERATION	1 (0.2%)	0 .
	VARICOSE VEIN	0 .	1 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED

CONFIDENTIAL

SB 207499

TABLE 15.3

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT, MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP=PLACEBO(N=452)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	MISSING	RELATIONSHIP NOT RELATED	RELATED	Total
TOTAL	TOTAL	0 .	296 (65.5%)	47 (10.4%)	343 (75.9%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	TOTAL	0 .	12 (2.7%)	1 (0.2%)	13 (2.9%)
	ANAEMIA	0 .	2 (0.4%)	0 .	2 (0.4%)
	EOSINOPHILIA	0 .	1 (0.2%)	0 .	1 (0.2%)
	IRON DEFICIENCY ANAEMIA	0 .	1 (0.2%)	0 .	1 (0.2%)
	LEUKOCYTOSIS	0 .	3 (0.7%)	0 .	3 (0.7%)
	LEUKOPENIA	0 .	2 (0.4%)	0 .	2 (0.4%)
	LYMPHADENOPATHY	0 .	1 (0.2%)	0 .	1 (0.2%)
	NEUTROPHILIA	0 .	1 (0.2%)	0 .	1 (0.2%)
	SECONDARY ANAEMIA	0 .	0 .	1 (0.2%)	1 (0.2%)
	THROMBOCYTHAEMIA	0 .	1 (0.2%)	0 .	1 (0.2%)
CARDIAC DISORDERS	TOTAL	0 .	20 (4.4%)	5 (1.1%)	25 (5.5%)
	ANGINA PECTORIS	0 .	2 (0.4%)	0 .	2 (0.4%)
	ANGINA UNSTABLE	0 .	1 (0.2%)	0 .	1 (0.2%)
	ARRHYTHMIA	0 .	1 (0.2%)	0 .	1 (0.2%)
	ATRIAL FIBRILLATION	0 .	1 (0.2%)	1 (0.2%)	2 (0.4%)
	ATRIAL FLUTTER	0 .	0 .	1 (0.2%)	1 (0.2%)
	BUNDLE BRANCH BLOCK LEFT	0 .	1 (0.2%)	1 (0.2%)	2 (0.4%)
	BUNDLE BRANCH BLOCK RIGHT	0 .	1 (0.2%)	0 .	1 (0.2%)
	CARDIAC FAILURE	0 .	1 (0.2%)	0 .	1 (0.2%)
	CARDIOVASCULAR DISORDER	0 .	1 (0.2%)	0 .	1 (0.2%)
	CORONARY ARTERY DISEASE	0 .	1 (0.2%)	0 .	1 (0.2%)
	HYPERTENSIVE HEART DISEASE	0 .	1 (0.2%)	0 .	1 (0.2%)
	MYOCARDIAL INFARCTION	0 .	1 (0.2%)	0 .	1 (0.2%)
	MYOCARDIAL ISCHAEMIA	0 .	4 (0.9%)	0 .	4 (0.9%)
	PALPITATIONS	0 .	0 .	1 (0.2%)	1 (0.2%)
	SINUS BRADYCARDIA	0 .	1 (0.2%)	0 .	1 (0.2%)
	SINUS TACHYCARDIA	0 .	2 (0.4%)	0 .	2 (0.4%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND RELATIONSHIP
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
3. WORST-CASE RELATIONSHIP IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. NR= UNLIKELY OR NOT RELATED TO TREATMENT, RELATED= SUSPECTED OR PROBABLY RELATED TO TREATMENT
5. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL

SB 207499

TABLE 15.3

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT, MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP=PLACEBO(N=452)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	RELATIONSHIP MISSING	NOT RELATED	RELATED	Total
CARDIAC DISORDERS	SUPRAVENTRICULAR EXTRASYSTOLES	0 .	3 (0.7%)	0 .	3 (0.7%)
	TACHYCARDIA	0 .	2 (0.4%)	0 .	2 (0.4%)
	VENTRICULAR EXTRASYSTOLES	0 .	0 .	1 (0.2%)	1 (0.2%)
	VENTRICULAR TACHYCARDIA	0 .	0 .	1 (0.2%)	1 (0.2%)
	WANDERING PACEMAKER	0 .	1 (0.2%)	0 .	1 (0.2%)
EAR AND LABYRINTH DISORDERS	TOTAL	0 .	13 (2.9%)	0 .	13 (2.9%)
	CERUMEN IMPACTION	0 .	2 (0.4%)	0 .	2 (0.4%)
	DEAFNESS	0 .	1 (0.2%)	0 .	1 (0.2%)
	EAR PAIN	0 .	1 (0.2%)	0 .	1 (0.2%)
	EAR PRURITUS	0 .	1 (0.2%)	0 .	1 (0.2%)
	HYPOACUSIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	MOTION SICKNESS	0 .	1 (0.2%)	0 .	1 (0.2%)
	TINNITUS	0 .	1 (0.2%)	0 .	1 (0.2%)
	VERTIGO	0 .	6 (1.3%)	0 .	6 (1.3%)
EYE DISORDERS	TOTAL	0 .	11 (2.4%)	1 (0.2%)	12 (2.7%)
	CATARACT	0 .	2 (0.4%)	0 .	2 (0.4%)
	CONJUNCTIVITIS	0 .	4 (0.9%)	0 .	4 (0.9%)
	EYE ALLERGY	0 .	1 (0.2%)	0 .	1 (0.2%)
	EYE INFLAMMATION	0 .	2 (0.4%)	0 .	2 (0.4%)
	EYELID OEDEMA	0 .	0 .	1 (0.2%)	1 (0.2%)
	GLAUCOMA	0 .	1 (0.2%)	0 .	1 (0.2%)
	RETINAL ARTERY THROMBOSIS	0 .	1 (0.2%)	0 .	1 (0.2%)
GASTROINTESTINAL DISORDERS	TOTAL	0 .	50 (11.1%)	17 (3.8%)	67 (14.8%)
	ABDOMINAL DISCOMFORT	0 .	1 (0.2%)	0 .	1 (0.2%)
	ABDOMINAL DISTENSION	0 .	1 (0.2%)	1 (0.2%)	2 (0.4%)
	ABDOMINAL PAIN	0 .	4 (0.9%)	1 (0.2%)	5 (1.1%)
	ABDOMINAL PAIN LOWER	0 .	1 (0.2%)	0 .	1 (0.2%)
	ABDOMINAL PAIN UPPER	0 .	3 (0.7%)	2 (0.4%)	5 (1.1%)
	ABDOMINAL SYMPTOM	0 .	1 (0.2%)	0 .	1 (0.2%)
	COLONIC POLYP	0 .	1 (0.2%)	0 .	1 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND RELATIONSHIP
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
3. WORST-CASE RELATIONSHIP IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. NR= UNLIKELY OR NOT RELATED TO TREATMENT, RELATED= SUSPECTED OR PROBABLY RELATED TO TREATMENT
5. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL

SB 207499

TABLE 15.3

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT, MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP=PLACEBO(N=452)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	MISSING	RELATIONSHIP NOT RELATED	RELATED	Total
GASTROINTESTINAL DISORDERS	CONSTIPATION	0 .	4 (0.9%)	0 .	4 (0.9%)
	DIARRHOEA	0 .	7 (1.5%)	6 (1.3%)	13 (2.9%)
	DIARRHOEA HAEMORRHAGIC	0 .	1 (0.2%)	0 .	1 (0.2%)
	DIVERTICULITIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	DIVERTICULUM INTESTINAL	0 .	3 (0.7%)	0 .	3 (0.7%)
	DRY MOUTH	0 .	1 (0.2%)	0 .	1 (0.2%)
	DUODENAL ULCER	0 .	1 (0.2%)	0 .	1 (0.2%)
	DYSPEPSIA	0 .	4 (0.9%)	2 (0.4%)	6 (1.3%)
	DYSPHAGIA	0 .	1 (0.2%)	0 .	1 (0.2%)
	FAECALOMA	0 .	1 (0.2%)	0 .	1 (0.2%)
	FAECES DISCOLOURED	0 .	1 (0.2%)	0 .	1 (0.2%)
	FAECES PALE	0 .	1 (0.2%)	0 .	1 (0.2%)
	FLATULENCE	0 .	1 (0.2%)	1 (0.2%)	2 (0.4%)
	FREQUENT BOWEL MOVEMENTS	0 .	2 (0.4%)	2 (0.4%)	4 (0.9%)
	GASTRIC ULCER	0 .	0 .	1 (0.2%)	1 (0.2%)
	GASTRITIS	0 .	3 (0.7%)	0 .	3 (0.7%)
	GASTROINTESTINAL OBSTRUCTION	0 .	1 (0.2%)	0 .	1 (0.2%)
	GASTROOESOPHAGEAL REFLUX DISEASE	0 .	1 (0.2%)	1 (0.2%)	2 (0.4%)
	GINGIVITIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	HAEMORRHOIDS	0 .	1 (0.2%)	0 .	1 (0.2%)
	HIATUS HERNIA	0 .	2 (0.4%)	0 .	2 (0.4%)
	ILEUS	0 .	1 (0.2%)	0 .	1 (0.2%)
	INGUINAL HERNIA	0 .	1 (0.2%)	0 .	1 (0.2%)
	INTESTINAL OBSTRUCTION	0 .	1 (0.2%)	0 .	1 (0.2%)
	INTESTINAL PERFORATION	0 .	1 (0.2%)	0 .	1 (0.2%)
	INTESTINAL POLYP	0 .	2 (0.4%)	0 .	2 (0.4%)
	LOOSE STOOLS	0 .	1 (0.2%)	1 (0.2%)	2 (0.4%)
	MOUTH ULCERATION	0 .	4 (0.9%)	0 .	4 (0.9%)
	NAUSEA	0 .	9 (2.0%)	5 (1.1%)	14 (3.1%)
	OESOPHAGITIS	0 .	2 (0.4%)	0 .	2 (0.4%)
	PANCREATITIS	0 .	1 (0.2%)	0 .	1 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND RELATIONSHIP
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
3. WORST-CASE RELATIONSHIP IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. NR= UNLIKELY OR NOT RELATED TO TREATMENT, RELATED= SUSPECTED OR PROBABLY RELATED TO TREATMENT
5. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL

SB 207499

TABLE 15.3

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT, MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP=PLACEBO(N=452)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	MISSING	RELATIONSHIP NOT RELATED	RELATED	Total
GASTROINTESTINAL DISORDERS	RECTAL HAEMORRHAGE	0 .	1 (0.2%)	0 .	1 (0.2%)
	REFLUX OESOPHAGITIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	TOOTHACHE	0 .	3 (0.7%)	0 .	3 (0.7%)
	VOMITING	0 .	5 (1.1%)	3 (0.7%)	8 (1.8%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	TOTAL	0 .	30 (6.6%)	4 (0.9%)	34 (7.5%)
	ASTHENIA	0 .	2 (0.4%)	0 .	2 (0.4%)
	AXILLARY PAIN	0 .	1 (0.2%)	0 .	1 (0.2%)
	CHEST DISCOMFORT	0 .	4 (0.9%)	0 .	4 (0.9%)
	CHEST PAIN	0 .	13 (2.9%)	0 .	13 (2.9%)
	FATIGUE	0 .	2 (0.4%)	0 .	2 (0.4%)
	FEELING HOT	0 .	0 .	1 (0.2%)	1 (0.2%)
	INFLUENZA LIKE ILLNESS	0 .	1 (0.2%)	0 .	1 (0.2%)
	LETHARGY	0 .	1 (0.2%)	1 (0.2%)	2 (0.4%)
	MALAISE	0 .	1 (0.2%)	0 .	1 (0.2%)
	OEDEMA	0 .	0 .	1 (0.2%)	1 (0.2%)
	OEDEMA PERIPHERAL	0 .	7 (1.5%)	1 (0.2%)	8 (1.8%)
	PAIN	0 .	1 (0.2%)	0 .	1 (0.2%)
	PYREXIA	0 .	2 (0.4%)	0 .	2 (0.4%)
	THIRST	0 .	1 (0.2%)	1 (0.2%)	2 (0.4%)
HEPATOBILIARY DISORDERS	TOTAL	0 .	6 (1.3%)	0 .	6 (1.3%)
	ALCOHOLIC LIVER DISEASE	0 .	1 (0.2%)	0 .	1 (0.2%)
	CHOLELITHIASIS	0 .	2 (0.4%)	0 .	2 (0.4%)
	HEPATIC STEATOSIS	0 .	3 (0.7%)	0 .	3 (0.7%)
IMMUNE SYSTEM DISORDERS	TOTAL	0 .	3 (0.7%)	0 .	3 (0.7%)
	ANAPHYLACTIC SHOCK	0 .	1 (0.2%)	0 .	1 (0.2%)
	HYPERSENSITIVITY	0 .	1 (0.2%)	0 .	1 (0.2%)
	SEASONAL ALLERGY	0 .	1 (0.2%)	0 .	1 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND RELATIONSHIP
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
3. WORST-CASE RELATIONSHIP IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. NR= UNLIKELY OR NOT RELATED TO TREATMENT, RELATED= SUSPECTED OR PROBABLY RELATED TO TREATMENT
5. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL

SB 207499

TABLE 15.3

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT,
MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP=PLACEBO(N=452)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	RELATIONSHIP MISSING	NOT RELATED	RELATED	Total
INFECTIONS AND INFESTATIONS	TOTAL	0 .	133 (29.4%)	0 .	133 (29.4%)
	BACTERIAL INFECTION	0 .	1 (0.2%)	0 .	1 (0.2%)
	BRONCHITIS	0 .	6 (1.3%)	0 .	6 (1.3%)
	BRONCHITIS ACUTE	0 .	2 (0.4%)	0 .	2 (0.4%)
	BRONCHOPNEUMONIA	0 .	3 (0.7%)	0 .	3 (0.7%)
	CANDIDIASIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	CYSTITIS	0 .	2 (0.4%)	0 .	2 (0.4%)
	DENTAL CARIES	0 .	1 (0.2%)	0 .	1 (0.2%)
	EAR INFECTION	0 .	5 (1.1%)	0 .	5 (1.1%)
	EAR LOBE INFECTION	0 .	1 (0.2%)	0 .	1 (0.2%)
	ERYSIPELAS	0 .	1 (0.2%)	0 .	1 (0.2%)
	FOLLICULITIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	FUNGAL INFECTION	0 .	1 (0.2%)	0 .	1 (0.2%)
	GASTROENTERITIS	0 .	7 (1.5%)	0 .	7 (1.5%)
	GASTROENTERITIS VIRAL	0 .	3 (0.7%)	0 .	3 (0.7%)
	HERPES SIMPLEX	0 .	1 (0.2%)	0 .	1 (0.2%)
	HERPES ZOSTER	0 .	2 (0.4%)	0 .	2 (0.4%)
	INFECTED INSECT BITE	0 .	1 (0.2%)	0 .	1 (0.2%)
	INFECTED SKIN ULCER	0 .	1 (0.2%)	0 .	1 (0.2%)
	INFECTION	0 .	1 (0.2%)	0 .	1 (0.2%)
	INFLUENZA	0 .	17 (3.8%)	0 .	17 (3.8%)
	LOBAR PNEUMONIA	0 .	1 (0.2%)	0 .	1 (0.2%)
	LOCALISED INFECTION	0 .	2 (0.4%)	0 .	2 (0.4%)
	LOWER RESPIRATORY TRACT INFECTION	0 .	4 (0.9%)	0 .	4 (0.9%)
	NASOPHARYNGITIS	0 .	54 (11.9%)	0 .	54 (11.9%)
	ONYCHOMYCOSIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	ORAL CANDIDIASIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	OROPHARYNGITIS FUNGAL	0 .	1 (0.2%)	0 .	1 (0.2%)
	PHARYNGITIS	0 .	2 (0.4%)	0 .	2 (0.4%)
	PNEUMONIA	0 .	3 (0.7%)	0 .	3 (0.7%)
	PNEUMONIA BACTERIAL	0 .	1 (0.2%)	0 .	1 (0.2%)
	PULPITIS DENTAL	0 .	1 (0.2%)	0 .	1 (0.2%)
	RESPIRATORY TRACT INFECTION	0 .	4 (0.9%)	0 .	4 (0.9%)
	SINUSITIS	0 .	7 (1.5%)	0 .	7 (1.5%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND RELATIONSHIP
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
3. WORST-CASE RELATIONSHIP IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. NR= UNLIKELY OR NOT RELATED TO TREATMENT, RELATED= SUSPECTED OR PROBABLY RELATED TO TREATMENT
5. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL

SB 207499

TABLE 15.3

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT, MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP=PLACEBO(N=452)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	RELATIONSHIP MISSING	NOT RELATED	RELATED	Total
INFECTIONS AND INFESTATIONS	STAPHYLOCOCCAL INFECTION	0 .	1 (0.2%)	0 .	1 (0.2%)
	TINEA INFECTION	0 .	1 (0.2%)	0 .	1 (0.2%)
	TONSILLITIS	0 .	2 (0.4%)	0 .	2 (0.4%)
	TOOTH ABSCESS	0 .	2 (0.4%)	0 .	2 (0.4%)
	TOOTH INFECTION	0 .	1 (0.2%)	0 .	1 (0.2%)
	UPPER RESPIRATORY TRACT INFECTION	0 .	11 (2.4%)	0 .	11 (2.4%)
	URINARY TRACT INFECTION	0 .	12 (2.7%)	0 .	12 (2.7%)
	VAGINAL MYCOSIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	VIRAL INFECTION	0 .	1 (0.2%)	0 .	1 (0.2%)
	VIRAL LABYRINTHITIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	VIRAL UPPER RESPIRATORY TRACT INFECTION	0 .	1 (0.2%)	0 .	1 (0.2%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	TOTAL	0 .	24 (5.3%)	0 .	24 (5.3%)
	ALCOHOL POISONING	0 .	1 (0.2%)	0 .	1 (0.2%)
	ANIMAL BITE	0 .	1 (0.2%)	0 .	1 (0.2%)
	ARTHROPOD BITE	0 .	1 (0.2%)	0 .	1 (0.2%)
	ARTHROPOD STING	0 .	1 (0.2%)	0 .	1 (0.2%)
	BACK INJURY	0 .	1 (0.2%)	0 .	1 (0.2%)
	BLISTER	0 .	2 (0.4%)	0 .	2 (0.4%)
	CONTUSION	0 .	2 (0.4%)	0 .	2 (0.4%)
	EPICONDYLITIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	FALL	0 .	2 (0.4%)	0 .	2 (0.4%)
	FOOT FRACTURE	0 .	1 (0.2%)	0 .	1 (0.2%)
	HAND FRACTURE	0 .	1 (0.2%)	0 .	1 (0.2%)
	HEART INJURY	0 .	1 (0.2%)	0 .	1 (0.2%)
	HIP FRACTURE	0 .	1 (0.2%)	0 .	1 (0.2%)
	HUMERUS FRACTURE	0 .	1 (0.2%)	0 .	1 (0.2%)
	JOINT SPRAIN	0 .	1 (0.2%)	0 .	1 (0.2%)
	LIMB INJURY	0 .	1 (0.2%)	0 .	1 (0.2%)
	MUSCLE INJURY	0 .	1 (0.2%)	0 .	1 (0.2%)
	MUSCLE STRAIN	0 .	1 (0.2%)	0 .	1 (0.2%)
	RIB FRACTURE	0 .	1 (0.2%)	0 .	1 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND RELATIONSHIP
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
3. WORST-CASE RELATIONSHIP IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. NR= UNLIKELY OR NOT RELATED TO TREATMENT, RELATED= SUSPECTED OR PROBABLY RELATED TO TREATMENT
5. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL

SB 207499

TABLE 15.3

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT, MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP=PLACEBO(N=452)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	MISSING	RELATIONSHIP NOT RELATED	RELATED	Total
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	SKELETAL INJURY	0 .	1 (0.2%)	0 .	1 (0.2%)
	SKIN LACERATION	0 .	1 (0.2%)	0 .	1 (0.2%)
	THERMAL BURN	0 .	1 (0.2%)	0 .	1 (0.2%)
	VACCINATION COMPLICATION	0 .	1 (0.2%)	0 .	1 (0.2%)
	WOUND	0 .	1 (0.2%)	0 .	1 (0.2%)
	WRIST FRACTURE	0 .	2 (0.4%)	0 .	2 (0.4%)
INVESTIGATIONS	TOTAL	0 .	31 (6.9%)	5 (1.1%)	36 (8.0%)
	ALANINE AMINOTRANSFERASE INCREASED	0 .	1 (0.2%)	3 (0.7%)	4 (0.9%)
	ASPARTATE AMINOTRANSFERASE INCREASED	0 .	1 (0.2%)	3 (0.7%)	4 (0.9%)
	BLOOD ALKALINE PHOSPHATASE INCREASED	0 .	3 (0.7%)	1 (0.2%)	4 (0.9%)
	BLOOD BILIRUBIN INCREASED	0 .	3 (0.7%)	1 (0.2%)	4 (0.9%)
	BLOOD CREATININE INCREASED	0 .	2 (0.4%)	0 .	2 (0.4%)
	BLOOD GLUCOSE INCREASED	0 .	2 (0.4%)	0 .	2 (0.4%)
	BLOOD IN STOOL	0 .	1 (0.2%)	0 .	1 (0.2%)
	BLOOD PRESSURE INCREASED	0 .	2 (0.4%)	0 .	2 (0.4%)
	BLOOD URIC ACID DECREASED	0 .	1 (0.2%)	0 .	1 (0.2%)
	BLOOD URINE	0 .	1 (0.2%)	0 .	1 (0.2%)
	BLOOD URINE PRESENT	0 .	4 (0.9%)	0 .	4 (0.9%)
	C-REACTIVE PROTEIN INCREASED	0 .	2 (0.4%)	0 .	2 (0.4%)
	ELECTROCARDIOGRAM P WAVE ABNORMAL	0 .	1 (0.2%)	0 .	1 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND RELATIONSHIP
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
3. WORST-CASE RELATIONSHIP IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. NR= UNLIKELY OR NOT RELATED TO TREATMENT, RELATED= SUSPECTED OR PROBABLY RELATED TO TREATMENT
5. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL

SB 207499

TABLE 15.3

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT, MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP=PLACEBO(N=452)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	MISSING	RELATIONSHIP NOT RELATED	RELATED	Total
INVESTIGATIONS	ELECTROCARDIOGRAM ST SEGMENT DEPRESSION	0 .	1 (0.2%)	0 .	1 (0.2%)
	FAECAL OCCULT BLOOD POSITIVE	0 .	2 (0.4%)	0 .	2 (0.4%)
	FORCED EXPIRATORY VOLUME DECREASED	0 .	1 (0.2%)	0 .	1 (0.2%)
	GAMMA-GLUTAMYLTRANSF ERASE INCREASED	0 .	5 (1.1%)	4 (0.9%)	9 (2.0%)
	HEPATIC ENZYME INCREASED	0 .	0 .	1 (0.2%)	1 (0.2%)
	PROTEIN URINE PRESENT	0 .	1 (0.2%)	0 .	1 (0.2%)
	URINARY OCCULT BLOOD POSITIVE	0 .	1 (0.2%)	0 .	1 (0.2%)
	WEIGHT DECREASED	0 .	1 (0.2%)	0 .	1 (0.2%)
	WEIGHT INCREASED	0 .	1 (0.2%)	0 .	1 (0.2%)
	WHITE BLOOD CELL COUNT INCREASED	0 .	1 (0.2%)	0 .	1 (0.2%)
METABOLISM AND NUTRITION DISORDERS	TOTAL	0 .	13 (2.9%)	4 (0.9%)	17 (3.8%)
	ANOREXIA	0 .	1 (0.2%)	0 .	1 (0.2%)
	DECREASED APPETITE	0 .	0 .	1 (0.2%)	1 (0.2%)
	DIABETES MELLITUS	0 .	6 (1.3%)	0 .	6 (1.3%)
	GLUCOSE TOLERANCE IMPAIRED	0 .	1 (0.2%)	0 .	1 (0.2%)
	HYPERCHOLESTEROLAEMI A	0 .	2 (0.4%)	0 .	2 (0.4%)
	HYPERGLYCAEMIA	0 .	3 (0.7%)	3 (0.7%)	6 (1.3%)
	HYPERURICAEMIA	0 .	1 (0.2%)	0 .	1 (0.2%)
	HYPOGLYCAEMIA	0 .	1 (0.2%)	0 .	1 (0.2%)
	HYPONATRAEMIA	0 .	1 (0.2%)	0 .	1 (0.2%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	TOTAL	0 .	52 (11.5%)	0 .	52 (11.5%)
	ARTHRALGIA	0 .	7 (1.5%)	0 .	7 (1.5%)
	ARTHRITIS	0 .	1 (0.2%)	0 .	1 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND RELATIONSHIP
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
3. WORST-CASE RELATIONSHIP IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. NR= UNLIKELY OR NOT RELATED TO TREATMENT, RELATED= SUSPECTED OR PROBABLY RELATED TO TREATMENT
5. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL

SB 207499

TABLE 15.3

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT, MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP=PLACEBO(N=452)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	MISSING	RELATIONSHIP NOT RELATED	RELATED	Total
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	BACK PAIN	0 .	20 (4.4%)	0 .	20 (4.4%)
	BURSITIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	FIBROMYALGIA	0 .	1 (0.2%)	0 .	1 (0.2%)
	JOINT SWELLING	0 .	2 (0.4%)	0 .	2 (0.4%)
	LOCAL SWELLING	0 .	1 (0.2%)	0 .	1 (0.2%)
	LOCALISED OSTEOARTHRITIS	0 .	2 (0.4%)	0 .	2 (0.4%)
	MONOARTHRITIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	MUSCLE CRAMP	0 .	3 (0.7%)	0 .	3 (0.7%)
	MUSCULOSKELETAL CHEST PAIN	0 .	1 (0.2%)	0 .	1 (0.2%)
	MUSCULOSKELETAL DISCOMFORT	0 .	1 (0.2%)	0 .	1 (0.2%)
	MYALGIA	0 .	2 (0.4%)	0 .	2 (0.4%)
	OSTEOARTHRITIS	0 .	3 (0.7%)	0 .	3 (0.7%)
	OSTEOPOROSIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	PAIN IN EXTREMITY	0 .	7 (1.5%)	0 .	7 (1.5%)
	SHOULDER BLADE PAIN	0 .	1 (0.2%)	0 .	1 (0.2%)
	SJOGREN'S SYNDROME	0 .	1 (0.2%)	0 .	1 (0.2%)
	SPINAL DISORDER	0 .	3 (0.7%)	0 .	3 (0.7%)
	TENDONITIS	0 .	1 (0.2%)	0 .	1 (0.2%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	TOTAL	0 .	9 (2.0%)	0 .	9 (2.0%)
	BASAL CELL CARCINOMA	0 .	1 (0.2%)	0 .	1 (0.2%)
	GASTRIC CANCER	0 .	1 (0.2%)	0 .	1 (0.2%)
	LUNG NEOPLASM MALIGNANT	0 .	1 (0.2%)	0 .	1 (0.2%)
	LUNG NODULE	0 .	1 (0.2%)	0 .	1 (0.2%)
	METASTASIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	PROSTATE CANCER	0 .	1 (0.2%)	0 .	1 (0.2%)
	RENAL CELL CARCINOMA STAGE UNSPECIFIED	0 .	1 (0.2%)	0 .	1 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND RELATIONSHIP
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
3. WORST-CASE RELATIONSHIP IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. NR= UNLIKELY OR NOT RELATED TO TREATMENT, RELATED= SUSPECTED OR PROBABLY RELATED TO TREATMENT
5. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL

SB 207499

TABLE 15.3

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT, MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP=PLACEBO(N=452)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	RELATIONSHIP MISSING	NOT RELATED	RELATED	Total
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	SEBORRHOEIC KERATOSIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	SQUAMOUS CELL CARCINOMA OF SKIN	0 .	2 (0.4%)	0 .	2 (0.4%)
	THYROID GLAND CANCER	0 .	1 (0.2%)	0 .	1 (0.2%)
NERVOUS SYSTEM DISORDERS	TOTAL	0 .	31 (6.9%)	6 (1.3%)	37 (8.2%)
	CARPAL TUNNEL SYNDROME	0 .	1 (0.2%)	0 .	1 (0.2%)
	CEREBRAL INFARCTION	0 .	1 (0.2%)	0 .	1 (0.2%)
	CEREBRAL THROMBOSIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	CEREBROVASCULAR ACCIDENT	0 .	1 (0.2%)	0 .	1 (0.2%)
	CEREBROVASCULAR DISORDER	0 .	1 (0.2%)	0 .	1 (0.2%)
	DIZZINESS	0 .	5 (1.1%)	0 .	5 (1.1%)
	DIZZINESS POSTURAL	0 .	1 (0.2%)	0 .	1 (0.2%)
	DYSGEUSIA	0 .	1 (0.2%)	0 .	1 (0.2%)
	ENCEPHALOPATHY	0 .	1 (0.2%)	0 .	1 (0.2%)
	ENTRAPMENT NEUROPATHY	0 .	1 (0.2%)	0 .	1 (0.2%)
	HEADACHE	0 .	16 (3.5%)	6 (1.3%)	22 (4.9%)
	MOTOR DYSFUNCTION	0 .	1 (0.2%)	0 .	1 (0.2%)
	NEUROPATHY	0 .	1 (0.2%)	0 .	1 (0.2%)
	PARAESTHESIA	0 .	2 (0.4%)	0 .	2 (0.4%)
	RADICULITIS LUMBOSACRAL	0 .	1 (0.2%)	0 .	1 (0.2%)
	SYNCOPE	0 .	2 (0.4%)	0 .	2 (0.4%)
	SYNCOPE VASOVAGAL	0 .	1 (0.2%)	0 .	1 (0.2%)
	TORTICOLLIS	0 .	1 (0.2%)	0 .	1 (0.2%)
PSYCHIATRIC DISORDERS	TOTAL	0 .	18 (4.0%)	2 (0.4%)	20 (4.4%)
	ABNORMAL DREAMS	0 .	1 (0.2%)	0 .	1 (0.2%)
	AFFECT LABILITY	0 .	1 (0.2%)	0 .	1 (0.2%)
	ALCOHOLISM	0 .	2 (0.4%)	0 .	2 (0.4%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND RELATIONSHIP
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
3. WORST-CASE RELATIONSHIP IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. NR= UNLIKELY OR NOT RELATED TO TREATMENT, RELATED= SUSPECTED OR PROBABLY RELATED TO TREATMENT
5. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL

SB 207499

TABLE 15.3

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT, MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP=PLACEBO(N=452)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	MISSING	RELATIONSHIP NOT RELATED	RELATED	Total
PSYCHIATRIC DISORDERS	ANXIETY	0 .	1 (0.2%)	0 .	1 (0.2%)
	BEREAVEMENT REACTION	0 .	1 (0.2%)	0 .	1 (0.2%)
	DEPRESSION	0 .	7 (1.5%)	0 .	7 (1.5%)
	INSOMNIA	0 .	4 (0.9%)	1 (0.2%)	5 (1.1%)
	MANIA	0 .	1 (0.2%)	0 .	1 (0.2%)
	NEUROSIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	PANIC ATTACK	0 .	1 (0.2%)	0 .	1 (0.2%)
	SLEEP DISORDER	0 .	0 .	1 (0.2%)	1 (0.2%)
RENAL AND URINARY DISORDERS	TOTAL	0 .	14 (3.1%)	3 (0.7%)	17 (3.8%)
	CALCULUS BLADDER	0 .	1 (0.2%)	0 .	1 (0.2%)
	CYSTITIS CHRONIC	0 .	1 (0.2%)	0 .	1 (0.2%)
	DYSURIA	0 .	1 (0.2%)	0 .	1 (0.2%)
	GLYCOSURIA	0 .	0 .	1 (0.2%)	1 (0.2%)
	HAEMATURIA	0 .	4 (0.9%)	0 .	4 (0.9%)
	NEPHROLITHIASIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	POLLAKIURIA	0 .	1 (0.2%)	1 (0.2%)	2 (0.4%)
	PROTEINURIA	0 .	2 (0.4%)	1 (0.2%)	3 (0.7%)
	RENAL COLIC	0 .	1 (0.2%)	0 .	1 (0.2%)
	RENAL CYST	0 .	1 (0.2%)	0 .	1 (0.2%)
	RENAL INSUFFICIENCY	0 .	1 (0.2%)	0 .	1 (0.2%)
	URINARY TRACT OBSTRUCTION	0 .	1 (0.2%)	0 .	1 (0.2%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	TOTAL	0 .	4 (0.9%)	0 .	4 (0.9%)
	GENITAL RASH	0 .	1 (0.2%)	0 .	1 (0.2%)
	PROSTATITIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	TESTICULAR PAIN	0 .	1 (0.2%)	0 .	1 (0.2%)
	TESTICULAR SWELLING	0 .	1 (0.2%)	0 .	1 (0.2%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	TOTAL	0 .	235 (52.0%)	7 (1.5%)	242 (53.5%)
	BRONCHOSPASM	0 .	1 (0.2%)	0 .	1 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND RELATIONSHIP
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
3. WORST-CASE RELATIONSHIP IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. NR= UNLIKELY OR NOT RELATED TO TREATMENT, RELATED= SUSPECTED OR PROBABLY RELATED TO TREATMENT
5. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL

SB 207499

TABLE 15.3

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT, MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP=PLACEBO(N=452)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	MISSING	RELATIONSHIP NOT RELATED	RELATED	Total
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE EXACERBATED	0 .	203 (44.9%)	6 (1.3%)	209 (46.2%)
	COUGH	0 .	11 (2.4%)	0 .	11 (2.4%)
	DRY THROAT	0 .	1 (0.2%)	0 .	1 (0.2%)
	DYSPNOEA	0 .	9 (2.0%)	0 .	9 (2.0%)
	DYSPNOEA EXACERBATED	0 .	1 (0.2%)	0 .	1 (0.2%)
	EPISTAXIS	0 .	5 (1.1%)	0 .	5 (1.1%)
	HAEMOPTYSIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	HOARSENESS	0 .	1 (0.2%)	0 .	1 (0.2%)
	HYPOXIA	0 .	1 (0.2%)	0 .	1 (0.2%)
	LUNG DISORDER	0 .	1 (0.2%)	1 (0.2%)	2 (0.4%)
	NASAL CONGESTION	0 .	1 (0.2%)	0 .	1 (0.2%)
	NASAL CYST	0 .	1 (0.2%)	0 .	1 (0.2%)
	NASAL MUCOSAL DISORDER	0 .	1 (0.2%)	0 .	1 (0.2%)
	NASAL POLYPS	0 .	1 (0.2%)	0 .	1 (0.2%)
	NASAL SEPTUM DEVIATION	0 .	1 (0.2%)	0 .	1 (0.2%)
	PHARYNGEAL ERYTHEMA	0 .	1 (0.2%)	0 .	1 (0.2%)
	PHARYNGOLARYNGEAL PAIN	0 .	16 (3.5%)	0 .	16 (3.5%)
	PLEURITIC PAIN	0 .	1 (0.2%)	0 .	1 (0.2%)
	PNEUMOTHORAX	0 .	1 (0.2%)	0 .	1 (0.2%)
	POSTNASAL DRIP	0 .	2 (0.4%)	0 .	2 (0.4%)
	PRODUCTIVE COUGH	0 .	1 (0.2%)	0 .	1 (0.2%)
	PULMONARY FIBROSIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	RHINITIS	0 .	11 (2.4%)	0 .	11 (2.4%)
	RHINITIS ALLERGIC	0 .	3 (0.7%)	0 .	3 (0.7%)
	RHINITIS SEASONAL	0 .	1 (0.2%)	0 .	1 (0.2%)
	RHINORRHOEA	0 .	4 (0.9%)	0 .	4 (0.9%)
	THROAT IRRITATION	0 .	1 (0.2%)	0 .	1 (0.2%)
	WHEEZING	0 .	3 (0.7%)	0 .	3 (0.7%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	TOTAL	0 .	16 (3.5%)	3 (0.7%)	19 (4.2%)
	DECUBITUS ULCER	0 .	1 (0.2%)	0 .	1 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND RELATIONSHIP
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
3. WORST-CASE RELATIONSHIP IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. NR= UNLIKELY OR NOT RELATED TO TREATMENT, RELATED= SUSPECTED OR PROBABLY RELATED TO TREATMENT
5. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL GM2004/00073/00 SB-207499/157

SB 207499

TABLE 15.3

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT, MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP=PLACEBO(N=452)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	MISSING	RELATIONSHIP NOT RELATED	RELATED	Total
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	DERMATITIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	DERMATITIS ALLERGIC	0 .	1 (0.2%)	0 .	1 (0.2%)
	DERMATITIS MEDICAMENTOSA	0 .	1 (0.2%)	0 .	1 (0.2%)
	DRY SKIN	0 .	1 (0.2%)	0 .	1 (0.2%)
	ECZEMA	0 .	3 (0.7%)	0 .	3 (0.7%)
	HEAT RASH	0 .	1 (0.2%)	0 .	1 (0.2%)
	HYPERHIDROSIS	0 .	0 .	1 (0.2%)	1 (0.2%)
	LICHEN PLANUS	0 .	1 (0.2%)	0 .	1 (0.2%)
	PRURITUS	0 .	2 (0.4%)	2 (0.4%)	4 (0.9%)
	PSORIASIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	RASH	0 .	2 (0.4%)	0 .	2 (0.4%)
	SEBORRHOEIC DERMATITIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	SKIN LESION	0 .	1 (0.2%)	0 .	1 (0.2%)
	SKIN ULCER	0 .	1 (0.2%)	0 .	1 (0.2%)
	STASIS DERMATITIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	URTICARIA	0 .	3 (0.7%)	0 .	3 (0.7%)
SOCIAL CIRCUMSTANCES	TOTAL	0 .	1 (0.2%)	0 .	1 (0.2%)
	ABSTAINS FROM ALCOHOL	0 .	1 (0.2%)	0 .	1 (0.2%)
SURGICAL AND MEDICAL PROCEDURES	TOTAL	0 .	2 (0.4%)	0 .	2 (0.4%)
	CATARACT EXTRACTION	0 .	2 (0.4%)	0 .	2 (0.4%)
VASCULAR DISORDERS	TOTAL	0 .	25 (5.5%)	1 (0.2%)	26 (5.8%)
	CIRCULATORY COLLAPSE	0 .	1 (0.2%)	0 .	1 (0.2%)
	HOT FLUSH	0 .	2 (0.4%)	1 (0.2%)	3 (0.7%)
	HYPERTENSION	0 .	18 (4.0%)	0 .	18 (4.0%)
	HYPERTENSIVE CRISIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	HYPOTENSION	0 .	1 (0.2%)	0 .	1 (0.2%)
	PALLOR	0 .	1 (0.2%)	0 .	1 (0.2%)
	PERIPHERAL COLDNESS	0 .	1 (0.2%)	0 .	1 (0.2%)
	THROMBOPHLEBITIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	VARICOSE ULCERATION	0 .	1 (0.2%)	0 .	1 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND RELATIONSHIP
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
3. WORST-CASE RELATIONSHIP IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. NR= UNLIKELY OR NOT RELATED TO TREATMENT, RELATED= SUSPECTED OR PROBABLY RELATED TO TREATMENT
5. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL

SB 207499

TABLE 15.3

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT,
MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP=SB 207499(N=455)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	MISSING	RELATIONSHIP NOT RELATED	RELATED	Total
TOTAL	TOTAL	0 .	253 (55.6%)	98 (21.5%)	351 (77.1%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	TOTAL	0 .	9 (2.0%)	0 .	9 (2.0%)
	ANAEMIA	0 .	2 (0.4%)	0 .	2 (0.4%)
	LEUKOCYTOSIS	0 .	4 (0.9%)	0 .	4 (0.9%)
	LYMPHADENOPATHY	0 .	1 (0.2%)	0 .	1 (0.2%)
	NEUTROPENIA	0 .	1 (0.2%)	0 .	1 (0.2%)
	POLYCYTHAEMIA	0 .	1 (0.2%)	0 .	1 (0.2%)
CARDIAC DISORDERS	TOTAL	0 .	35 (7.7%)	3 (0.7%)	38 (8.4%)
	ACUTE MYOCARDIAL INFARCTION	0 .	1 (0.2%)	0 .	1 (0.2%)
	AGE INDETERMINATE MYOCARDIAL INFARCTION	0 .	1 (0.2%)	0 .	1 (0.2%)
	ANGINA PECTORIS	0 .	2 (0.4%)	0 .	2 (0.4%)
	AORTIC VALVE CALCIFICATION	0 .	1 (0.2%)	0 .	1 (0.2%)
	ARRHYTHMIA	0 .	2 (0.4%)	0 .	2 (0.4%)
	ATRIAL FIBRILLATION	0 .	4 (0.9%)	0 .	4 (0.9%)
	ATRIAL FLUTTER	0 .	2 (0.4%)	0 .	2 (0.4%)
	BRADYARRHYTHMIA	0 .	1 (0.2%)	0 .	1 (0.2%)
	BUNDLE BRANCH BLOCK LEFT	0 .	1 (0.2%)	0 .	1 (0.2%)
	CARDIAC FAILURE	0 .	1 (0.2%)	0 .	1 (0.2%)
	CARDIAC FAILURE ACUTE	0 .	1 (0.2%)	0 .	1 (0.2%)
	CARDIAC FAILURE CONGESTIVE	0 .	2 (0.4%)	0 .	2 (0.4%)
	CORONARY ARTERY DISEASE	0 .	3 (0.7%)	0 .	3 (0.7%)
	CORONARY ARTERY INSUFFICIENCY	0 .	1 (0.2%)	0 .	1 (0.2%)
	MYOCARDIAL INFARCTION	0 .	1 (0.2%)	0 .	1 (0.2%)
	MYOCARDIAL ISCHAEMIA	0 .	2 (0.4%)	0 .	2 (0.4%)
	PALPITATIONS	0 .	3 (0.7%)	0 .	3 (0.7%)
	SINUS BRADYCARDIA	0 .	1 (0.2%)	0 .	1 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND RELATIONSHIP
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
3. WORST-CASE RELATIONSHIP IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. NR= UNLIKELY OR NOT RELATED TO TREATMENT, RELATED= SUSPECTED OR PROBABLY RELATED TO TREATMENT
5. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL

SB 207499

TABLE 15.3

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT, MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP=SB 207499(N=455)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	MISSING	RELATIONSHIP NOT RELATED	RELATED	Total
CARDIAC DISORDERS	SINUS TACHYCARDIA	0 .	4 (0.9%)	0 .	4 (0.9%)
	SUPRAVENTRICULAR EXTRASYSTOLES	0 .	2 (0.4%)	1 (0.2%)	3 (0.7%)
	SUPRAVENTRICULAR TACHYCARDIA	0 .	1 (0.2%)	1 (0.2%)	2 (0.4%)
	TACHYCARDIA	0 .	1 (0.2%)	0 .	1 (0.2%)
	VENTRICULAR EXTRASYSTOLES	0 .	0 .	1 (0.2%)	1 (0.2%)
	VENTRICULAR HYPERTROPHY	0 .	1 (0.2%)	0 .	1 (0.2%)
	VENTRICULAR TACHYCARDIA	0 .	0 .	1 (0.2%)	1 (0.2%)
EAR AND LABYRINTH DISORDERS	TOTAL	0 .	5 (1.1%)	0 .	5 (1.1%)
	EAR DISORDER	0 .	1 (0.2%)	0 .	1 (0.2%)
	EAR PAIN	0 .	1 (0.2%)	0 .	1 (0.2%)
	VERTIGO	0 .	3 (0.7%)	0 .	3 (0.7%)
EYE DISORDERS	TOTAL	0 .	7 (1.5%)	0 .	7 (1.5%)
	CATARACT	0 .	2 (0.4%)	0 .	2 (0.4%)
	CHALAZION	0 .	1 (0.2%)	0 .	1 (0.2%)
	CONJUNCTIVAL HAEMORRHAGE	0 .	1 (0.2%)	0 .	1 (0.2%)
	CONJUNCTIVITIS	0 .	2 (0.4%)	0 .	2 (0.4%)
	KERATOCONJUNCTIVITIS SICCA	0 .	1 (0.2%)	0 .	1 (0.2%)
GASTROINTESTINAL DISORDERS	TOTAL	0 .	57 (12.5%)	71 (15.6%)	128 (28.1%)
	ABDOMINAL DISCOMFORT	0 .	2 (0.4%)	0 .	2 (0.4%)
	ABDOMINAL DISTENSION	0 .	0 .	2 (0.4%)	2 (0.4%)
	ABDOMINAL PAIN	0 .	1 (0.2%)	8 (1.8%)	9 (2.0%)
	ABDOMINAL PAIN UPPER	0 .	4 (0.9%)	9 (2.0%)	13 (2.9%)
	ABNORMAL FAECES	0 .	1 (0.2%)	0 .	1 (0.2%)
	COLONIC HAEMORRHAGE	0 .	1 (0.2%)	0 .	1 (0.2%)
	COLONIC POLYP	0 .	1 (0.2%)	0 .	1 (0.2%)
	CONSTIPATION	0 .	4 (0.9%)	1 (0.2%)	5 (1.1%)
	DIARRHOEA	0 .	13 (2.9%)	20 (4.4%)	33 (7.3%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND RELATIONSHIP
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
3. WORST-CASE RELATIONSHIP IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. NR= UNLIKELY OR NOT RELATED TO TREATMENT, RELATED= SUSPECTED OR PROBABLY RELATED TO TREATMENT
5. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL

SB 207499

TABLE 15.3

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT,
MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP=SB 207499(N=455)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	RELATIONSHIP MISSING	NOT RELATED	RELATED	Total
GASTROINTESTINAL DISORDERS	DIVERTICULITIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	DIVERTICULUM	0 .	3 (0.7%)	0 .	3 (0.7%)
	DRY MOUTH	0 .	2 (0.4%)	0 .	2 (0.4%)
	DUODENAL ULCER	0 .	1 (0.2%)	1 (0.2%)	2 (0.4%)
	DYSPEPSIA	0 .	8 (1.8%)	10 (2.2%)	18 (4.0%)
	EPIGASTRIC DISCOMFORT	0 .	2 (0.4%)	0 .	2 (0.4%)
	FAECES DISCOLOURED	0 .	1 (0.2%)	0 .	1 (0.2%)
	FAECES HARD	0 .	1 (0.2%)	0 .	1 (0.2%)
	FLATULENCE	0 .	1 (0.2%)	1 (0.2%)	2 (0.4%)
	FOOD POISONING	0 .	1 (0.2%)	0 .	1 (0.2%)
	FREQUENT BOWEL MOVEMENTS	0 .	1 (0.2%)	2 (0.4%)	3 (0.7%)
	GASTRIC DISORDER	0 .	1 (0.2%)	0 .	1 (0.2%)
	GASTRIC ULCER	0 .	1 (0.2%)	0 .	1 (0.2%)
	GASTRITIS	0 .	1 (0.2%)	2 (0.4%)	3 (0.7%)
	GASTRODUODENITIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	GASTROINTESTINAL DISORDER	0 .	1 (0.2%)	1 (0.2%)	2 (0.4%)
	GASTROINTESTINAL UPSET	0 .	1 (0.2%)	0 .	1 (0.2%)
	GASTROOESOPHAGEAL REFLUX DISEASE	0 .	3 (0.7%)	0 .	3 (0.7%)
	GLOSSITIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	HAEMORRHOIDAL HAEMORRHAGE	0 .	1 (0.2%)	0 .	1 (0.2%)
	ILEUS	0 .	1 (0.2%)	0 .	1 (0.2%)
	INGUINAL HERNIA	0 .	4 (0.9%)	0 .	4 (0.9%)
	LOOSE STOOLS	0 .	1 (0.2%)	6 (1.3%)	7 (1.5%)
	NAUSEA	0 .	11 (2.4%)	33 (7.3%)	44 (9.7%)
	OESOPHAGITIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	PANCREATITIS	0 .	0 .	1 (0.2%)	1 (0.2%)
	PEPTIC ULCER	0 .	1 (0.2%)	0 .	1 (0.2%)
	RECTAL HAEMORRHAGE	0 .	1 (0.2%)	0 .	1 (0.2%)
	REFLUX OESOPHAGITIS	0 .	0 .	2 (0.4%)	2 (0.4%)
	TOOTH DISORDER	0 .	1 (0.2%)	0 .	1 (0.2%)
	TOOTHACHE	0 .	2 (0.4%)	0 .	2 (0.4%)
	UMBILICAL HERNIA	0 .	1 (0.2%)	0 .	1 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND RELATIONSHIP
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
3. WORST-CASE RELATIONSHIP IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. NR= UNLIKELY OR NOT RELATED TO TREATMENT, RELATED= SUSPECTED OR PROBABLY RELATED TO TREATMENT
5. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL GM2004/00073/00 SB-207499/157

SB 207499

TABLE 15.3

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT, MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP=SB 207499(N=455)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	MISSING	RELATIONSHIP NOT RELATED	RELATED	Total
GASTROINTESTINAL DISORDERS	VOMITING	0 .	10 (2.2%)	11 (2.4%)	21 (4.6%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	TOTAL	0 .	27 (5.9%)	5 (1.1%)	32 (7.0%)
	ASTHENIA	0 .	2 (0.4%)	0 .	2 (0.4%)
	CHEST DISCOMFORT	0 .	5 (1.1%)	0 .	5 (1.1%)
	CHEST PAIN	0 .	5 (1.1%)	0 .	5 (1.1%)
	FATIGUE	0 .	5 (1.1%)	3 (0.7%)	8 (1.8%)
	FEELING ABNORMAL	0 .	0 .	1 (0.2%)	1 (0.2%)
	INFLUENZA LIKE ILLNESS	0 .	3 (0.7%)	0 .	3 (0.7%)
	LETHARGY	0 .	0 .	1 (0.2%)	1 (0.2%)
	MALAISE	0 .	2 (0.4%)	0 .	2 (0.4%)
	OEDEMA PERIPHERAL	0 .	3 (0.7%)	0 .	3 (0.7%)
	PAIN	0 .	2 (0.4%)	0 .	2 (0.4%)
	PYREXIA	0 .	2 (0.4%)	0 .	2 (0.4%)
	THIRST	0 .	0 .	1 (0.2%)	1 (0.2%)
HEPATOBILIARY DISORDERS	TOTAL	0 .	8 (1.8%)	0 .	8 (1.8%)
	BILIARY COLIC	0 .	1 (0.2%)	0 .	1 (0.2%)
	CHOLECYSTITIS CHRONIC	0 .	1 (0.2%)	0 .	1 (0.2%)
	CHOLELITHIASIS	0 .	3 (0.7%)	0 .	3 (0.7%)
	CHRONIC HEPATITIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	HEPATIC STEATOSIS	0 .	3 (0.7%)	0 .	3 (0.7%)
IMMUNE SYSTEM DISORDERS	TOTAL	0 .	2 (0.4%)	0 .	2 (0.4%)
	HYPERSENSITIVITY	0 .	1 (0.2%)	0 .	1 (0.2%)
	SEASONAL ALLERGY	0 .	1 (0.2%)	0 .	1 (0.2%)
INFECTIONS AND INFESTATIONS	TOTAL	0 .	125 (27.5%)	1 (0.2%)	126 (27.7%)
	BLADDER INFECTION	0 .	1 (0.2%)	0 .	1 (0.2%)
	BRONCHITIS	0 .	6 (1.3%)	0 .	6 (1.3%)
	BRONCHITIS ACUTE	0 .	1 (0.2%)	0 .	1 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND RELATIONSHIP
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
3. WORST-CASE RELATIONSHIP IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. NR= UNLIKELY OR NOT RELATED TO TREATMENT, RELATED= SUSPECTED OR PROBABLY RELATED TO TREATMENT
5. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL

SB 207499

TABLE 15.3

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT, MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP=SB 207499(N=455)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	RELATIONSHIP MISSING	NOT RELATED	RELATED	Total
INFECTIONS AND INFESTATIONS	BRONCHITIS ACUTE VIRAL	0 .	1 (0.2%)	0 .	1 (0.2%)
	BRONCHITIS VIRAL	0 .	1 (0.2%)	0 .	1 (0.2%)
	BRONCHOPNEUMONIA	0 .	1 (0.2%)	0 .	1 (0.2%)
	CANDIDIASIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	CHRONIC SINUSITIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	CYSTITIS	0 .	2 (0.4%)	0 .	2 (0.4%)
	CYSTITIS ACUTE	0 .	1 (0.2%)	0 .	1 (0.2%)
	EAR INFECTION	0 .	3 (0.7%)	0 .	3 (0.7%)
	EYE INFECTION	0 .	2 (0.4%)	0 .	2 (0.4%)
	FUNGAL INFECTION	0 .	3 (0.7%)	0 .	3 (0.7%)
	FURUNCLE	0 .	1 (0.2%)	0 .	1 (0.2%)
	GASTRIC INFECTION	0 .	1 (0.2%)	0 .	1 (0.2%)
	GASTROENTERITIS	0 .	2 (0.4%)	1 (0.2%)	3 (0.7%)
	GASTROENTERITIS VIRAL	0 .	3 (0.7%)	0 .	3 (0.7%)
	HELICOBACTER GASTRITIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	HELICOBACTER INFECTION	0 .	1 (0.2%)	0 .	1 (0.2%)
	HERPES SIMPLEX	0 .	1 (0.2%)	0 .	1 (0.2%)
	HERPES ZOSTER	0 .	4 (0.9%)	0 .	4 (0.9%)
	HORDEOLUM	0 .	1 (0.2%)	0 .	1 (0.2%)
	INFECTED SEBACEOUS CYST	0 .	1 (0.2%)	0 .	1 (0.2%)
	INFLUENZA	0 .	14 (3.1%)	0 .	14 (3.1%)
	JOINT ABSCESS	0 .	1 (0.2%)	0 .	1 (0.2%)
	LOBAR PNEUMONIA	0 .	1 (0.2%)	0 .	1 (0.2%)
	LOWER RESPIRATORY TRACT INFECTION	0 .	6 (1.3%)	0 .	6 (1.3%)
	NASOPHARYNGITIS	0 .	43 (9.5%)	0 .	43 (9.5%)
	ONYCHOMYCOSIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	ORAL CANDIDIASIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	ORAL FUNGAL INFECTION	0 .	1 (0.2%)	0 .	1 (0.2%)
	OTITIS EXTERNA	0 .	1 (0.2%)	0 .	1 (0.2%)
	PHARYNGITIS	0 .	6 (1.3%)	0 .	6 (1.3%)
	PNEUMONIA	0 .	5 (1.1%)	0 .	5 (1.1%)
	PNEUMONIA CHLAMYDIAL	0 .	1 (0.2%)	0 .	1 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND RELATIONSHIP
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
3. WORST-CASE RELATIONSHIP IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. NR= UNLIKELY OR NOT RELATED TO TREATMENT, RELATED= SUSPECTED OR PROBABLY RELATED TO TREATMENT
5. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL

SB 207499

TABLE 15.3

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT,
MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP=SB 207499(N=455)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	RELATIONSHIP MISSING	NOT RELATED	RELATED	Total
INFECTIONS AND INFESTATIONS	RESPIRATORY TRACT INFECTION	0 .	5 (1.1%)	0 .	5 (1.1%)
	RHINITIS INFECTIVE	0 .	1 (0.2%)	0 .	1 (0.2%)
	SALPINGITIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	SINUSITIS	0 .	4 (0.9%)	0 .	4 (0.9%)
	SKIN INFECTION	0 .	1 (0.2%)	0 .	1 (0.2%)
	TINEA PEDIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	TOOTH ABSCESS	0 .	1 (0.2%)	0 .	1 (0.2%)
	TOOTH INFECTION	0 .	1 (0.2%)	0 .	1 (0.2%)
	UPPER RESPIRATORY TRACT INFECTION	0 .	12 (2.6%)	0 .	12 (2.6%)
	URINARY TRACT INFECTION	0 .	2 (0.4%)	0 .	2 (0.4%)
	VIRAL UPPER RESPIRATORY TRACT INFECTION	0 .	2 (0.4%)	0 .	2 (0.4%)
	VULVITIS	0 .	1 (0.2%)	0 .	1 (0.2%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	TOTAL	0 .	24 (5.3%)	0 .	24 (5.3%)
	ANIMAL BITE	0 .	1 (0.2%)	0 .	1 (0.2%)
	BACK INJURY	0 .	1 (0.2%)	0 .	1 (0.2%)
	BLISTER	0 .	2 (0.4%)	0 .	2 (0.4%)
	CHEST INJURY	0 .	2 (0.4%)	0 .	2 (0.4%)
	CONTRAST MEDIA REACTION	0 .	1 (0.2%)	0 .	1 (0.2%)
	CONTUSION	0 .	3 (0.7%)	0 .	3 (0.7%)
	EPICONDYLITIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	FALL	0 .	1 (0.2%)	0 .	1 (0.2%)
	JOINT INJURY	0 .	4 (0.9%)	0 .	4 (0.9%)
	LIMB INJURY	0 .	2 (0.4%)	0 .	2 (0.4%)
	MUSCLE STRAIN	0 .	2 (0.4%)	0 .	2 (0.4%)
	POST PROCEDURAL PAIN	0 .	1 (0.2%)	0 .	1 (0.2%)
	RADIATION ASSOCIATED PAIN	0 .	1 (0.2%)	0 .	1 (0.2%)
	RADIUS FRACTURE	0 .	1 (0.2%)	0 .	1 (0.2%)
	RIB FRACTURE	0 .	2 (0.4%)	0 .	2 (0.4%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND RELATIONSHIP
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
3. WORST-CASE RELATIONSHIP IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. NR= UNLIKELY OR NOT RELATED TO TREATMENT, RELATED= SUSPECTED OR PROBABLY RELATED TO TREATMENT
5. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL

SB 207499

TABLE 15.3

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT, MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP=SB 207499(N=455)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	RELATIONSHIP MISSING	NOT RELATED	RELATED	Total
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	ROAD TRAFFIC ACCIDENT	0 .	1 (0.2%)	0 .	1 (0.2%)
	SKIN LACERATION	0 .	2 (0.4%)	0 .	2 (0.4%)
	TENDON INJURY	0 .	1 (0.2%)	0 .	1 (0.2%)
	TOOTH INJURY	0 .	1 (0.2%)	0 .	1 (0.2%)
INVESTIGATIONS	TOTAL	0 .	29 (6.4%)	5 (1.1%)	34 (7.5%)
	ALANINE AMINOTRANSFERASE INCREASED	0 .	1 (0.2%)	0 .	1 (0.2%)
	ASPARTATE AMINOTRANSFERASE INCREASED	0 .	1 (0.2%)	0 .	1 (0.2%)
	BLOOD ALKALINE PHOSPHATASE INCREASED	0 .	1 (0.2%)	0 .	1 (0.2%)
	BLOOD BILIRUBIN INCREASED	0 .	0 .	1 (0.2%)	1 (0.2%)
	BLOOD GLUCOSE INCREASED	0 .	4 (0.9%)	0 .	4 (0.9%)
	BLOOD HOMOCYSTEINE DECREASED	0 .	1 (0.2%)	0 .	1 (0.2%)
	BLOOD IN STOOL	0 .	2 (0.4%)	1 (0.2%)	3 (0.7%)
	BLOOD PRESSURE INCREASED	0 .	2 (0.4%)	0 .	2 (0.4%)
	BLOOD SODIUM DECREASED	0 .	1 (0.2%)	0 .	1 (0.2%)
	BODY TEMPERATURE INCREASED	0 .	2 (0.4%)	0 .	2 (0.4%)
	C-REACTIVE PROTEIN INCREASED	0 .	2 (0.4%)	0 .	2 (0.4%)
	ECG SIGNS OF MYOCARDIAL ISCHAEMIA	0 .	1 (0.2%)	0 .	1 (0.2%)
	EJECTION FRACTION DECREASED	0 .	1 (0.2%)	0 .	1 (0.2%)
	ELECTROCARDIOGRAM T WAVE INVERSION	0 .	1 (0.2%)	0 .	1 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND RELATIONSHIP
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
3. WORST-CASE RELATIONSHIP IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. NR= UNLIKELY OR NOT RELATED TO TREATMENT, RELATED= SUSPECTED OR PROBABLY RELATED TO TREATMENT
5. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL

SB 207499

TABLE 15.3

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT, MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP=SB 207499(N=455)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	RELATIONSHIP MISSING	NOT RELATED	RELATED	Total
INVESTIGATIONS	GAMMA-GLUTAMYLTRANSF ERASE INCREASED	0 .	3 (0.7%)	0 .	3 (0.7%)
	HEART RATE INCREASED	0 .	2 (0.4%)	0 .	2 (0.4%)
	HEPATIC ENZYME INCREASED	0 .	2 (0.4%)	0 .	2 (0.4%)
	PLATELET COUNT INCREASED	0 .	1 (0.2%)	0 .	1 (0.2%)
	QRS AXIS ABNORMAL	0 .	1 (0.2%)	0 .	1 (0.2%)
	SPUTUM INCREASED	0 .	1 (0.2%)	1 (0.2%)	2 (0.4%)
	SPUTUM TEST	0 .	1 (0.2%)	0 .	1 (0.2%)
	URINARY OCCULT BLOOD POSITIVE	0 .	1 (0.2%)	0 .	1 (0.2%)
	URINE KETONE BODY PRESENT	0 .	1 (0.2%)	0 .	1 (0.2%)
	WEIGHT DECREASED	0 .	3 (0.7%)	2 (0.4%)	5 (1.1%)
METABOLISM AND NUTRITION DISORDERS	TOTAL	0 .	30 (6.6%)	7 (1.5%)	37 (8.1%)
	ABDOMINAL OBESITY	0 .	1 (0.2%)	0 .	1 (0.2%)
	ANOREXIA	0 .	11 (2.4%)	7 (1.5%)	18 (4.0%)
	DECREASED APPETITE	0 .	2 (0.4%)	0 .	2 (0.4%)
	DIABETES MELLITUS	0 .	3 (0.7%)	0 .	3 (0.7%)
	GOUT	0 .	4 (0.9%)	0 .	4 (0.9%)
	HYPERCHOLESTEROLAEMI A	0 .	1 (0.2%)	0 .	1 (0.2%)
	HYPERGLYCAEMIA	0 .	6 (1.3%)	0 .	6 (1.3%)
	HYPERLIPIDAEMIA	0 .	1 (0.2%)	0 .	1 (0.2%)
	HYPERURICAEMIA	0 .	1 (0.2%)	0 .	1 (0.2%)
	HYPOKALAEMIA	0 .	2 (0.4%)	0 .	2 (0.4%)
	VITAMIN B12 DEFICIENCY	0 .	2 (0.4%)	0 .	2 (0.4%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	TOTAL	0 .	35 (7.7%)	1 (0.2%)	36 (7.9%)
	ARTHRALGIA	0 .	5 (1.1%)	0 .	5 (1.1%)
	BACK PAIN	0 .	6 (1.3%)	0 .	6 (1.3%)
	BONE PAIN	0 .	1 (0.2%)	0 .	1 (0.2%)
	BURSITIS	0 .	3 (0.7%)	0 .	3 (0.7%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND RELATIONSHIP
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
3. WORST-CASE RELATIONSHIP IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. NR= UNLIKELY OR NOT RELATED TO TREATMENT, RELATED= SUSPECTED OR PROBABLY RELATED TO TREATMENT
5. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL

SB 207499

TABLE 15.3

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT, MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP=SB 207499(N=455)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	MISSING	RELATIONSHIP NOT RELATED	RELATED	Total
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	FASCIITIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	JOINT EFFUSION	0 .	1 (0.2%)	0 .	1 (0.2%)
	JOINT SWELLING	0 .	1 (0.2%)	0 .	1 (0.2%)
	MONOARTHRITIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	MUSCLE CRAMP	0 .	1 (0.2%)	0 .	1 (0.2%)
	MUSCLE RIGIDITY	0 .	1 (0.2%)	1 (0.2%)	2 (0.4%)
	MUSCLE TIGHTNESS	0 .	1 (0.2%)	0 .	1 (0.2%)
	MUSCULOSKELETAL PAIN	0 .	1 (0.2%)	0 .	1 (0.2%)
	MYALGIA	0 .	3 (0.7%)	0 .	3 (0.7%)
	OSTEOARTHRITIS	0 .	3 (0.7%)	0 .	3 (0.7%)
	OSTEOPOROSIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	PAIN IN EXTREMITY	0 .	5 (1.1%)	0 .	5 (1.1%)
	PERIARTHRITIS	0 .	2 (0.4%)	0 .	2 (0.4%)
	RHEUMATOID ARTHRITIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	SPINAL DISORDER	0 .	2 (0.4%)	0 .	2 (0.4%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	TOTAL	0 .	4 (0.9%)	0 .	4 (0.9%)
	BLADDER CANCER	0 .	1 (0.2%)	0 .	1 (0.2%)
	LUNG NEOPLASM MALIGNANT	0 .	1 (0.2%)	0 .	1 (0.2%)
	SKIN PAPILLOMA	0 .	1 (0.2%)	0 .	1 (0.2%)
	SQUAMOUS CELL CARCINOMA	0 .	1 (0.2%)	0 .	1 (0.2%)
NERVOUS SYSTEM DISORDERS	TOTAL	0 .	35 (7.7%)	20 (4.4%)	55 (12.1%)
	CEREBROVASCULAR ACCIDENT	0 .	1 (0.2%)	0 .	1 (0.2%)
	CEREBROVASCULAR DISORDER	0 .	1 (0.2%)	0 .	1 (0.2%)
	CONVULSION	0 .	1 (0.2%)	0 .	1 (0.2%)
	DISTURBANCE IN ATTENTION	0 .	0 .	1 (0.2%)	1 (0.2%)
	DIZZINESS	0 .	6 (1.3%)	7 (1.5%)	13 (2.9%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND RELATIONSHIP
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
3. WORST-CASE RELATIONSHIP IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. NR= UNLIKELY OR NOT RELATED TO TREATMENT, RELATED= SUSPECTED OR PROBABLY RELATED TO TREATMENT
5. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL

SB 207499

TABLE 15.3

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT, MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP=SB 207499(N=455)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	MISSING	RELATIONSHIP NOT RELATED	RELATED	Total
NERVOUS SYSTEM DISORDERS	DIZZINESS POSTURAL	0 .	1 (0.2%)	0 .	1 (0.2%)
	DYSGEUSIA	0 .	0 .	1 (0.2%)	1 (0.2%)
	FACIAL PALSY	0 .	2 (0.4%)	0 .	2 (0.4%)
	HEADACHE	0 .	23 (5.1%)	12 (2.6%)	35 (7.7%)
	HYPOAESTHESIA	0 .	1 (0.2%)	0 .	1 (0.2%)
	LUMBAR SPINAL STENOSIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	PARKINSON'S DISEASE	0 .	1 (0.2%)	0 .	1 (0.2%)
	SPINAL COLUMN STENOSIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	SYNCOPE	0 .	1 (0.2%)	1 (0.2%)	2 (0.4%)
	TRANSIENT ISCHAEMIC ATTACK	0 .	1 (0.2%)	0 .	1 (0.2%)
	TREMOR	0 .	1 (0.2%)	1 (0.2%)	2 (0.4%)
	VERTEBRAL ARTERY OCCLUSION	0 .	1 (0.2%)	0 .	1 (0.2%)
PSYCHIATRIC DISORDERS	TOTAL	0 .	16 (3.5%)	7 (1.5%)	23 (5.1%)
	AFFECT LABILITY	0 .	1 (0.2%)	0 .	1 (0.2%)
	ANXIETY	0 .	6 (1.3%)	1 (0.2%)	7 (1.5%)
	DEPRESSION	0 .	6 (1.3%)	1 (0.2%)	7 (1.5%)
	EMOTIONAL DISTRESS	0 .	0 .	1 (0.2%)	1 (0.2%)
	INSOMNIA	0 .	1 (0.2%)	1 (0.2%)	2 (0.4%)
	MIDDLE INSOMNIA	0 .	0 .	1 (0.2%)	1 (0.2%)
	PANIC ATTACK	0 .	1 (0.2%)	0 .	1 (0.2%)
	SLEEP DISORDER	0 .	2 (0.4%)	2 (0.4%)	4 (0.9%)
RENAL AND URINARY DISORDERS	TOTAL	0 .	14 (3.1%)	0 .	14 (3.1%)
	HAEMATURIA	0 .	3 (0.7%)	0 .	3 (0.7%)
	HYPERTONIC BLADDER	0 .	1 (0.2%)	0 .	1 (0.2%)
	KIDNEY HYPERMOBILITY	0 .	1 (0.2%)	0 .	1 (0.2%)
	NEPHROLITHIASIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	NOCTURIA	0 .	1 (0.2%)	0 .	1 (0.2%)
	PROTEINURIA	0 .	4 (0.9%)	0 .	4 (0.9%)
	RENAL COLIC	0 .	2 (0.4%)	0 .	2 (0.4%)
	RENAL IMPAIRMENT	0 .	1 (0.2%)	0 .	1 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND RELATIONSHIP
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
3. WORST-CASE RELATIONSHIP IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. NR= UNLIKELY OR NOT RELATED TO TREATMENT, RELATED= SUSPECTED OR PROBABLY RELATED TO TREATMENT
5. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL

SB 207499

TABLE 15.3

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT, MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP=SB 207499(N=455)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	MISSING	RELATIONSHIP NOT RELATED	RELATED	Total
RENAL AND URINARY DISORDERS	STRANGURY	0 .	1 (0.2%)	0 .	1 (0.2%)
	URINARY RETENTION	0 .	1 (0.2%)	0 .	1 (0.2%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	TOTAL	0 .	8 (1.8%)	0 .	8 (1.8%)
	BENIGN PROSTATIC HYPERPLASIA	0 .	1 (0.2%)	0 .	1 (0.2%)
	EPIDIDYMITIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	GYNAECOMASTIA	0 .	1 (0.2%)	0 .	1 (0.2%)
	PROSTATIC HYPERTROPHY	0 .	1 (0.2%)	0 .	1 (0.2%)
	PROSTATISM	0 .	1 (0.2%)	0 .	1 (0.2%)
	PROSTATITIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	SEXUAL DYSFUNCTION	0 .	1 (0.2%)	0 .	1 (0.2%)
	VAGINAL HAEMORRHAGE	0 .	1 (0.2%)	0 .	1 (0.2%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	TOTAL	0 .	210 (46.2%)	10 (2.2%)	220 (48.4%)
	ACUTE RESPIRATORY FAILURE	0 .	1 (0.2%)	0 .	1 (0.2%)
	CATARRH	0 .	1 (0.2%)	0 .	1 (0.2%)
	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE EXACERBATED	0 .	183 (40.2%)	8 (1.8%)	191 (42.0%)
	COUGH	0 .	14 (3.1%)	0 .	14 (3.1%)
	DYSPHONIA	0 .	1 (0.2%)	0 .	1 (0.2%)
	DYSPNOEA	0 .	2 (0.4%)	1 (0.2%)	3 (0.7%)
	DYSPNOEA EXACERBATED	0 .	7 (1.5%)	0 .	7 (1.5%)
	EPISTAXIS	0 .	4 (0.9%)	0 .	4 (0.9%)
	INCREASED BRONCHIAL SECRETION	0 .	1 (0.2%)	0 .	1 (0.2%)
	NASAL CONGESTION	0 .	2 (0.4%)	0 .	2 (0.4%)
	NASAL SEPTUM DEVIATION	0 .	1 (0.2%)	0 .	1 (0.2%)
	PHARYNGOLARYNGEAL PAIN	0 .	6 (1.3%)	0 .	6 (1.3%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND RELATIONSHIP
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
3. WORST-CASE RELATIONSHIP IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. NR= UNLIKELY OR NOT RELATED TO TREATMENT, RELATED= SUSPECTED OR PROBABLY RELATED TO TREATMENT
5. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL

SB 207499

TABLE 15.3

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT, MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP=SB 207499(N=455)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	RELATIONSHIP MISSING	NOT RELATED	RELATED	Total
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	PLEURISY	0 .	1 (0.2%)	0 .	1 (0.2%)
	POSTNASAL DRIP	0 .	2 (0.4%)	0 .	2 (0.4%)
	RESPIRATORY ALKALOSIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	RHINITIS	0 .	12 (2.6%)	0 .	12 (2.6%)
	RHINITIS ALLERGIC	0 .	4 (0.9%)	0 .	4 (0.9%)
	RHINORRHOEA	0 .	2 (0.4%)	0 .	2 (0.4%)
	THROAT IRRITATION	1 (0.2%)	1 (0.2%)	0 .	2 (0.4%)
	WHEEZING	0 .	1 (0.2%)	1 (0.2%)	2 (0.4%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	TOTAL	0 .	15 (3.3%)	3 (0.7%)	18 (4.0%)
	DERMATITIS CONTACT	0 .	1 (0.2%)	0 .	1 (0.2%)
	DRY SKIN	0 .	1 (0.2%)	0 .	1 (0.2%)
	ECZEMA	0 .	2 (0.4%)	0 .	2 (0.4%)
	HYPERHIDROSIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	NEURODERMATITIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	PRURITUS	0 .	3 (0.7%)	1 (0.2%)	4 (0.9%)
	RASH	0 .	1 (0.2%)	0 .	1 (0.2%)
	RASH PRURITIC	0 .	0 .	1 (0.2%)	1 (0.2%)
	SKIN ATROPHY	0 .	1 (0.2%)	0 .	1 (0.2%)
	SKIN BURNING SENSATION	0 .	1 (0.2%)	0 .	1 (0.2%)
	SKIN HYPERTROPHY	0 .	1 (0.2%)	0 .	1 (0.2%)
	SKIN LESION	0 .	1 (0.2%)	0 .	1 (0.2%)
	URTICARIA	0 .	3 (0.7%)	1 (0.2%)	4 (0.9%)
	URTICARIA PAPULAR	0 .	1 (0.2%)	0 .	1 (0.2%)
	VASCULAR SKIN DISORDER	0 .	1 (0.2%)	0 .	1 (0.2%)
SOCIAL CIRCUMSTANCES	TOTAL	0 .	1 (0.2%)	0 .	1 (0.2%)
	ALCOHOL USE	0 .	1 (0.2%)	0 .	1 (0.2%)
SURGICAL AND MEDICAL PROCEDURES	TOTAL	0 .	1 (0.2%)	0 .	1 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND RELATIONSHIP
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
3. WORST-CASE RELATIONSHIP IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. NR= UNLIKELY OR NOT RELATED TO TREATMENT, RELATED= SUSPECTED OR PROBABLY RELATED TO TREATMENT
5. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL

SB 207499

TABLE 15.3

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT,
MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP=SB 207499(N=455)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	RELATIONSHIP MISSING	NOT RELATED	RELATED	Total
SURGICAL AND MEDICAL PROCEDURES	TOOTH EXTRACTION	0 .	1 (0.2%)	0 .	1 (0.2%)
VASCULAR DISORDERS	TOTAL	0 .	21 (4.6%)	1 (0.2%)	22 (4.8%)
	AORTIC ANEURYSM	0 .	1 (0.2%)	0 .	1 (0.2%)
	AORTIC DISSECTION	0 .	1 (0.2%)	0 .	1 (0.2%)
	CIRCULATORY COLLAPSE	0 .	1 (0.2%)	0 .	1 (0.2%)
	DIASTOLIC HYPERTENSION	0 .	1 (0.2%)	0 .	1 (0.2%)
	HAEMATOMA	0 .	1 (0.2%)	0 .	1 (0.2%)
	HOT FLUSH	0 .	0 .	1 (0.2%)	1 (0.2%)
	HYPERTENSION	0 .	13 (2.9%)	0 .	13 (2.9%)
	HYPOTENSION	0 .	2 (0.4%)	0 .	2 (0.4%)
	ORTHOSTATIC HYPOTENSION	0 .	1 (0.2%)	0 .	1 (0.2%)
	PHLEBITIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	VARICOSE VEIN	0 .	1 (0.2%)	0 .	1 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND RELATIONSHIP
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
3. WORST-CASE RELATIONSHIP IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. NR= UNLIKELY OR NOT RELATED TO TREATMENT, RELATED= SUSPECTED OR PROBABLY RELATED TO TREATMENT
5. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL

SB 207499

TABLE 15.4

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY,
MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP=PLACEBO (N=452)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	Intensity Mild	Moderate	Severe	Total
TOTAL	TOTAL	96 (21.2%)	197 (43.6%)	50 (11.1%)	343 (75.9%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	TOTAL	8 (1.8%)	4 (0.9%)	1 (0.2%)	13 (2.9%)
	ANAEMIA	1 (0.2%)	1 (0.2%)	0 .	2 (0.4%)
	EOSINOPHILIA	0 .	1 (0.2%)	0 .	1 (0.2%)
	IRON DEFICIENCY ANAEMIA	0 .	0 .	1 (0.2%)	1 (0.2%)
	LEUKOCYTOSIS	3 (0.7%)	0 .	0 .	3 (0.7%)
	LEUKOPENIA	2 (0.4%)	0 .	0 .	2 (0.4%)
	LYMPHADENOPATHY	0 .	1 (0.2%)	0 .	1 (0.2%)
	NEUTROPHILIA	0 .	1 (0.2%)	0 .	1 (0.2%)
	SECONDARY ANAEMIA	1 (0.2%)	0 .	0 .	1 (0.2%)
	THROMBOCYTHAEMIA	1 (0.2%)	0 .	0 .	1 (0.2%)
CARDIAC DISORDERS	TOTAL	12 (2.7%)	8 (1.8%)	5 (1.1%)	25 (5.5%)
	ANGINA PECTORIS	1 (0.2%)	1 (0.2%)	0 .	2 (0.4%)
	ANGINA UNSTABLE	0 .	0 .	1 (0.2%)	1 (0.2%)
	ARRHYTHMIA	0 .	1 (0.2%)	0 .	1 (0.2%)
	ATRIAL FIBRILLATION	0 .	1 (0.2%)	1 (0.2%)	2 (0.4%)
	ATRIAL FLUTTER	1 (0.2%)	0 .	0 .	1 (0.2%)
	BUNDLE BRANCH BLOCK LEFT	1 (0.2%)	0 .	1 (0.2%)	2 (0.4%)
	BUNDLE BRANCH BLOCK RIGHT	0 .	1 (0.2%)	0 .	1 (0.2%)
	CARDIAC FAILURE	0 .	1 (0.2%)	0 .	1 (0.2%)
	CARDIOVASCULAR DISORDER	1 (0.2%)	0 .	0 .	1 (0.2%)
	CORONARY ARTERY DISEASE	0 .	0 .	1 (0.2%)	1 (0.2%)
	HYPERTENSIVE HEART DISEASE	1 (0.2%)	0 .	0 .	1 (0.2%)
	MYOCARDIAL INFARCTION	0 .	0 .	1 (0.2%)	1 (0.2%)
	MYOCARDIAL ISCHAEMIA	2 (0.4%)	2 (0.4%)	0 .	4 (0.9%)
	PALPITATIONS	1 (0.2%)	0 .	0 .	1 (0.2%)
	SINUS BRADYCARDIA	1 (0.2%)	0 .	0 .	1 (0.2%)
	SINUS TACHYCARDIA	2 (0.4%)	0 .	0 .	2 (0.4%)
	SUPRAVENTRICULAR EXTRASYSTOLES	3 (0.7%)	0 .	0 .	3 (0.7%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND INTENSITY
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
3. MAXIMUM INTENSITY IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL

SB 207499

TABLE 15.4

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY,
MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP=PLACEBO (N=452)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	Intensity Mild	Moderate	Severe	Total
CARDIAC DISORDERS	TACHYCARDIA	0 .	2 (0.4%)	0 .	2 (0.4%)
	VENTRICULAR EXTRASYSTOLES	1 (0.2%)	0 .	0 .	1 (0.2%)
	VENTRICULAR TACHYCARDIA	1 (0.2%)	0 .	0 .	1 (0.2%)
	WANDERING PACEMAKER	1 (0.2%)	0 .	0 .	1 (0.2%)
EAR AND LABYRINTH DISORDERS	TOTAL	8 (1.8%)	5 (1.1%)	0 .	13 (2.9%)
	CERUMEN IMPACTION	2 (0.4%)	0 .	0 .	2 (0.4%)
	DEAFNESS	1 (0.2%)	0 .	0 .	1 (0.2%)
	EAR PAIN	1 (0.2%)	0 .	0 .	1 (0.2%)
	EAR PRURITUS	1 (0.2%)	0 .	0 .	1 (0.2%)
	HYPOACUSIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	MOTION SICKNESS	1 (0.2%)	0 .	0 .	1 (0.2%)
	TINNITUS	0 .	1 (0.2%)	0 .	1 (0.2%)
	VERTIGO	3 (0.7%)	3 (0.7%)	0 .	6 (1.3%)
EYE DISORDERS	TOTAL	5 (1.1%)	4 (0.9%)	3 (0.7%)	12 (2.7%)
	CATARACT	1 (0.2%)	0 .	1 (0.2%)	2 (0.4%)
	CONJUNCTIVITIS	2 (0.4%)	2 (0.4%)	0 .	4 (0.9%)
	EYE ALLERGY	1 (0.2%)	0 .	0 .	1 (0.2%)
	EYE INFLAMMATION	0 .	2 (0.4%)	0 .	2 (0.4%)
	EYELID OEDEMA	0 .	0 .	1 (0.2%)	1 (0.2%)
	GLAUCOMA	1 (0.2%)	0 .	0 .	1 (0.2%)
	RETINAL ARTERY THROMBOSIS	0 .	0 .	1 (0.2%)	1 (0.2%)
GASTROINTESTINAL DISORDERS	TOTAL	30 (6.6%)	32 (7.1%)	5 (1.1%)	67 (14.8%)
	ABDOMINAL DISCOMFORT	0 .	1 (0.2%)	0 .	1 (0.2%)
	ABDOMINAL DISTENSION	0 .	2 (0.4%)	0 .	2 (0.4%)
	ABDOMINAL PAIN	1 (0.2%)	3 (0.7%)	1 (0.2%)	5 (1.1%)
	ABDOMINAL PAIN LOWER	1 (0.2%)	0 .	0 .	1 (0.2%)
	ABDOMINAL PAIN UPPER	4 (0.9%)	0 .	1 (0.2%)	5 (1.1%)
	ABDOMINAL SYMPTOM	1 (0.2%)	0 .	0 .	1 (0.2%)
	COLONIC POLYP	0 .	1 (0.2%)	0 .	1 (0.2%)
	CONSTIPATION	3 (0.7%)	1 (0.2%)	0 .	4 (0.9%)
	DIARRHOEA	7 (1.5%)	6 (1.3%)	0 .	13 (2.9%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND INTENSITY
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
3. MAXIMUM INTENSITY IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL

SB 207499

TABLE 15.4

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY,
MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP=PLACEBO (N=452)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	Intensity Mild	Moderate	Severe	Total
GASTROINTESTINAL DISORDERS	DIARRHOEA	0 .	1 (0.2%)	0 .	1 (0.2%)
	HAEMORRHAGIC DIVERTICULITIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	DIVERTICULUM INTESTINAL	1 (0.2%)	2 (0.4%)	0 .	3 (0.7%)
	DRY MOUTH	1 (0.2%)	0 .	0 .	1 (0.2%)
	DUODENAL ULCER	1 (0.2%)	0 .	0 .	1 (0.2%)
	DYSPEPSIA	3 (0.7%)	3 (0.7%)	0 .	6 (1.3%)
	DYSPHAGIA	0 .	1 (0.2%)	0 .	1 (0.2%)
	FAECALOMA	0 .	1 (0.2%)	0 .	1 (0.2%)
	FAECES DISCOLOURED	1 (0.2%)	0 .	0 .	1 (0.2%)
	FAECES PALE	0 .	1 (0.2%)	0 .	1 (0.2%)
	FLATULENCE	2 (0.4%)	0 .	0 .	2 (0.4%)
	FREQUENT BOWEL MOVEMENTS	2 (0.4%)	2 (0.4%)	0 .	4 (0.9%)
	GASTRIC ULCER	0 .	1 (0.2%)	0 .	1 (0.2%)
	GASTRITIS	1 (0.2%)	2 (0.4%)	0 .	3 (0.7%)
	GASTROINTESTINAL OBSTRUCTION	0 .	0 .	1 (0.2%)	1 (0.2%)
	GASTROOESOPHAGEAL REFLUX DISEASE	1 (0.2%)	1 (0.2%)	0 .	2 (0.4%)
	GINGIVITIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	HAEMORRHOIDS	1 (0.2%)	0 .	0 .	1 (0.2%)
	HIATUS HERNIA	0 .	2 (0.4%)	0 .	2 (0.4%)
	ILEUS	0 .	0 .	1 (0.2%)	1 (0.2%)
	INGUINAL HERNIA	0 .	1 (0.2%)	0 .	1 (0.2%)
	INTESTINAL OBSTRUCTION	0 .	0 .	1 (0.2%)	1 (0.2%)
	INTESTINAL PERFORATION	0 .	0 .	1 (0.2%)	1 (0.2%)
	INTESTINAL POLYP	2 (0.4%)	0 .	0 .	2 (0.4%)
	LOOSE STOOLS	2 (0.4%)	0 .	0 .	2 (0.4%)
	MOUTH ULCERATION	4 (0.9%)	0 .	0 .	4 (0.9%)
	NAUSEA	9 (2.0%)	5 (1.1%)	0 .	14 (3.1%)
	OESOPHAGITIS	0 .	2 (0.4%)	0 .	2 (0.4%)
	PANCREATITIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	RECTAL HAEMORRHAGE	0 .	1 (0.2%)	0 .	1 (0.2%)
	REFLUX OESOPHAGITIS	1 (0.2%)	0 .	0 .	1 (0.2%)
	TOOTHACHE	2 (0.4%)	1 (0.2%)	0 .	3 (0.7%)
	VOMITING	6 (1.3%)	2 (0.4%)	0 .	8 (1.8%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND INTENSITY
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
3. MAXIMUM INTENSITY IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL

SB 207499

TABLE 15.4

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY,
MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP=PLACEBO (N=452)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	Intensity Mild	Moderate	Severe	Total
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	TOTAL	17 (3.8%)	16 (3.5%)	1 (0.2%)	34 (7.5%)
	ASTHENIA	1 (0.2%)	1 (0.2%)	0 .	2 (0.4%)
	AXILLARY PAIN	1 (0.2%)	0 .	0 .	1 (0.2%)
	CHEST DISCOMFORT	3 (0.7%)	1 (0.2%)	0 .	4 (0.9%)
	CHEST PAIN	6 (1.3%)	6 (1.3%)	1 (0.2%)	13 (2.9%)
	FATIGUE	1 (0.2%)	1 (0.2%)	0 .	2 (0.4%)
	FEELING HOT	1 (0.2%)	0 .	0 .	1 (0.2%)
	INFLUENZA LIKE ILLNESS	1 (0.2%)	0 .	0 .	1 (0.2%)
	LETHARGY	1 (0.2%)	1 (0.2%)	0 .	2 (0.4%)
	MALAISE	1 (0.2%)	0 .	0 .	1 (0.2%)
	OEDEMA	1 (0.2%)	0 .	0 .	1 (0.2%)
	OEDEMA PERIPHERAL	4 (0.9%)	4 (0.9%)	0 .	8 (1.8%)
	PAIN	1 (0.2%)	0 .	0 .	1 (0.2%)
	PYREXIA	0 .	2 (0.4%)	0 .	2 (0.4%)
	THIRST	2 (0.4%)	0 .	0 .	2 (0.4%)
HEPATOBILIARY DISORDERS	TOTAL	2 (0.4%)	4 (0.9%)	0 .	6 (1.3%)
	ALCOHOLIC LIVER DISEASE	0 .	1 (0.2%)	0 .	1 (0.2%)
	CHOLELITHIASIS	0 .	2 (0.4%)	0 .	2 (0.4%)
	HEPATIC STEATOSIS	2 (0.4%)	1 (0.2%)	0 .	3 (0.7%)
IMMUNE SYSTEM DISORDERS	TOTAL	1 (0.2%)	1 (0.2%)	1 (0.2%)	3 (0.7%)
	ANAPHYLACTIC SHOCK	0 .	0 .	1 (0.2%)	1 (0.2%)
	HYPERSENSITIVITY	0 .	1 (0.2%)	0 .	1 (0.2%)
	SEASONAL ALLERGY	1 (0.2%)	0 .	0 .	1 (0.2%)
INFECTIONS AND INFESTATIONS	TOTAL	60 (13.3%)	70 (15.5%)	3 (0.7%)	133 (29.4%)
	BACTERIAL INFECTION	1 (0.2%)	0 .	0 .	1 (0.2%)
	BRONCHITIS	1 (0.2%)	5 (1.1%)	0 .	6 (1.3%)
	BRONCHITIS ACUTE	2 (0.4%)	0 .	0 .	2 (0.4%)
	BRONCHOPNEUMONIA	0 .	2 (0.4%)	1 (0.2%)	3 (0.7%)
	CANDIDIASIS	1 (0.2%)	0 .	0 .	1 (0.2%)
	CYSTITIS	1 (0.2%)	1 (0.2%)	0 .	2 (0.4%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND INTENSITY
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
3. MAXIMUM INTENSITY IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL

SB 207499

TABLE 15.4

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY,
MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP=PLACEBO (N=452)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	Intensity Mild	Moderate	Severe	Total
INFECTIONS AND INFESTATIONS	DENTAL CARIES	1 (0.2%)	0 .	0 .	1 (0.2%)
	EAR INFECTION	1 (0.2%)	4 (0.9%)	0 .	5 (1.1%)
	EAR LOBE INFECTION	0 .	1 (0.2%)	0 .	1 (0.2%)
	ERYSIPELAS	0 .	1 (0.2%)	0 .	1 (0.2%)
	FOLLICULITIS	1 (0.2%)	0 .	0 .	1 (0.2%)
	FUNGAL INFECTION	0 .	1 (0.2%)	0 .	1 (0.2%)
	GASTROENTERITIS	4 (0.9%)	3 (0.7%)	0 .	7 (1.5%)
	GASTROENTERITIS VIRAL	1 (0.2%)	2 (0.4%)	0 .	3 (0.7%)
	HERPES SIMPLEX	0 .	1 (0.2%)	0 .	1 (0.2%)
	HERPES ZOSTER	1 (0.2%)	1 (0.2%)	0 .	2 (0.4%)
	INFECTED INSECT BITE	1 (0.2%)	0 .	0 .	1 (0.2%)
	INFECTED SKIN ULCER	0 .	1 (0.2%)	0 .	1 (0.2%)
	INFECTION	1 (0.2%)	0 .	0 .	1 (0.2%)
	INFLUENZA	4 (0.9%)	13 (2.9%)	0 .	17 (3.8%)
	LOBAR PNEUMONIA	0 .	1 (0.2%)	0 .	1 (0.2%)
	LOCALISED INFECTION	1 (0.2%)	1 (0.2%)	0 .	2 (0.4%)
	LOWER RESPIRATORY TRACT INFECTION	0 .	4 (0.9%)	0 .	4 (0.9%)
	NASOPHARYNGITIS	31 (6.9%)	22 (4.9%)	1 (0.2%)	54 (11.9%)
	ONYCHOMYCOSIS	1 (0.2%)	0 .	0 .	1 (0.2%)
	ORAL CANDIDIASIS	1 (0.2%)	0 .	0 .	1 (0.2%)
	OROPHARYNGITIS FUNGAL	1 (0.2%)	0 .	0 .	1 (0.2%)
	PHARYNGITIS	0 .	2 (0.4%)	0 .	2 (0.4%)
	PNEUMONIA	0 .	3 (0.7%)	0 .	3 (0.7%)
	PNEUMONIA BACTERIAL	0 .	1 (0.2%)	0 .	1 (0.2%)
	PULPITIS DENTAL	0 .	1 (0.2%)	0 .	1 (0.2%)
	RESPIRATORY TRACT INFECTION	0 .	4 (0.9%)	0 .	4 (0.9%)
	SINUSITIS	1 (0.2%)	6 (1.3%)	0 .	7 (1.5%)
	STAPHYLOCOCCAL INFECTION	0 .	1 (0.2%)	0 .	1 (0.2%)
	TINEA INFECTION	1 (0.2%)	0 .	0 .	1 (0.2%)
	TONSILLITIS	0 .	2 (0.4%)	0 .	2 (0.4%)
	TOOTH ABSCESS	1 (0.2%)	1 (0.2%)	0 .	2 (0.4%)
	TOOTH INFECTION	1 (0.2%)	0 .	0 .	1 (0.2%)
	UPPER RESPIRATORY TRACT INFECTION	8 (1.8%)	3 (0.7%)	0 .	11 (2.4%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND INTENSITY
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
3. MAXIMUM INTENSITY IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL

SB 207499

TABLE 15.4

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY,
MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP=PLACEBO (N=452)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	Intensity Mild	Moderate	Severe	Total
INFECTIONS AND INFESTATIONS	URINARY TRACT INFECTION	7 (1.5%)	5 (1.1%)	0 .	12 (2.7%)
	VAGINAL MYCOSIS	1 (0.2%)	0 .	0 .	1 (0.2%)
	VIRAL INFECTION	0 .	1 (0.2%)	0 .	1 (0.2%)
	VIRAL LABYRINTHITIS	0 .	0 .	1 (0.2%)	1 (0.2%)
	VIRAL UPPER RESPIRATORY TRACT INFECTION	1 (0.2%)	0 .	0 .	1 (0.2%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	TOTAL	11 (2.4%)	9 (2.0%)	4 (0.9%)	24 (5.3%)
	ALCOHOL POISONING	0 .	0 .	1 (0.2%)	1 (0.2%)
	ANIMAL BITE	0 .	0 .	1 (0.2%)	1 (0.2%)
	ARTHROPOD BITE	1 (0.2%)	0 .	0 .	1 (0.2%)
	ARTHROPOD STING	1 (0.2%)	0 .	0 .	1 (0.2%)
	BACK INJURY	0 .	1 (0.2%)	0 .	1 (0.2%)
	BLISTER	1 (0.2%)	1 (0.2%)	0 .	2 (0.4%)
	CONTUSION	1 (0.2%)	1 (0.2%)	0 .	2 (0.4%)
	EPICONDYLITIS	1 (0.2%)	0 .	0 .	1 (0.2%)
	FALL	1 (0.2%)	1 (0.2%)	0 .	2 (0.4%)
	FOOT FRACTURE	1 (0.2%)	0 .	0 .	1 (0.2%)
	HAND FRACTURE	0 .	1 (0.2%)	0 .	1 (0.2%)
	HEART INJURY	1 (0.2%)	0 .	0 .	1 (0.2%)
	HIP FRACTURE	0 .	0 .	1 (0.2%)	1 (0.2%)
	HUMERUS FRACTURE	0 .	1 (0.2%)	0 .	1 (0.2%)
	JOINT SPRAIN	0 .	1 (0.2%)	0 .	1 (0.2%)
	LIMB INJURY	1 (0.2%)	0 .	0 .	1 (0.2%)
	MUSCLE INJURY	0 .	1 (0.2%)	0 .	1 (0.2%)
	MUSCLE STRAIN	0 .	1 (0.2%)	0 .	1 (0.2%)
	RIB FRACTURE	0 .	1 (0.2%)	0 .	1 (0.2%)
	SKELETAL INJURY	0 .	1 (0.2%)	0 .	1 (0.2%)
	SKIN LACERATION	1 (0.2%)	0 .	0 .	1 (0.2%)
	THERMAL BURN	0 .	0 .	1 (0.2%)	1 (0.2%)
	VACCINATION COMPLICATION	1 (0.2%)	0 .	0 .	1 (0.2%)
	WOUND	0 .	1 (0.2%)	0 .	1 (0.2%)
	WRIST FRACTURE	2 (0.4%)	0 .	0 .	2 (0.4%)
INVESTIGATIONS	TOTAL	26 (5.8%)	9 (2.0%)	1 (0.2%)	36 (8.0%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND INTENSITY
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
3. MAXIMUM INTENSITY IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL GM2004/00073/00 SB-207499/157

SB 207499

TABLE 15.4

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY,
MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP=PLACEBO (N=452)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	Intensity Mild	Moderate	Severe	Total
INVESTIGATIONS	ALANINE AMINOTRANSFERASE INCREASED	3 (0.7%)	1 (0.2%)	0 .	4 (0.9%)
	ASPARTATE AMINOTRANSFERASE INCREASED	3 (0.7%)	1 (0.2%)	0 .	4 (0.9%)
	BLOOD ALKALINE PHOSPHATASE INCREASED	3 (0.7%)	1 (0.2%)	0 .	4 (0.9%)
	BLOOD BILIRUBIN INCREASED	4 (0.9%)	0 .	0 .	4 (0.9%)
	BLOOD CREATININE INCREASED	2 (0.4%)	0 .	0 .	2 (0.4%)
	BLOOD GLUCOSE INCREASED	1 (0.2%)	1 (0.2%)	0 .	2 (0.4%)
	BLOOD IN STOOL	1 (0.2%)	0 .	0 .	1 (0.2%)
	BLOOD PRESSURE INCREASED	1 (0.2%)	1 (0.2%)	0 .	2 (0.4%)
	BLOOD URIC ACID DECREASED	0 .	1 (0.2%)	0 .	1 (0.2%)
	BLOOD URINE	1 (0.2%)	0 .	0 .	1 (0.2%)
	BLOOD URINE PRESENT	4 (0.9%)	0 .	0 .	4 (0.9%)
	C-REACTIVE PROTEIN INCREASED	1 (0.2%)	0 .	1 (0.2%)	2 (0.4%)
	ELECTROCARDIOGRAM P WAVE ABNORMAL	1 (0.2%)	0 .	0 .	1 (0.2%)
	ELECTROCARDIOGRAM ST SEGMENT DEPRESSION	1 (0.2%)	0 .	0 .	1 (0.2%)
	FAECAL OCCULT BLOOD POSITIVE	2 (0.4%)	0 .	0 .	2 (0.4%)
	FORCED EXPIRATORY VOLUME DECREASED	0 .	1 (0.2%)	0 .	1 (0.2%)
	GAMMA-GLUTAMYLTRANSF ERASE INCREASED	7 (1.5%)	2 (0.4%)	0 .	9 (2.0%)
	HEPATIC ENZYME INCREASED	0 .	1 (0.2%)	0 .	1 (0.2%)
	PROTEIN URINE PRESENT	0 .	1 (0.2%)	0 .	1 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND INTENSITY
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
3. MAXIMUM INTENSITY IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL

SB 207499

TABLE 15.4

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY,
MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP=PLACEBO (N=452)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	Intensity Mild	Moderate	Severe	Total
INVESTIGATIONS	URINARY OCCULT BLOOD POSITIVE	1 (0.2%)	0 .	0 .	1 (0.2%)
	WEIGHT DECREASED	0 .	1 (0.2%)	0 .	1 (0.2%)
	WEIGHT INCREASED	0 .	1 (0.2%)	0 .	1 (0.2%)
	WHITE BLOOD CELL COUNT INCREASED	1 (0.2%)	0 .	0 .	1 (0.2%)
METABOLISM AND NUTRITION DISORDERS	TOTAL	12 (2.7%)	5 (1.1%)	0 .	17 (3.8%)
	ANOREXIA	1 (0.2%)	0 .	0 .	1 (0.2%)
	DECREASED APPETITE	0 .	1 (0.2%)	0 .	1 (0.2%)
	DIABETES MELLITUS	5 (1.1%)	1 (0.2%)	0 .	6 (1.3%)
	GLUCOSE TOLERANCE IMPAIRED	0 .	1 (0.2%)	0 .	1 (0.2%)
	HYPERCHOLESTEROLAEMIA	1 (0.2%)	1 (0.2%)	0 .	2 (0.4%)
	HYPERGLYCAEMIA	4 (0.9%)	2 (0.4%)	0 .	6 (1.3%)
	HYPERURICAEMIA	0 .	1 (0.2%)	0 .	1 (0.2%)
	HYPOGLYCAEMIA	1 (0.2%)	0 .	0 .	1 (0.2%)
	HYPONATRAEMIA	1 (0.2%)	0 .	0 .	1 (0.2%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	TOTAL	23 (5.1%)	29 (6.4%)	0 .	52 (11.5%)
	ARTHRALGIA	3 (0.7%)	4 (0.9%)	0 .	7 (1.5%)
	ARTHRITIS	1 (0.2%)	0 .	0 .	1 (0.2%)
	BACK PAIN	7 (1.5%)	13 (2.9%)	0 .	20 (4.4%)
	BURSITIS	1 (0.2%)	0 .	0 .	1 (0.2%)
	FIBROMYALGIA	0 .	1 (0.2%)	0 .	1 (0.2%)
	JOINT SWELLING	2 (0.4%)	0 .	0 .	2 (0.4%)
	LOCAL SWELLING	1 (0.2%)	0 .	0 .	1 (0.2%)
	LOCALISED OSTEOARTHRITIS	1 (0.2%)	1 (0.2%)	0 .	2 (0.4%)
	MONOARTHRITIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	MUSCLE CRAMP	1 (0.2%)	2 (0.4%)	0 .	3 (0.7%)
	MUSCULOSKELETAL CHEST PAIN	1 (0.2%)	0 .	0 .	1 (0.2%)
	MUSCULOSKELETAL DISCOMFORT	1 (0.2%)	0 .	0 .	1 (0.2%)
	MYALGIA	1 (0.2%)	1 (0.2%)	0 .	2 (0.4%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND INTENSITY
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
3. MAXIMUM INTENSITY IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL

SB 207499

TABLE 15.4

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY,
MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP=PLACEBO (N=452)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	Intensity Mild	Moderate	Severe	Total
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	OSTEOARTHRITIS	1 (0.2%)	2 (0.4%)	0 .	3 (0.7%)
	OSTEOPOROSIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	PAIN IN EXTREMITY	4 (0.9%)	3 (0.7%)	0 .	7 (1.5%)
	SHOULDER BLADE PAIN	1 (0.2%)	0 .	0 .	1 (0.2%)
	SJOGREN'S SYNDROME	0 .	1 (0.2%)	0 .	1 (0.2%)
	SPINAL DISORDER	2 (0.4%)	1 (0.2%)	0 .	3 (0.7%)
	TENDONITIS	0 .	1 (0.2%)	0 .	1 (0.2%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	TOTAL	3 (0.7%)	2 (0.4%)	4 (0.9%)	9 (2.0%)
	BASAL CELL CARCINOMA	1 (0.2%)	0 .	0 .	1 (0.2%)
	GASTRIC CANCER	0 .	0 .	1 (0.2%)	1 (0.2%)
	LUNG NEOPLASM MALIGNANT	0 .	0 .	1 (0.2%)	1 (0.2%)
	LUNG NODULE	0 .	1 (0.2%)	0 .	1 (0.2%)
	METASTASIS	0 .	0 .	1 (0.2%)	1 (0.2%)
	PROSTATE CANCER	0 .	0 .	1 (0.2%)	1 (0.2%)
	RENAL CELL CARCINOMA STAGE UNSPECIFIED	0 .	1 (0.2%)	0 .	1 (0.2%)
	SEBORRHOEIC KERATOSIS	1 (0.2%)	0 .	0 .	1 (0.2%)
	SQUAMOUS CELL CARCINOMA OF SKIN	2 (0.4%)	0 .	0 .	2 (0.4%)
	THYROID GLAND CANCER	0 .	0 .	1 (0.2%)	1 (0.2%)
NERVOUS SYSTEM DISORDERS	TOTAL	20 (4.4%)	14 (3.1%)	3 (0.7%)	37 (8.2%)
	CARPAL TUNNEL SYNDROME	0 .	1 (0.2%)	0 .	1 (0.2%)
	CEREBRAL INFARCTION	0 .	1 (0.2%)	0 .	1 (0.2%)
	CEREBRAL THROMBOSIS	0 .	0 .	1 (0.2%)	1 (0.2%)
	CEREBROVASCULAR ACCIDENT	0 .	0 .	1 (0.2%)	1 (0.2%)
	CEREBROVASCULAR DISORDER	1 (0.2%)	0 .	0 .	1 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND INTENSITY
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
3. MAXIMUM INTENSITY IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL

SB 207499

TABLE 15.4

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY,
MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP=PLACEBO (N=452)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	Intensity Mild	Moderate	Severe	Total
NERVOUS SYSTEM DISORDERS	DIZZINESS	3 (0.7%)	2 (0.4%)	0 .	5 (1.1%)
	DIZZINESS POSTURAL	1 (0.2%)	0 .	0 .	1 (0.2%)
	DYSGEUSIA	1 (0.2%)	0 .	0 .	1 (0.2%)
	ENCEPHALOPATHY	0 .	1 (0.2%)	0 .	1 (0.2%)
	ENTRAPMENT NEUROPATHY	0 .	1 (0.2%)	0 .	1 (0.2%)
	HEADACHE	12 (2.7%)	9 (2.0%)	1 (0.2%)	22 (4.9%)
	MOTOR DYSFUNCTION	1 (0.2%)	0 .	0 .	1 (0.2%)
	NEUROPATHY	0 .	1 (0.2%)	0 .	1 (0.2%)
	PARAESTHESIA	2 (0.4%)	0 .	0 .	2 (0.4%)
	RADICULITIS LUMBOSACRAL	1 (0.2%)	0 .	0 .	1 (0.2%)
	SYNCOPE	1 (0.2%)	1 (0.2%)	0 .	2 (0.4%)
	SYNCOPE VASOVAGAL	0 .	1 (0.2%)	0 .	1 (0.2%)
	TORTICOLLIS	1 (0.2%)	0 .	0 .	1 (0.2%)
PSYCHIATRIC DISORDERS	TOTAL	6 (1.3%)	11 (2.4%)	3 (0.7%)	20 (4.4%)
	ABNORMAL DREAMS	1 (0.2%)	0 .	0 .	1 (0.2%)
	AFFECT LABILITY	0 .	1 (0.2%)	0 .	1 (0.2%)
	ALCOHOLISM	0 .	1 (0.2%)	1 (0.2%)	2 (0.4%)
	ANXIETY	0 .	1 (0.2%)	0 .	1 (0.2%)
	BEREAVEMENT REACTION	0 .	1 (0.2%)	0 .	1 (0.2%)
	DEPRESSION	1 (0.2%)	5 (1.1%)	1 (0.2%)	7 (1.5%)
	INSOMNIA	3 (0.7%)	2 (0.4%)	0 .	5 (1.1%)
	MANIA	0 .	0 .	1 (0.2%)	1 (0.2%)
	NEUROSIS	1 (0.2%)	0 .	0 .	1 (0.2%)
	PANIC ATTACK	0 .	1 (0.2%)	0 .	1 (0.2%)
	SLEEP DISORDER	1 (0.2%)	0 .	0 .	1 (0.2%)
RENAL AND URINARY DISORDERS	TOTAL	11 (2.4%)	4 (0.9%)	2 (0.4%)	17 (3.8%)
	CALCULUS BLADDER	0 .	0 .	1 (0.2%)	1 (0.2%)
	CYSTITIS CHRONIC	1 (0.2%)	0 .	0 .	1 (0.2%)
	DYSURIA	1 (0.2%)	0 .	0 .	1 (0.2%)
	GLYCOSURIA	1 (0.2%)	0 .	0 .	1 (0.2%)
	HAEMATURIA	3 (0.7%)	1 (0.2%)	0 .	4 (0.9%)
	NEPHROLITHIASIS	1 (0.2%)	0 .	0 .	1 (0.2%)
	POLLAKIURIA	0 .	2 (0.4%)	0 .	2 (0.4%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND INTENSITY
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
3. MAXIMUM INTENSITY IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL

SB 207499

TABLE 15.4

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY,
MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP=PLACEBO (N=452)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	Intensity Mild	Moderate	Severe	Total
RENAL AND URINARY DISORDERS	PROTEINURIA	2 (0.4%)	1 (0.2%)	0 .	3 (0.7%)
	RENAL COLIC	0 .	0 .	1 (0.2%)	1 (0.2%)
	RENAL CYST	1 (0.2%)	0 .	0 .	1 (0.2%)
	RENAL INSUFFICIENCY	1 (0.2%)	0 .	0 .	1 (0.2%)
	URINARY TRACT OBSTRUCTION	0 .	1 (0.2%)	0 .	1 (0.2%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	TOTAL	1 (0.2%)	3 (0.7%)	0 .	4 (0.9%)
	GENITAL RASH	0 .	1 (0.2%)	0 .	1 (0.2%)
	PROSTATITIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	TESTICULAR PAIN	1 (0.2%)	0 .	0 .	1 (0.2%)
	TESTICULAR SWELLING	0 .	1 (0.2%)	0 .	1 (0.2%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	TOTAL	92 (20.4%)	130 (28.8%)	20 (4.4%)	242 (53.5%)
	BRONCHOSPASM	1 (0.2%)	0 .	0 .	1 (0.2%)
	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE EXACERBATED	77 (17.0%)	117 (25.9%)	15 (3.3%)	209 (46.2%)
	COUGH	5 (1.1%)	6 (1.3%)	0 .	11 (2.4%)
	DRY THROAT	1 (0.2%)	0 .	0 .	1 (0.2%)
	DYSPNOEA	2 (0.4%)	5 (1.1%)	2 (0.4%)	9 (2.0%)
	DYSPNOEA EXACERBATED	0 .	1 (0.2%)	0 .	1 (0.2%)
	EPISTAXIS	4 (0.9%)	1 (0.2%)	0 .	5 (1.1%)
	HAEMOPTYSIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	HOARSENESS	1 (0.2%)	0 .	0 .	1 (0.2%)
	HYPOXIA	1 (0.2%)	0 .	0 .	1 (0.2%)
	LUNG DISORDER	0 .	2 (0.4%)	0 .	2 (0.4%)
	NASAL CONGESTION	1 (0.2%)	0 .	0 .	1 (0.2%)
	NASAL CYST	1 (0.2%)	0 .	0 .	1 (0.2%)
	NASAL MUCOSAL DISORDER	0 .	1 (0.2%)	0 .	1 (0.2%)
	NASAL POLYPS	0 .	1 (0.2%)	0 .	1 (0.2%)
	NASAL SEPTUM DEVIATION	1 (0.2%)	0 .	0 .	1 (0.2%)
	PHARYNGEAL ERYTHEMA	1 (0.2%)	0 .	0 .	1 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND INTENSITY
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
3. MAXIMUM INTENSITY IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL

SB 207499

TABLE 15.4

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY,
MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP=PLACEBO (N=452)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	Intensity Mild	Moderate	Severe	Total
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	PHARYNGOLARYNGEAL PAIN	11 (2.4%)	4 (0.9%)	1 (0.2%)	16 (3.5%)
	PLEURITIC PAIN	0 .	0 .	1 (0.2%)	1 (0.2%)
	PNEUMOTHORAX	0 .	1 (0.2%)	0 .	1 (0.2%)
	POSTNASAL DRIP	2 (0.4%)	0 .	0 .	2 (0.4%)
	PRODUCTIVE COUGH	1 (0.2%)	0 .	0 .	1 (0.2%)
	PULMONARY FIBROSIS	0 .	0 .	1 (0.2%)	1 (0.2%)
	RHINITIS	9 (2.0%)	2 (0.4%)	0 .	11 (2.4%)
	RHINITIS ALLERGIC	1 (0.2%)	2 (0.4%)	0 .	3 (0.7%)
	RHINITIS SEASONAL	1 (0.2%)	0 .	0 .	1 (0.2%)
	RHINORRHOEA	4 (0.9%)	0 .	0 .	4 (0.9%)
	THROAT IRRITATION	0 .	1 (0.2%)	0 .	1 (0.2%)
	WHEEZING	2 (0.4%)	1 (0.2%)	0 .	3 (0.7%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	TOTAL	5 (1.1%)	13 (2.9%)	1 (0.2%)	19 (4.2%)
	DECUBITUS ULCER	1 (0.2%)	0 .	0 .	1 (0.2%)
	DERMATITIS	1 (0.2%)	0 .	0 .	1 (0.2%)
	DERMATITIS ALLERGIC	1 (0.2%)	0 .	0 .	1 (0.2%)
	DERMATITIS MEDICAMENTOSA	0 .	0 .	1 (0.2%)	1 (0.2%)
	DRY SKIN	1 (0.2%)	0 .	0 .	1 (0.2%)
	ECZEMA	1 (0.2%)	2 (0.4%)	0 .	3 (0.7%)
	HEAT RASH	1 (0.2%)	0 .	0 .	1 (0.2%)
	HYPERHIDROSIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	LICHEN PLANUS	0 .	1 (0.2%)	0 .	1 (0.2%)
	PRURITUS	1 (0.2%)	3 (0.7%)	0 .	4 (0.9%)
	PSORIASIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	RASH	1 (0.2%)	1 (0.2%)	0 .	2 (0.4%)
	SEBORRHOEIC DERMATITIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	SKIN LESION	0 .	1 (0.2%)	0 .	1 (0.2%)
	SKIN ULCER	0 .	1 (0.2%)	0 .	1 (0.2%)
	STASIS DERMATITIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	URTICARIA	1 (0.2%)	2 (0.4%)	0 .	3 (0.7%)
SOCIAL CIRCUMSTANCES	TOTAL	0 .	1 (0.2%)	0 .	1 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND INTENSITY
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
3. MAXIMUM INTENSITY IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL

SB 207499

TABLE 15.4

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY,
MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP=PLACEBO (N=452)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	Intensity Mild	Moderate	Severe	Total
SOCIAL CIRCUMSTANCES	ABSTAINS FROM ALCOHOL	0 .	1 (0.2%)	0 .	1 (0.2%)
SURGICAL AND MEDICAL PROCEDURES	TOTAL	0 .	2 (0.4%)	0 .	2 (0.4%)
	CATARACT EXTRACTION	0 .	2 (0.4%)	0 .	2 (0.4%)
VASCULAR DISORDERS	TOTAL	11 (2.4%)	14 (3.1%)	1 (0.2%)	26 (5.8%)
	CIRCULATORY COLLAPSE	1 (0.2%)	0 .	0 .	1 (0.2%)
	HOT FLUSH	1 (0.2%)	2 (0.4%)	0 .	3 (0.7%)
	HYPERTENSION	8 (1.8%)	10 (2.2%)	0 .	18 (4.0%)
	HYPERTENSIVE CRISIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	HYPOTENSION	1 (0.2%)	0 .	0 .	1 (0.2%)
	PALLOR	0 .	1 (0.2%)	0 .	1 (0.2%)
	PERIPHERAL COLDNESS	1 (0.2%)	0 .	0 .	1 (0.2%)
	THROMBOPHLEBITIS	0 .	0 .	1 (0.2%)	1 (0.2%)
	VARICOSE ULCERATION	0 .	1 (0.2%)	0 .	1 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND INTENSITY
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
3. MAXIMUM INTENSITY IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.4

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY,
MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP=SB 207499 (N=455)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	Intensity Mild	Moderate	Severe	Total
TOTAL	TOTAL	91 (20.0%)	211 (46.4%)	49 (10.8%)	351 (77.1%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	TOTAL	7 (1.5%)	1 (0.2%)	1 (0.2%)	9 (2.0%)
	ANAEMIA	2 (0.4%)	0 .	0 .	2 (0.4%)
	LEUKOCYTOSIS	4 (0.9%)	0 .	0 .	4 (0.9%)
	LYMPHADENOPATHY	0 .	1 (0.2%)	0 .	1 (0.2%)
	NEUTROPENIA	0 .	0 .	1 (0.2%)	1 (0.2%)
	POLYCYTHAEMIA	1 (0.2%)	0 .	0 .	1 (0.2%)
CARDIAC DISORDERS	TOTAL	17 (3.7%)	15 (3.3%)	6 (1.3%)	38 (8.4%)
	ACUTE MYOCARDIAL INFARCTION	0 .	0 .	1 (0.2%)	1 (0.2%)
	AGE INDETERMINATE MYOCARDIAL INFARCTION	0 .	0 .	1 (0.2%)	1 (0.2%)
	ANGINA PECTORIS	0 .	2 (0.4%)	0 .	2 (0.4%)
	AORTIC VALVE CALCIFICATION	1 (0.2%)	0 .	0 .	1 (0.2%)
	ARRHYTHMIA	1 (0.2%)	1 (0.2%)	0 .	2 (0.4%)
	ATRIAL FIBRILLATION	1 (0.2%)	1 (0.2%)	2 (0.4%)	4 (0.9%)
	ATRIAL FLUTTER	0 .	1 (0.2%)	1 (0.2%)	2 (0.4%)
	BRADYARRHYTHMIA	0 .	1 (0.2%)	0 .	1 (0.2%)
	BUNDLE BRANCH BLOCK LEFT	1 (0.2%)	0 .	0 .	1 (0.2%)
	CARDIAC FAILURE	0 .	1 (0.2%)	0 .	1 (0.2%)
	CARDIAC FAILURE ACUTE	0 .	0 .	1 (0.2%)	1 (0.2%)
	CARDIAC FAILURE CONGESTIVE	0 .	2 (0.4%)	0 .	2 (0.4%)
	CORONARY ARTERY DISEASE	1 (0.2%)	1 (0.2%)	1 (0.2%)	3 (0.7%)
	CORONARY ARTERY INSUFFICIENCY	0 .	1 (0.2%)	0 .	1 (0.2%)
	MYOCARDIAL INFARCTION	1 (0.2%)	0 .	0 .	1 (0.2%)
	MYOCARDIAL ISCHAEMIA	0 .	1 (0.2%)	1 (0.2%)	2 (0.4%)
	PALPITATIONS	3 (0.7%)	0 .	0 .	3 (0.7%)
	SINUS BRADYCARDIA	1 (0.2%)	0 .	0 .	1 (0.2%)
	SINUS TACHYCARDIA	4 (0.9%)	0 .	0 .	4 (0.9%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND INTENSITY
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
3. MAXIMUM INTENSITY IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL

SB 207499

TABLE 15.4

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY,
MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP=SB 207499 (N=455)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	Intensity Mild	Moderate	Severe	Total
CARDIAC DISORDERS	SUPRAVENTRICULAR EXTRASYSTOLES	3 (0.7%)	0 .	0 .	3 (0.7%)
	SUPRAVENTRICULAR TACHYCARDIA	0 .	2 (0.4%)	0 .	2 (0.4%)
	TACHYCARDIA	0 .	1 (0.2%)	0 .	1 (0.2%)
	VENTRICULAR EXTRASYSTOLES	1 (0.2%)	0 .	0 .	1 (0.2%)
	VENTRICULAR HYPERTROPHY	1 (0.2%)	0 .	0 .	1 (0.2%)
	VENTRICULAR TACHYCARDIA	0 .	1 (0.2%)	0 .	1 (0.2%)
EAR AND LABYRINTH DISORDERS	TOTAL	4 (0.9%)	1 (0.2%)	0 .	5 (1.1%)
	EAR DISORDER	1 (0.2%)	0 .	0 .	1 (0.2%)
	EAR PAIN	1 (0.2%)	0 .	0 .	1 (0.2%)
	VERTIGO	2 (0.4%)	1 (0.2%)	0 .	3 (0.7%)
EYE DISORDERS	TOTAL	3 (0.7%)	4 (0.9%)	0 .	7 (1.5%)
	CATARACT	1 (0.2%)	1 (0.2%)	0 .	2 (0.4%)
	CHALAZION	1 (0.2%)	0 .	0 .	1 (0.2%)
	CONJUNCTIVAL HAEMORRHAGE	0 .	1 (0.2%)	0 .	1 (0.2%)
	CONJUNCTIVITIS	0 .	2 (0.4%)	0 .	2 (0.4%)
	KERATOCONJUNCTIVITIS SICCA	1 (0.2%)	0 .	0 .	1 (0.2%)
GASTROINTESTINAL DISORDERS	TOTAL	58 (12.7%)	56 (12.3%)	14 (3.1%)	128 (28.1%)
	ABDOMINAL DISCOMFORT	2 (0.4%)	0 .	0 .	2 (0.4%)
	ABDOMINAL DISTENSION	2 (0.4%)	0 .	0 .	2 (0.4%)
	ABDOMINAL PAIN	3 (0.7%)	6 (1.3%)	0 .	9 (2.0%)
	ABDOMINAL PAIN UPPER	8 (1.8%)	4 (0.9%)	1 (0.2%)	13 (2.9%)
	ABNORMAL FAECES	1 (0.2%)	0 .	0 .	1 (0.2%)
	COLONIC HAEMORRHAGE	0 .	1 (0.2%)	0 .	1 (0.2%)
	COLONIC POLYP	0 .	1 (0.2%)	0 .	1 (0.2%)
	CONSTIPATION	3 (0.7%)	2 (0.4%)	0 .	5 (1.1%)
	DIARRHOEA	13 (2.9%)	17 (3.7%)	3 (0.7%)	33 (7.3%)
	DIVERTICULITIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	DIVERTICULUM	0 .	3 (0.7%)	0 .	3 (0.7%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND INTENSITY
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
3. MAXIMUM INTENSITY IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL

SB 207499

TABLE 15.4

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY,
MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP=SB 207499 (N=455)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	Intensity Mild	Moderate	Severe	Total
GASTROINTESTINAL DISORDERS	DRY MOUTH	1 (0.2%)	1 (0.2%)	0 .	2 (0.4%)
	DUODENAL ULCER	0 .	2 (0.4%)	0 .	2 (0.4%)
	DYSPEPSIA	12 (2.6%)	3 (0.7%)	3 (0.7%)	18 (4.0%)
	EPIGASTRIC DISCOMFORT	0 .	2 (0.4%)	0 .	2 (0.4%)
	FAECES DISCOLOURED	1 (0.2%)	0 .	0 .	1 (0.2%)
	FAECES HARD	1 (0.2%)	0 .	0 .	1 (0.2%)
	FLATULENCE	2 (0.4%)	0 .	0 .	2 (0.4%)
	FOOD POISONING	0 .	1 (0.2%)	0 .	1 (0.2%)
	FREQUENT BOWEL MOVEMENTS	2 (0.4%)	1 (0.2%)	0 .	3 (0.7%)
	GASTRIC DISORDER	1 (0.2%)	0 .	0 .	1 (0.2%)
	GASTRIC ULCER	1 (0.2%)	0 .	0 .	1 (0.2%)
	GASTRITIS	0 .	2 (0.4%)	1 (0.2%)	3 (0.7%)
	GASTRODUODENITIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	GASTROINTESTINAL DISORDER	1 (0.2%)	0 .	1 (0.2%)	2 (0.4%)
	GASTROINTESTINAL UPSET	1 (0.2%)	0 .	0 .	1 (0.2%)
	GASTROOESOPHAGEAL REFLUX DISEASE	0 .	2 (0.4%)	1 (0.2%)	3 (0.7%)
	GLOSSITIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	HAEMORRHOIDAL HAEMORRHAGE	1 (0.2%)	0 .	0 .	1 (0.2%)
	ILEUS	0 .	0 .	1 (0.2%)	1 (0.2%)
	INGUINAL HERNIA	3 (0.7%)	1 (0.2%)	0 .	4 (0.9%)
	LOOSE STOOLS	6 (1.3%)	1 (0.2%)	0 .	7 (1.5%)
	NAUSEA	23 (5.1%)	15 (3.3%)	6 (1.3%)	44 (9.7%)
	OESOPHAGITIS	1 (0.2%)	0 .	0 .	1 (0.2%)
	PANCREATITIS	0 .	0 .	1 (0.2%)	1 (0.2%)
	PEPTIC ULCER	0 .	1 (0.2%)	0 .	1 (0.2%)
	RECTAL HAEMORRHAGE	1 (0.2%)	0 .	0 .	1 (0.2%)
	REFLUX OESOPHAGITIS	0 .	1 (0.2%)	1 (0.2%)	2 (0.4%)
	TOOTH DISORDER	0 .	1 (0.2%)	0 .	1 (0.2%)
	TOOTHACHE	1 (0.2%)	1 (0.2%)	0 .	2 (0.4%)
	UMBILICAL HERNIA	1 (0.2%)	0 .	0 .	1 (0.2%)
	VOMITING	8 (1.8%)	13 (2.9%)	0 .	21 (4.6%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND INTENSITY
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
3. MAXIMUM INTENSITY IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL

SB 207499

TABLE 15.4

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY,
MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP=SB 207499 (N=455)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	Intensity Mild	Moderate	Severe	Total
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	TOTAL	18 (4.0%)	12 (2.6%)	2 (0.4%)	32 (7.0%)
	ASTHENIA	2 (0.4%)	0 .	0 .	2 (0.4%)
	CHEST DISCOMFORT	4 (0.9%)	1 (0.2%)	0 .	5 (1.1%)
	CHEST PAIN	2 (0.4%)	2 (0.4%)	1 (0.2%)	5 (1.1%)
	FATIGUE	4 (0.9%)	3 (0.7%)	1 (0.2%)	8 (1.8%)
	FEELING ABNORMAL	0 .	1 (0.2%)	0 .	1 (0.2%)
	INFLUENZA LIKE ILLNESS	1 (0.2%)	2 (0.4%)	0 .	3 (0.7%)
	LETHARGY	0 .	1 (0.2%)	0 .	1 (0.2%)
	MALAISE	2 (0.4%)	0 .	0 .	2 (0.4%)
	OEDEMA PERIPHERAL	3 (0.7%)	0 .	0 .	3 (0.7%)
	PAIN	0 .	2 (0.4%)	0 .	2 (0.4%)
	PYREXIA	1 (0.2%)	1 (0.2%)	0 .	2 (0.4%)
	THIRST	1 (0.2%)	0 .	0 .	1 (0.2%)
HEPATOBILIARY DISORDERS	TOTAL	5 (1.1%)	2 (0.4%)	1 (0.2%)	8 (1.8%)
	BILIARY COLIC	1 (0.2%)	0 .	0 .	1 (0.2%)
	CHOLECYSTITIS CHRONIC	1 (0.2%)	0 .	0 .	1 (0.2%)
	CHOLELITHIASIS	2 (0.4%)	0 .	1 (0.2%)	3 (0.7%)
	CHRONIC HEPATITIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	HEPATIC STEATOSIS	1 (0.2%)	2 (0.4%)	0 .	3 (0.7%)
IMMUNE SYSTEM DISORDERS	TOTAL	1 (0.2%)	1 (0.2%)	0 .	2 (0.4%)
	HYPERSENSITIVITY	0 .	1 (0.2%)	0 .	1 (0.2%)
	SEASONAL ALLERGY	1 (0.2%)	0 .	0 .	1 (0.2%)
INFECTIONS AND INFESTATIONS	TOTAL	57 (12.5%)	66 (14.5%)	3 (0.7%)	126 (27.7%)
	BLADDER INFECTION	0 .	1 (0.2%)	0 .	1 (0.2%)
	BRONCHITIS	3 (0.7%)	3 (0.7%)	0 .	6 (1.3%)
	BRONCHITIS ACUTE	0 .	1 (0.2%)	0 .	1 (0.2%)
	BRONCHITIS ACUTE VIRAL	0 .	1 (0.2%)	0 .	1 (0.2%)
	BRONCHITIS VIRAL	1 (0.2%)	0 .	0 .	1 (0.2%)
	BRONCHOPNEUMONIA	0 .	1 (0.2%)	0 .	1 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND INTENSITY
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
3. MAXIMUM INTENSITY IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL

SB 207499

TABLE 15.4

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY,
MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP=SB 207499 (N=455)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	Intensity Mild	Moderate	Severe	Total
INFECTIONS AND INFESTATIONS	CANDIDIASIS	1 (0.2%)	0 .	0 .	1 (0.2%)
	CHRONIC SINUSITIS	1 (0.2%)	0 .	0 .	1 (0.2%)
	CYSTITIS	0 .	2 (0.4%)	0 .	2 (0.4%)
	CYSTITIS ACUTE	1 (0.2%)	0 .	0 .	1 (0.2%)
	EAR INFECTION	2 (0.4%)	1 (0.2%)	0 .	3 (0.7%)
	EYE INFECTION	1 (0.2%)	1 (0.2%)	0 .	2 (0.4%)
	FUNGAL INFECTION	3 (0.7%)	0 .	0 .	3 (0.7%)
	FURUNCLE	0 .	1 (0.2%)	0 .	1 (0.2%)
	GASTRIC INFECTION	1 (0.2%)	0 .	0 .	1 (0.2%)
	GASTROENTERITIS	2 (0.4%)	0 .	1 (0.2%)	3 (0.7%)
	GASTROENTERITIS VIRAL	2 (0.4%)	1 (0.2%)	0 .	3 (0.7%)
	HELICOBACTER GASTRITIS	1 (0.2%)	0 .	0 .	1 (0.2%)
	HELICOBACTER INFECTION	1 (0.2%)	0 .	0 .	1 (0.2%)
	HERPES SIMPLEX	1 (0.2%)	0 .	0 .	1 (0.2%)
	HERPES ZOSTER	0 .	4 (0.9%)	0 .	4 (0.9%)
	HORDEOLUM	0 .	1 (0.2%)	0 .	1 (0.2%)
	INFECTED SEBACEOUS CYST	1 (0.2%)	0 .	0 .	1 (0.2%)
	INFLUENZA	3 (0.7%)	11 (2.4%)	0 .	14 (3.1%)
	JOINT ABSCESS	0 .	1 (0.2%)	0 .	1 (0.2%)
	LOBAR PNEUMONIA	0 .	1 (0.2%)	0 .	1 (0.2%)
	LOWER RESPIRATORY TRACT INFECTION	2 (0.4%)	4 (0.9%)	0 .	6 (1.3%)
	NASOPHARYNGITIS	29 (6.4%)	14 (3.1%)	0 .	43 (9.5%)
	ONYCHOMYCOSIS	1 (0.2%)	0 .	0 .	1 (0.2%)
	ORAL CANDIDIASIS	1 (0.2%)	0 .	0 .	1 (0.2%)
	ORAL FUNGAL INFECTION	0 .	1 (0.2%)	0 .	1 (0.2%)
	OTITIS EXTERNA	0 .	1 (0.2%)	0 .	1 (0.2%)
	PHARYNGITIS	4 (0.9%)	2 (0.4%)	0 .	6 (1.3%)
	PNEUMONIA	0 .	3 (0.7%)	2 (0.4%)	5 (1.1%)
	PNEUMONIA CHLAMYDIAL	0 .	1 (0.2%)	0 .	1 (0.2%)
	RESPIRATORY TRACT INFECTION	3 (0.7%)	2 (0.4%)	0 .	5 (1.1%)
	RHINITIS INFECTIVE	1 (0.2%)	0 .	0 .	1 (0.2%)
	SALPINGITIS	0 .	1 (0.2%)	0 .	1 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND INTENSITY
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
3. MAXIMUM INTENSITY IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL GM2004/00073/00 SB-207499/157

SB 207499

TABLE 15.4

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY,
MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP=SB 207499 (N=455)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	Intensity Mild	Moderate	Severe	Total
INFECTIONS AND INFESTATIONS	SINUSITIS	2 (0.4%)	2 (0.4%)	0 .	4 (0.9%)
	SKIN INFECTION	0 .	1 (0.2%)	0 .	1 (0.2%)
	TINEA PEDIS	1 (0.2%)	0 .	0 .	1 (0.2%)
	TOOTH ABSCESS	0 .	1 (0.2%)	0 .	1 (0.2%)
	TOOTH INFECTION	0 .	1 (0.2%)	0 .	1 (0.2%)
	UPPER RESPIRATORY TRACT INFECTION	5 (1.1%)	7 (1.5%)	0 .	12 (2.6%)
	URINARY TRACT INFECTION	2 (0.4%)	0 .	0 .	2 (0.4%)
	VIRAL UPPER RESPIRATORY TRACT INFECTION	2 (0.4%)	0 .	0 .	2 (0.4%)
	VULVITIS	0 .	1 (0.2%)	0 .	1 (0.2%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	TOTAL	12 (2.6%)	11 (2.4%)	1 (0.2%)	24 (5.3%)
	ANIMAL BITE	1 (0.2%)	0 .	0 .	1 (0.2%)
	BACK INJURY	0 .	0 .	1 (0.2%)	1 (0.2%)
	BLISTER	1 (0.2%)	1 (0.2%)	0 .	2 (0.4%)
	CHEST INJURY	2 (0.4%)	0 .	0 .	2 (0.4%)
	CONTRAST MEDIA REACTION	1 (0.2%)	0 .	0 .	1 (0.2%)
	CONTUSION	2 (0.4%)	1 (0.2%)	0 .	3 (0.7%)
	EPICONDYLITIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	FALL	0 .	1 (0.2%)	0 .	1 (0.2%)
	JOINT INJURY	1 (0.2%)	2 (0.4%)	1 (0.2%)	4 (0.9%)
	LIMB INJURY	2 (0.4%)	0 .	0 .	2 (0.4%)
	MUSCLE STRAIN	0 .	2 (0.4%)	0 .	2 (0.4%)
	POST PROCEDURAL PAIN	0 .	1 (0.2%)	0 .	1 (0.2%)
	RADIATION ASSOCIATED PAIN	0 .	0 .	1 (0.2%)	1 (0.2%)
	RADIUS FRACTURE	0 .	1 (0.2%)	0 .	1 (0.2%)
	RIB FRACTURE	0 .	2 (0.4%)	0 .	2 (0.4%)
	ROAD TRAFFIC ACCIDENT	1 (0.2%)	0 .	0 .	1 (0.2%)
	SKIN LACERATION	1 (0.2%)	1 (0.2%)	0 .	2 (0.4%)
	TENDON INJURY	1 (0.2%)	0 .	0 .	1 (0.2%)
	TOOTH INJURY	1 (0.2%)	0 .	0 .	1 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND INTENSITY
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
3. MAXIMUM INTENSITY IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL

SB 207499

TABLE 15.4

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY,
MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP=SB 207499 (N=455)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	Intensity Mild	Moderate	Severe	Total
INVESTIGATIONS	TOTAL	20 (4.4%)	12 (2.6%)	2 (0.4%)	34 (7.5%)
	ALANINE AMINOTRANSFERASE INCREASED	1 (0.2%)	0 .	0 .	1 (0.2%)
	ASPARTATE AMINOTRANSFERASE INCREASED	1 (0.2%)	0 .	0 .	1 (0.2%)
	BLOOD ALKALINE PHOSPHATASE INCREASED	1 (0.2%)	0 .	0 .	1 (0.2%)
	BLOOD BILIRUBIN INCREASED	1 (0.2%)	0 .	0 .	1 (0.2%)
	BLOOD GLUCOSE INCREASED	3 (0.7%)	1 (0.2%)	0 .	4 (0.9%)
	BLOOD HOMOCYSTEINE DECREASED	1 (0.2%)	0 .	0 .	1 (0.2%)
	BLOOD IN STOOL	1 (0.2%)	1 (0.2%)	1 (0.2%)	3 (0.7%)
	BLOOD PRESSURE INCREASED	1 (0.2%)	1 (0.2%)	0 .	2 (0.4%)
	BLOOD SODIUM DECREASED	0 .	1 (0.2%)	0 .	1 (0.2%)
	BODY TEMPERATURE INCREASED	2 (0.4%)	0 .	0 .	2 (0.4%)
	C-REACTIVE PROTEIN INCREASED	1 (0.2%)	1 (0.2%)	0 .	2 (0.4%)
	ECG SIGNS OF MYOCARDIAL ISCHAEMIA	1 (0.2%)	0 .	0 .	1 (0.2%)
	EJECTION FRACTION DECREASED	0 .	1 (0.2%)	0 .	1 (0.2%)
	ELECTROCARDIOGRAM T WAVE INVERSION	0 .	1 (0.2%)	0 .	1 (0.2%)
	GAMMA-GLUTAMYLTRANSF ERASE INCREASED	3 (0.7%)	0 .	0 .	3 (0.7%)
	HEART RATE INCREASED	0 .	2 (0.4%)	0 .	2 (0.4%)
	HEPATIC ENZYME INCREASED	1 (0.2%)	1 (0.2%)	0 .	2 (0.4%)
	PLATELET COUNT INCREASED	1 (0.2%)	0 .	0 .	1 (0.2%)
	QRS AXIS ABNORMAL	1 (0.2%)	0 .	0 .	1 (0.2%)
	SPUTUM INCREASED	1 (0.2%)	1 (0.2%)	0 .	2 (0.4%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND INTENSITY
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
3. MAXIMUM INTENSITY IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL

SB 207499

TABLE 15.4

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY,
MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP=SB 207499 (N=455)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	Intensity Mild	Moderate	Severe	Total
INVESTIGATIONS	SPUTUM TEST	1 (0.2%)	0 .	0 .	1 (0.2%)
	URINARY OCCULT BLOOD POSITIVE	0 .	1 (0.2%)	0 .	1 (0.2%)
	URINE KETONE BODY PRESENT	1 (0.2%)	0 .	0 .	1 (0.2%)
	WEIGHT DECREASED	3 (0.7%)	1 (0.2%)	1 (0.2%)	5 (1.1%)
METABOLISM AND NUTRITION DISORDERS	TOTAL	21 (4.6%)	16 (3.5%)	0 .	37 (8.1%)
	ABDOMINAL OBESITY	1 (0.2%)	0 .	0 .	1 (0.2%)
	ANOREXIA	9 (2.0%)	9 (2.0%)	0 .	18 (4.0%)
	DECREASED APPETITE	2 (0.4%)	0 .	0 .	2 (0.4%)
	DIABETES MELLITUS	0 .	3 (0.7%)	0 .	3 (0.7%)
	GOUT	0 .	4 (0.9%)	0 .	4 (0.9%)
	HYPERCHOLESTEROLAEMIA	1 (0.2%)	0 .	0 .	1 (0.2%)
	HYPERGLYCAEMIA	5 (1.1%)	1 (0.2%)	0 .	6 (1.3%)
	HYPERLIPIDAEMIA	1 (0.2%)	0 .	0 .	1 (0.2%)
	HYPERURICAEMIA	1 (0.2%)	0 .	0 .	1 (0.2%)
	HYPOKALAEMIA	2 (0.4%)	0 .	0 .	2 (0.4%)
	VITAMIN B12 DEFICIENCY	2 (0.4%)	0 .	0 .	2 (0.4%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	TOTAL	19 (4.2%)	15 (3.3%)	2 (0.4%)	36 (7.9%)
	ARTHRALGIA	5 (1.1%)	0 .	0 .	5 (1.1%)
	BACK PAIN	1 (0.2%)	4 (0.9%)	1 (0.2%)	6 (1.3%)
	BONE PAIN	1 (0.2%)	0 .	0 .	1 (0.2%)
	BURSITIS	1 (0.2%)	2 (0.4%)	0 .	3 (0.7%)
	FASCIITIS	1 (0.2%)	0 .	0 .	1 (0.2%)
	JOINT EFFUSION	1 (0.2%)	0 .	0 .	1 (0.2%)
	JOINT SWELLING	1 (0.2%)	0 .	0 .	1 (0.2%)
	MONOARTHRITIS	1 (0.2%)	0 .	0 .	1 (0.2%)
	MUSCLE CRAMP	1 (0.2%)	0 .	0 .	1 (0.2%)
	MUSCLE RIGIDITY	0 .	2 (0.4%)	0 .	2 (0.4%)
	MUSCLE TIGHTNESS	1 (0.2%)	0 .	0 .	1 (0.2%)
	MUSCULOSKELETAL PAIN	1 (0.2%)	0 .	0 .	1 (0.2%)
	MYALGIA	3 (0.7%)	0 .	0 .	3 (0.7%)
	OSTEOARTHRITIS	1 (0.2%)	2 (0.4%)	0 .	3 (0.7%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND INTENSITY
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
3. MAXIMUM INTENSITY IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL

SB 207499

TABLE 15.4

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY,
MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP=SB 207499 (N=455)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	Intensity Mild	Moderate	Severe	Total
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	OSTEOPOROSIS	1 (0.2%)	0 .	0 .	1 (0.2%)
	PAIN IN EXTREMITY	2 (0.4%)	2 (0.4%)	1 (0.2%)	5 (1.1%)
	PERIARTHRITIS	0 .	2 (0.4%)	0 .	2 (0.4%)
	RHEUMATOID ARTHRITIS	1 (0.2%)	0 .	0 .	1 (0.2%)
	SPINAL DISORDER	1 (0.2%)	1 (0.2%)	0 .	2 (0.4%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	TOTAL	1 (0.2%)	2 (0.4%)	1 (0.2%)	4 (0.9%)
	BLADDER CANCER	0 .	1 (0.2%)	0 .	1 (0.2%)
	LUNG NEOPLASM MALIGNANT	0 .	0 .	1 (0.2%)	1 (0.2%)
	SKIN PAPILLOMA	1 (0.2%)	0 .	0 .	1 (0.2%)
	SQUAMOUS CELL CARCINOMA	0 .	1 (0.2%)	0 .	1 (0.2%)
NERVOUS SYSTEM DISORDERS	TOTAL	25 (5.5%)	29 (6.4%)	1 (0.2%)	55 (12.1%)
	CEREBROVASCULAR ACCIDENT	1 (0.2%)	0 .	0 .	1 (0.2%)
	CEREBROVASCULAR DISORDER	1 (0.2%)	0 .	0 .	1 (0.2%)
	CONVULSION	0 .	1 (0.2%)	0 .	1 (0.2%)
	DISTURBANCE IN ATTENTION	1 (0.2%)	0 .	0 .	1 (0.2%)
	DIZZINESS	6 (1.3%)	7 (1.5%)	0 .	13 (2.9%)
	DIZZINESS POSTURAL	1 (0.2%)	0 .	0 .	1 (0.2%)
	DYSGEUSIA	0 .	1 (0.2%)	0 .	1 (0.2%)
	FACIAL PALSY	0 .	2 (0.4%)	0 .	2 (0.4%)
	HEADACHE	19 (4.2%)	15 (3.3%)	1 (0.2%)	35 (7.7%)
	HYPOAESTHESIA	0 .	1 (0.2%)	0 .	1 (0.2%)
	LUMBAR SPINAL STENOSIS	1 (0.2%)	0 .	0 .	1 (0.2%)
	PARKINSON'S DISEASE	1 (0.2%)	0 .	0 .	1 (0.2%)
	SPINAL COLUMN STENOSIS	1 (0.2%)	0 .	0 .	1 (0.2%)
	SYNCOPE	0 .	2 (0.4%)	0 .	2 (0.4%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND INTENSITY
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
3. MAXIMUM INTENSITY IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL

SB 207499

TABLE 15.4

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY,
MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP=SB 207499 (N=455)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	Intensity Mild	Moderate	Severe	Total
NERVOUS SYSTEM DISORDERS	TRANSIENT ISCHAEMIC ATTACK	0 .	1 (0.2%)	0 .	1 (0.2%)
	TREMOR	1 (0.2%)	1 (0.2%)	0 .	2 (0.4%)
	VERTEBRAL ARTERY OCCLUSION	1 (0.2%)	0 .	0 .	1 (0.2%)
PSYCHIATRIC DISORDERS	TOTAL	8 (1.8%)	14 (3.1%)	1 (0.2%)	23 (5.1%)
	AFFECT LABILITY	0 .	1 (0.2%)	0 .	1 (0.2%)
	ANXIETY	4 (0.9%)	3 (0.7%)	0 .	7 (1.5%)
	DEPRESSION	2 (0.4%)	5 (1.1%)	0 .	7 (1.5%)
	EMOTIONAL DISTRESS	0 .	1 (0.2%)	0 .	1 (0.2%)
	INSOMNIA	1 (0.2%)	1 (0.2%)	0 .	2 (0.4%)
	MIDDLE INSOMNIA	1 (0.2%)	0 .	0 .	1 (0.2%)
	PANIC ATTACK	0 .	0 .	1 (0.2%)	1 (0.2%)
	SLEEP DISORDER	1 (0.2%)	3 (0.7%)	0 .	4 (0.9%)
RENAL AND URINARY DISORDERS	TOTAL	9 (2.0%)	5 (1.1%)	0 .	14 (3.1%)
	HAEMATURIA	2 (0.4%)	1 (0.2%)	0 .	3 (0.7%)
	HYPERTONIC BLADDER	1 (0.2%)	0 .	0 .	1 (0.2%)
	KIDNEY HYPERMOBILITY	1 (0.2%)	0 .	0 .	1 (0.2%)
	NEPHROLITHIASIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	NOCTURIA	1 (0.2%)	0 .	0 .	1 (0.2%)
	PROTEINURIA	2 (0.4%)	2 (0.4%)	0 .	4 (0.9%)
	RENAL COLIC	0 .	2 (0.4%)	0 .	2 (0.4%)
	RENAL IMPAIRMENT	1 (0.2%)	0 .	0 .	1 (0.2%)
	STRANGURY	1 (0.2%)	0 .	0 .	1 (0.2%)
	URINARY RETENTION	1 (0.2%)	0 .	0 .	1 (0.2%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	TOTAL	5 (1.1%)	3 (0.7%)	0 .	8 (1.8%)
	BENIGN PROSTATIC HYPERPLASIA	1 (0.2%)	0 .	0 .	1 (0.2%)
	EPIDIDYMITIS	0 .	1 (0.2%)	0 .	1 (0.2%)
	GYNAECOMASTIA	0 .	1 (0.2%)	0 .	1 (0.2%)
	PROSTATIC HYPERTROPHY	0 .	1 (0.2%)	0 .	1 (0.2%)
	PROSTATISM	1 (0.2%)	0 .	0 .	1 (0.2%)
	PROSTATITIS	1 (0.2%)	0 .	0 .	1 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND INTENSITY
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
3. MAXIMUM INTENSITY IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.4

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY,
MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP=SB 207499 (N=455)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	Intensity Mild	Moderate	Severe	Total
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	SEXUAL DYSFUNCTION	1 (0.2%)	0 .	0 .	1 (0.2%)
	VAGINAL HAEMORRHAGE	1 (0.2%)	0 .	0 .	1 (0.2%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	TOTAL	81 (17.8%)	118 (25.9%)	21 (4.6%)	220 (48.4%)
	ACUTE RESPIRATORY FAILURE	0 .	0 .	1 (0.2%)	1 (0.2%)
	CATARRH	1 (0.2%)	0 .	0 .	1 (0.2%)
	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE EXACERBATED	66 (14.5%)	108 (23.7%)	17 (3.7%)	191 (42.0%)
	COUGH	8 (1.8%)	6 (1.3%)	0 .	14 (3.1%)
	DYSPHONIA	1 (0.2%)	0 .	0 .	1 (0.2%)
	DYSPNOEA	1 (0.2%)	0 .	2 (0.4%)	3 (0.7%)
	DYSPNOEA EXACERBATED	0 .	6 (1.3%)	1 (0.2%)	7 (1.5%)
	EPISTAXIS	3 (0.7%)	1 (0.2%)	0 .	4 (0.9%)
	INCREASED BRONCHIAL SECRETION	1 (0.2%)	0 .	0 .	1 (0.2%)
	NASAL CONGESTION	1 (0.2%)	1 (0.2%)	0 .	2 (0.4%)
	NASAL SEPTUM DEVIATION	0 .	1 (0.2%)	0 .	1 (0.2%)
	PHARYNGOLARYNGEAL PAIN	5 (1.1%)	1 (0.2%)	0 .	6 (1.3%)
	PLEURISY	0 .	1 (0.2%)	0 .	1 (0.2%)
	POSTNASAL DRIP	2 (0.4%)	0 .	0 .	2 (0.4%)
	RESPIRATORY ALKALOSIS	0 .	0 .	1 (0.2%)	1 (0.2%)
	RHINITIS	10 (2.2%)	2 (0.4%)	0 .	12 (2.6%)
	RHINITIS ALLERGIC	3 (0.7%)	1 (0.2%)	0 .	4 (0.9%)
	RHINORRHOEA	1 (0.2%)	1 (0.2%)	0 .	2 (0.4%)
	THROAT IRRITATION	2 (0.4%)	0 .	0 .	2 (0.4%)
	WHEEZING	1 (0.2%)	1 (0.2%)	0 .	2 (0.4%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	TOTAL	10 (2.2%)	8 (1.8%)	0 .	18 (4.0%)
	DERMATITIS CONTACT	0 .	1 (0.2%)	0 .	1 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND INTENSITY
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
3. MAXIMUM INTENSITY IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL

SB 207499

TABLE 15.4

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY,
MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP=SB 207499 (N=455)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	Intensity Mild	Moderate	Severe	Total
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	DRY SKIN	1 (0.2%)	0 .	0 .	1 (0.2%)
	ECZEMA	2 (0.4%)	0 .	0 .	2 (0.4%)
	HYPERHIDROSIS	1 (0.2%)	0 .	0 .	1 (0.2%)
	NEURODERMATITIS	1 (0.2%)	0 .	0 .	1 (0.2%)
	PRURITUS	2 (0.4%)	2 (0.4%)	0 .	4 (0.9%)
	RASH	0 .	1 (0.2%)	0 .	1 (0.2%)
	RASH PRURITIC	0 .	1 (0.2%)	0 .	1 (0.2%)
	SKIN ATROPHY	0 .	1 (0.2%)	0 .	1 (0.2%)
	SKIN BURNING SENSATION	1 (0.2%)	0 .	0 .	1 (0.2%)
	SKIN HYPERTROPHY	0 .	1 (0.2%)	0 .	1 (0.2%)
	SKIN LESION	1 (0.2%)	0 .	0 .	1 (0.2%)
	URTICARIA	2 (0.4%)	2 (0.4%)	0 .	4 (0.9%)
	URTICARIA PAPULAR	1 (0.2%)	0 .	0 .	1 (0.2%)
	VASCULAR SKIN DISORDER	0 .	1 (0.2%)	0 .	1 (0.2%)
SOCIAL CIRCUMSTANCES	TOTAL	1 (0.2%)	0 .	0 .	1 (0.2%)
	ALCOHOL USE	1 (0.2%)	0 .	0 .	1 (0.2%)
SURGICAL AND MEDICAL PROCEDURES	TOTAL	0 .	1 (0.2%)	0 .	1 (0.2%)
	TOOTH EXTRACTION	0 .	1 (0.2%)	0 .	1 (0.2%)
VASCULAR DISORDERS	TOTAL	18 (4.0%)	4 (0.9%)	0 .	22 (4.8%)
	AORTIC ANEURYSM	1 (0.2%)	0 .	0 .	1 (0.2%)
	AORTIC DISSECTION	1 (0.2%)	0 .	0 .	1 (0.2%)
	CIRCULATORY COLLAPSE	0 .	1 (0.2%)	0 .	1 (0.2%)
	DIASTOLIC HYPERTENSION	1 (0.2%)	0 .	0 .	1 (0.2%)
	HAEMATOMA	0 .	1 (0.2%)	0 .	1 (0.2%)
	HOT FLUSH	1 (0.2%)	0 .	0 .	1 (0.2%)
	HYPERTENSION	11 (2.4%)	2 (0.4%)	0 .	13 (2.9%)
	HYPOTENSION	2 (0.4%)	0 .	0 .	2 (0.4%)
	ORTHOSTATIC HYPOTENSION	1 (0.2%)	0 .	0 .	1 (0.2%)
	PHLEBITIS	1 (0.2%)	0 .	0 .	1 (0.2%)
	VARICOSE VEIN	1 (0.2%)	0 .	0 .	1 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND INTENSITY
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
3. MAXIMUM INTENSITY IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL

SB 207499

TABLE 15.5

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES (>= 2%) BY INITIAL TIME OF ONSET, MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP: PLACEBO

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE: 1 (N= 452) n	(%)	2-7 (N= 450) n	(%)	8-14 (N= 447) n	(%)	15-21 (N= 438) n	(%)	22-28 (N= 434) n	(%)
TOTAL PATIENTS WITH ADVERSE EXPERIENCES	TOTAL	13	2.9%	37	8.2%	36	8.1%	32	7.3%	30	6.9%
GASTROINTESTINAL DISORDERS	TOTAL	0	.	3	0.7%	6	1.3%	4	0.9%	2	0.5%
	ABDOMINAL PAIN	0	.	0	.	1	0.2%	0	.	0	.
	ABDOMINAL PAIN UPPER	0	.	2	0.4%	0	.	0	.	1	0.2%
	DIARRHOEA	0	.	1	0.2%	3	0.7%	3	0.7%	0	.
	DYSPEPSIA	0	.	0	.	0	.	1	0.2%	0	.
	NAUSEA	0	.	1	0.2%	3	0.7%	1	0.2%	1	0.2%
	VOMITING	0	.	1	0.2%	0	.	0	.	0	.
INFECTIONS AND INFESTATIONS	TOTAL	0	.	6	1.3%	1	0.2%	4	0.9%	6	1.4%
	INFLUENZA	0	.	1	0.2%	0	.	1	0.2%	2	0.5%
	NASOPHARYNGITIS	0	.	4	0.9%	1	0.2%	3	0.7%	3	0.7%
	UPPER RESPIRATORY TRACT INFECTION	0	.	1	0.2%	0	.	0	.	1	0.2%
METABOLISM AND NUTRITION DISORDERS	TOTAL	0	.	0	.	0	.	1	0.2%	0	.
	ANOREXIA	0	.	0	.	0	.	1	0.2%	0	.
NERVOUS SYSTEM DISORDERS	TOTAL	1	0.2%	3	0.7%	2	0.4%	3	0.7%	0	.
	DIZZINESS	0	.	1	0.2%	0	.	0	.	0	.
	HEADACHE	1	0.2%	2	0.4%	2	0.4%	3	0.7%	0	.
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	TOTAL	0	.	12	2.7%	15	3.4%	10	2.3%	5	1.2%
	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE EXACERBATED	0	.	11	2.4%	12	2.7%	9	2.1%	4	0.9%
	COUGH	0	.	1	0.2%	2	0.4%	1	0.2%	1	0.2%
	RHINITIS	0	.	0	.	1	0.2%	1	0.2%	0	.
VASCULAR DISORDERS	TOTAL	1	0.2%	0	.	0	.	0	.	0	.
	HYPERTENSION	1	0.2%	0	.	0	.	0	.	0	.

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND ONSET
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS EXPOSED TO STUDY MEDICATION WITHIN EACH TIME INTERVAL
4. EVENTS OCCURING IN AT LEAST 2% OF PATIENTS IN THE SB 207499 GROUP ARE INCLUDED
5. EVENTS FOR WHICH THE ONSET IS UNDETERMINED ARE ASSUMED TO HAVE OCCURRED AT DAY 1

CONFIDENTIAL

SB 207499

TABLE 15.5

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES (>= 2%) BY INITIAL TIME OF ONSET, MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP: PLACEBO

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE: 29-56 (N= 430) n	(%)	57-84 (N= 416) n	(%)	85-112 (N= 404) n	(%)	113-140 (N= 396) n	(%)	141-168 (N= 391) n	(%)
TOTAL PATIENTS WITH ADVERSE EXPERIENCES	TOTAL	106	24.7%	82	19.7%	62	15.3%	48	12.1%	48	12.3%
GASTROINTESTINAL DISORDERS	TOTAL	7	1.6%	6	1.4%	3	0.7%	2	0.5%	2	0.5%
	ABDOMINAL PAIN	2	0.5%	0	.	0	.	1	0.3%	1	0.3%
	ABDOMINAL PAIN UPPER	1	0.2%	1	0.2%	0	.	0	.	0	.
	DIARRHOEA	1	0.2%	2	0.5%	1	0.2%	1	0.3%	0	.
	DYSPEPSIA	0	.	1	0.2%	1	0.2%	0	.	0	.
	NAUSEA	2	0.5%	2	0.5%	0	.	0	.	1	0.3%
	VOMITING	2	0.5%	2	0.5%	1	0.2%	0	.	0	.
INFECTIONS AND INFESTATIONS	TOTAL	7	1.6%	7	1.7%	2	0.5%	4	1.0%	6	1.5%
	INFLUENZA	0	.	2	0.5%	1	0.2%	1	0.3%	2	0.5%
	NASOPHARYNGITIS	7	1.6%	4	1.0%	1	0.2%	2	0.5%	3	0.8%
	UPPER RESPIRATORY TRACT INFECTION	0	.	1	0.2%	0	.	1	0.3%	1	0.3%
METABOLISM AND NUTRITION DISORDERS	TOTAL	0	.	0	.	0	.	0	.	0	.
	ANOREXIA	0	.	0	.	0	.	0	.	0	.
NERVOUS SYSTEM DISORDERS	TOTAL	6	1.4%	3	0.7%	1	0.2%	1	0.3%	0	.
	DIZZINESS	0	.	0	.	0	.	1	0.3%	0	.
	HEADACHE	6	1.4%	3	0.7%	1	0.2%	0	.	0	.
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	TOTAL	41	9.5%	33	7.9%	21	5.2%	17	4.3%	15	3.8%
	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE EXACERBATED	41	9.5%	30	7.2%	18	4.5%	15	3.8%	14	3.6%
	COUGH	0	.	1	0.2%	1	0.2%	0	.	1	0.3%
	RHINITIS	0	.	2	0.5%	2	0.5%	2	0.5%	0	.
VASCULAR DISORDERS	TOTAL	2	0.5%	3	0.7%	1	0.2%	1	0.3%	2	0.5%
	HYPERTENSION	2	0.5%	3	0.7%	1	0.2%	1	0.3%	2	0.5%

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND ONSET
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS EXPOSED TO STUDY MEDICATION WITHIN EACH TIME INTERVAL
4. EVENTS OCCURING IN AT LEAST 2% OF PATIENTS IN THE SB 207499 GROUP ARE INCLUDED
5. EVENTS FOR WHICH THE ONSET IS UNDETERMINED ARE ASSUMED TO HAVE OCCURRED AT DAY 1

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.5

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES (>= 2%) BY INITIAL TIME OF ONSET, MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP: PLACEBO

		DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE			
		>168 (N= 386)		TOTAL (N= 452)	
MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	n	(%)	n	(%)
TOTAL PATIENTS WITH ADVERSE EXPERIENCES	TOTAL	181	46.9%	343	75.9%
GASTROINTESTINAL DISORDERS	TOTAL	7	1.8%	38	8.4%
	ABDOMINAL PAIN	0	.	5	1.1%
	ABDOMINAL PAIN UPPER	0	.	5	1.1%
	DIARRHOEA	1	0.3%	13	2.9%
	DYSPEPSIA	3	0.8%	6	1.3%
	NAUSEA	3	0.8%	14	3.1%
	VOMITING	2	0.5%	8	1.8%
INFECTIONS AND INFESTATIONS	TOTAL	36	9.3%	75	16.6%
	INFLUENZA	7	1.8%	17	3.8%
	NASOPHARYNGITIS	26	6.7%	54	11.9%
	UPPER RESPIRATORY TRACT INFECTION	6	1.6%	11	2.4%
METABOLISM AND NUTRITION DISORDERS	TOTAL	0	.	1	0.2%
	ANOREXIA	0	.	1	0.2%
NERVOUS SYSTEM DISORDERS	TOTAL	6	1.6%	24	5.3%
	DIZZINESS	3	0.8%	5	1.1%
	HEADACHE	4	1.0%	22	4.9%
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	TOTAL	60	15.5%	216	47.8%
	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE EXACERBATED	55	14.2%	209	46.2%
	COUGH	3	0.8%	11	2.4%
	RHINITIS	3	0.8%	11	2.4%
VASCULAR DISORDERS	TOTAL	8	2.1%	18	4.0%
	HYPERTENSION	8	2.1%	18	4.0%

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND ONSET
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS EXPOSED TO STUDY MEDICATION WITHIN EACH TIME INTERVAL
4. EVENTS OCCURING IN AT LEAST 2% OF PATIENTS IN THE SB 207499 GROUP ARE INCLUDED
5. EVENTS FOR WHICH THE ONSET IS UNDETERMINED ARE ASSUMED TO HAVE OCCURRED AT DAY 1

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.5

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES (>= 2%) BY INITIAL TIME OF ONSET, MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP: SB 207499

		DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE									
		1 (N= 455)		2-7 (N= 451)		8-14 (N= 443)		15-21 (N= 433)		22-28 (N= 417)	
MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
TOTAL PATIENTS WITH ADVERSE EXPERIENCES	TOTAL	25	5.5%	62	13.7%	46	10.4%	47	10.9%	39	9.4%
GASTROINTESTINAL DISORDERS	TOTAL	11	2.4%	31	6.9%	10	2.3%	13	3.0%	9	2.2%
	ABDOMINAL PAIN	2	0.4%	1	0.2%	2	0.5%	1	0.2%	1	0.2%
	ABDOMINAL PAIN UPPER	1	0.2%	3	0.7%	2	0.5%	2	0.5%	0	.
	DIARRHOEA	3	0.7%	10	2.2%	3	0.7%	2	0.5%	4	1.0%
	DYSPEPSIA	4	0.9%	4	0.9%	2	0.5%	2	0.5%	2	0.5%
	NAUSEA	4	0.9%	18	4.0%	3	0.7%	4	0.9%	1	0.2%
	VOMITING	2	0.4%	1	0.2%	0	.	4	0.9%	1	0.2%
INFECTIONS AND INFESTATIONS	TOTAL	0	.	2	0.4%	3	0.7%	3	0.7%	1	0.2%
	INFLUENZA	0	.	0	.	0	.	1	0.2%	0	.
	NASOPHARYNGITIS	0	.	2	0.4%	2	0.5%	2	0.5%	0	.
	UPPER RESPIRATORY TRACT INFECTION	0	.	0	.	1	0.2%	0	.	1	0.2%
METABOLISM AND NUTRITION DISORDERS	TOTAL	0	.	4	0.9%	3	0.7%	1	0.2%	0	.
	ANOREXIA	0	.	4	0.9%	3	0.7%	1	0.2%	0	.
NERVOUS SYSTEM DISORDERS	TOTAL	4	0.9%	12	2.7%	3	0.7%	6	1.4%	2	0.5%
	DIZZINESS	0	.	4	0.9%	0	.	2	0.5%	1	0.2%
	HEADACHE	4	0.9%	9	2.0%	3	0.7%	4	0.9%	2	0.5%
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	TOTAL	1	0.2%	11	2.4%	15	3.4%	13	3.0%	9	2.2%
	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE EXACERBATED	1	0.2%	10	2.2%	13	2.9%	12	2.8%	9	2.2%
	COUGH	0	.	1	0.2%	2	0.5%	0	.	0	.
	RHINITIS	0	.	0	.	0	.	1	0.2%	0	.
VASCULAR DISORDERS	TOTAL	0	.	0	.	2	0.5%	0	.	0	.
	HYPERTENSION	0	.	0	.	2	0.5%	0	.	0	.

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND ONSET
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS EXPOSED TO STUDY MEDICATION WITHIN EACH TIME INTERVAL
4. EVENTS OCCURING IN AT LEAST 2% OF PATIENTS IN THE SB 207499 GROUP ARE INCLUDED
5. EVENTS FOR WHICH THE ONSET IS UNDETERMINED ARE ASSUMED TO HAVE OCCURRED AT DAY 1

CONFIDENTIAL

SB 207499

TABLE 15.5

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES (>= 2%) BY INITIAL TIME OF ONSET, MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP: SB 207499

		DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE									
		29-56 (N= 412)		57-84 (N= 392)		85-112 (N= 368)		113-140 (N= 354)		141-168 (N= 346)	
MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
TOTAL PATIENTS WITH ADVERSE EXPERIENCES	TOTAL	90	21.8%	89	22.7%	59	16.0%	60	16.9%	45	13.0%
GASTROINTESTINAL DISORDERS	TOTAL	13	3.2%	8	2.0%	6	1.6%	2	0.6%	2	0.6%
	ABDOMINAL PAIN	1	0.2%	0	.	0	.	0	.	0	.
	ABDOMINAL PAIN UPPER	1	0.2%	0	.	2	0.5%	0	.	0	.
	DIARRHOEA	4	1.0%	3	0.8%	1	0.3%	0	.	1	0.3%
	DYSPEPSIA	2	0.5%	1	0.3%	0	.	0	.	0	.
	NAUSEA	5	1.2%	4	1.0%	2	0.5%	0	.	0	.
	VOMITING	2	0.5%	4	1.0%	1	0.3%	2	0.6%	1	0.3%
INFECTIONS AND INFESTATIONS	TOTAL	9	2.2%	7	1.8%	7	1.9%	11	3.1%	3	0.9%
	INFLUENZA	1	0.2%	4	1.0%	0	.	1	0.3%	2	0.6%
	NASOPHARYNGITIS	7	1.7%	1	0.3%	6	1.6%	9	2.5%	1	0.3%
	UPPER RESPIRATORY TRACT INFECTION	1	0.2%	2	0.5%	1	0.3%	1	0.3%	0	.
METABOLISM AND NUTRITION DISORDERS	TOTAL	0	.	1	0.3%	5	1.4%	0	.	2	0.6%
	ANOREXIA	0	.	1	0.3%	5	1.4%	0	.	2	0.6%
NERVOUS SYSTEM DISORDERS	TOTAL	6	1.5%	4	1.0%	1	0.3%	1	0.3%	2	0.6%
	DIZZINESS	2	0.5%	2	0.5%	0	.	0	.	0	.
	HEADACHE	4	1.0%	2	0.5%	1	0.3%	1	0.3%	2	0.6%
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	TOTAL	31	7.5%	36	9.2%	19	5.2%	23	6.5%	11	3.2%
	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE EXACERBATED	27	6.6%	34	8.7%	18	4.9%	19	5.4%	10	2.9%
	COUGH	3	0.7%	2	0.5%	1	0.3%	1	0.3%	1	0.3%
	RHINITIS	3	0.7%	0	.	0	.	3	0.8%	0	.
VASCULAR DISORDERS	TOTAL	0	.	2	0.5%	1	0.3%	1	0.3%	1	0.3%
	HYPERTENSION	0	.	2	0.5%	1	0.3%	1	0.3%	1	0.3%

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND ONSET
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS EXPOSED TO STUDY MEDICATION WITHIN EACH TIME INTERVAL
4. EVENTS OCCURING IN AT LEAST 2% OF PATIENTS IN THE SB 207499 GROUP ARE INCLUDED
5. EVENTS FOR WHICH THE ONSET IS UNDETERMINED ARE ASSUMED TO HAVE OCCURRED AT DAY 1

CONFIDENTIAL

SB 207499

TABLE 15.5

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES (>= 2%) BY INITIAL TIME OF ONSET, MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

TREATMENT GROUP: SB 207499

		DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE			
		>168 (N= 337)		TOTAL (N= 455)	
MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	n	(%)	n	(%)
TOTAL PATIENTS WITH ADVERSE EXPERIENCES	TOTAL	148	43.9%	351	77.1%
GASTROINTESTINAL DISORDERS	TOTAL	9	2.7%	96	21.1%
	ABDOMINAL PAIN	1	0.3%	9	2.0%
	ABDOMINAL PAIN UPPER	2	0.6%	13	2.9%
	DIARRHOEA	2	0.6%	33	7.3%
	DYSPEPSIA	1	0.3%	18	4.0%
	NAUSEA	3	0.9%	44	9.7%
	VOMITING	3	0.9%	21	4.6%
INFECTIONS AND INFESTATIONS	TOTAL	22	6.5%	64	14.1%
	INFLUENZA	5	1.5%	14	3.1%
	NASOPHARYNGITIS	13	3.9%	43	9.5%
	UPPER RESPIRATORY TRACT INFECTION	5	1.5%	12	2.6%
METABOLISM AND NUTRITION DISORDERS	TOTAL	2	0.6%	18	4.0%
	ANOREXIA	2	0.6%	18	4.0%
NERVOUS SYSTEM DISORDERS	TOTAL	4	1.2%	43	9.5%
	DIZZINESS	2	0.6%	13	2.9%
	HEADACHE	3	0.9%	35	7.7%
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	TOTAL	44	13.1%	203	44.6%
	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE EXACERBATED	38	11.3%	191	42.0%
	COUGH	3	0.9%	14	3.1%
	RHINITIS	5	1.5%	12	2.6%
VASCULAR DISORDERS	TOTAL	6	1.8%	13	2.9%
	HYPERTENSION	6	1.8%	13	2.9%

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND ONSET
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS EXPOSED TO STUDY MEDICATION WITHIN EACH TIME INTERVAL
4. EVENTS OCCURING IN AT LEAST 2% OF PATIENTS IN THE SB 207499 GROUP ARE INCLUDED
5. EVENTS FOR WHICH THE ONSET IS UNDETERMINED ARE ASSUMED TO HAVE OCCURRED AT DAY 1

CONFIDENTIAL

SB 207499

TABLE 15.6

ON-THERAPY ADVERSE EXPERIENCES THAT LED TO INTERRUPTION BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
TOTAL	TOTAL	24 (5.3%)	40 (8.8%)	64 (7.1%)
CARDIAC DISORDERS	TOTAL	2 (0.4%)	3 (0.7%)	5 (0.6%)
	ACUTE MYOCARDIAL INFARCTION	0 .	1 (0.2%)	1 (0.1%)
	ANGINA PECTORIS	0 .	1 (0.2%)	1 (0.1%)
	ANGINA UNSTABLE	1 (0.2%)	0 .	1 (0.1%)
	ATRIAL FLUTTER	0 .	1 (0.2%)	1 (0.1%)
	MYOCARDIAL ISCHAEMIA	1 (0.2%)	0 .	1 (0.1%)
EAR AND LABYRINTH DISORDERS	TOTAL	1 (0.2%)	0 .	1 (0.1%)
	VERTIGO	1 (0.2%)	0 .	1 (0.1%)
GASTROINTESTINAL DISORDERS	TOTAL	9 (2.0%)	15 (3.3%)	24 (2.6%)
	ABDOMINAL DISTENSION	1 (0.2%)	0 .	1 (0.1%)
	ABDOMINAL PAIN	1 (0.2%)	1 (0.2%)	2 (0.2%)
	ABDOMINAL PAIN UPPER	1 (0.2%)	2 (0.4%)	3 (0.3%)
	DIARRHOEA	1 (0.2%)	2 (0.4%)	3 (0.3%)
	DIVERTICULUM	0 .	1 (0.2%)	1 (0.1%)
	DYSPEPSIA	1 (0.2%)	2 (0.4%)	3 (0.3%)
	FAECES PALE	1 (0.2%)	0 .	1 (0.1%)
	FREQUENT BOWEL MOVEMENTS	1 (0.2%)	0 .	1 (0.1%)
	GASTRITIS	0 .	1 (0.2%)	1 (0.1%)
	GASTROINTESTINAL DISORDER	0 .	1 (0.2%)	1 (0.1%)
	GASTROINTESTINAL UPSET	0 .	1 (0.2%)	1 (0.1%)
	INTESTINAL OBSTRUCTION	1 (0.2%)	0 .	1 (0.1%)
	INTESTINAL PERFORATION	1 (0.2%)	0 .	1 (0.1%)
	LOOSE STOOLS	0 .	1 (0.2%)	1 (0.1%)
	NAUSEA	4 (0.9%)	6 (1.3%)	10 (1.1%)
	VOMITING	1 (0.2%)	1 (0.2%)	2 (0.2%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	TOTAL	2 (0.4%)	1 (0.2%)	3 (0.3%)
	CHEST DISCOMFORT	1 (0.2%)	0 .	1 (0.1%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED

CONFIDENTIAL

SB 207499

TABLE 15.6

ON-THERAPY ADVERSE EXPERIENCES THAT LED TO INTERRUPTION BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	FATIGUE	0 .	1 (0.2%)	1 (0.1%)
	PYREXIA	1 (0.2%)	0 .	1 (0.1%)
	THIRST	0 .	1 (0.2%)	1 (0.1%)
HEPATOBILIARY DISORDERS	TOTAL	0 .	1 (0.2%)	1 (0.1%)
	CHOLELITHIASIS	0 .	1 (0.2%)	1 (0.1%)
IMMUNE SYSTEM DISORDERS	TOTAL	1 (0.2%)	0 .	1 (0.1%)
	ANAPHYLACTIC SHOCK	1 (0.2%)	0 .	1 (0.1%)
INFECTIONS AND INFESTATIONS	TOTAL	2 (0.4%)	4 (0.9%)	6 (0.7%)
	EAR INFECTION	0 .	1 (0.2%)	1 (0.1%)
	GASTROENTERITIS	0 .	2 (0.4%)	2 (0.2%)
	HERPES ZOSTER	1 (0.2%)	0 .	1 (0.1%)
	PNEUMONIA	0 .	1 (0.2%)	1 (0.1%)
	RESPIRATORY TRACT INFECTION	1 (0.2%)	0 .	1 (0.1%)
	URINARY TRACT INFECTION	1 (0.2%)	0 .	1 (0.1%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	TOTAL	2 (0.4%)	0 .	2 (0.2%)
	HIP FRACTURE	1 (0.2%)	0 .	1 (0.1%)
	THERMAL BURN	1 (0.2%)	0 .	1 (0.1%)
INVESTIGATIONS	TOTAL	0 .	1 (0.2%)	1 (0.1%)
	BLOOD IN STOOL	0 .	1 (0.2%)	1 (0.1%)
METABOLISM AND NUTRITION DISORDERS	TOTAL	0 .	3 (0.7%)	3 (0.3%)
	ANOREXIA	0 .	3 (0.7%)	3 (0.3%)
NERVOUS SYSTEM DISORDERS	TOTAL	4 (0.9%)	8 (1.8%)	12 (1.3%)
	CEREBROVASCULAR ACCIDENT	1 (0.2%)	1 (0.2%)	2 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED

CONFIDENTIAL

SB 207499

TABLE 15.6

ON-THERAPY ADVERSE EXPERIENCES THAT LED TO INTERRUPTION BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
NERVOUS SYSTEM DISORDERS	DIZZINESS	0 .	1 (0.2%)	1 (0.1%)
	HEADACHE	3 (0.7%)	5 (1.1%)	8 (0.9%)
	LUMBAR SPINAL STENOSIS	0 .	1 (0.2%)	1 (0.1%)
PSYCHIATRIC DISORDERS	TOTAL	1 (0.2%)	2 (0.4%)	3 (0.3%)
	ANXIETY	0 .	1 (0.2%)	1 (0.1%)
	DEPRESSION	1 (0.2%)	1 (0.2%)	2 (0.2%)
RENAL AND URINARY DISORDERS	TOTAL	1 (0.2%)	0 .	1 (0.1%)
	CALCULUS BLADDER	1 (0.2%)	0 .	1 (0.1%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	TOTAL	6 (1.3%)	8 (1.8%)	14 (1.5%)
	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE EXACERBATED	4 (0.9%)	6 (1.3%)	10 (1.1%)
	COUGH	1 (0.2%)	0 .	1 (0.1%)
	DYSPNOEA	0 .	1 (0.2%)	1 (0.1%)
	EPISTAXIS	1 (0.2%)	0 .	1 (0.1%)
	PNEUMOTHORAX	1 (0.2%)	0 .	1 (0.1%)
	RESPIRATORY ALKALOSIS	0 .	1 (0.2%)	1 (0.1%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	TOTAL	1 (0.2%)	2 (0.4%)	3 (0.3%)
	DERMATITIS MEDICAMENTOSA	1 (0.2%)	0 .	1 (0.1%)
	RASH PRURITIC	0 .	1 (0.2%)	1 (0.1%)
	URTICARIA	0 .	1 (0.2%)	1 (0.1%)
VASCULAR DISORDERS	TOTAL	1 (0.2%)	1 (0.2%)	2 (0.2%)
	HYPERTENSIVE CRISIS	1 (0.2%)	0 .	1 (0.1%)
	HYPOTENSION	0 .	1 (0.2%)	1 (0.1%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED

CONFIDENTIAL

SB 207499

TABLE 15.7

ON-THERAPY ADVERSE EXPERIENCES THAT REQUIRED CORRECTIVE THERAPY BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
TOTAL	TOTAL	288 (63.7%)	285 (62.6%)	573 (63.2%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	TOTAL	6 (1.3%)	3 (0.7%)	9 (1.0%)
	ANAEMIA	2 (0.4%)	1 (0.2%)	3 (0.3%)
	IRON DEFICIENCY ANAEMIA	1 (0.2%)	0 .	1 (0.1%)
	LEUKOCYTOSIS	1 (0.2%)	1 (0.2%)	2 (0.2%)
	LYMPHADENOPATHY	1 (0.2%)	1 (0.2%)	2 (0.2%)
	SECONDARY ANAEMIA	1 (0.2%)	0 .	1 (0.1%)
CARDIAC DISORDERS	TOTAL	13 (2.9%)	24 (5.3%)	37 (4.1%)
	ACUTE MYOCARDIAL INFARCTION	0 .	1 (0.2%)	1 (0.1%)
	AGE INDETERMINATE MYOCARDIAL INFARCTION	0 .	1 (0.2%)	1 (0.1%)
	ANGINA PECTORIS	1 (0.2%)	2 (0.4%)	3 (0.3%)
	ANGINA UNSTABLE	1 (0.2%)	0 .	1 (0.1%)
	ARRHYTHMIA	0 .	2 (0.4%)	2 (0.2%)
	ATRIAL FIBRILLATION	2 (0.4%)	3 (0.7%)	5 (0.6%)
	ATRIAL FLUTTER	1 (0.2%)	2 (0.4%)	3 (0.3%)
	CARDIAC FAILURE	1 (0.2%)	1 (0.2%)	2 (0.2%)
	CARDIAC FAILURE CONGESTIVE	0 .	2 (0.4%)	2 (0.2%)
	CORONARY ARTERY DISEASE	1 (0.2%)	3 (0.7%)	4 (0.4%)
	CORONARY ARTERY INSUFFICIENCY	0 .	1 (0.2%)	1 (0.1%)
	HYPERTENSIVE HEART DISEASE	1 (0.2%)	0 .	1 (0.1%)
	MYOCARDIAL INFARCTION	0 .	1 (0.2%)	1 (0.1%)
	MYOCARDIAL ISCHAEMIA	3 (0.7%)	2 (0.4%)	5 (0.6%)
	PALPITATIONS	1 (0.2%)	2 (0.4%)	3 (0.3%)
	SINUS TACHYCARDIA	1 (0.2%)	0 .	1 (0.1%)
	SUPRAVENTRICULAR TACHYCARDIA	0 .	2 (0.4%)	2 (0.2%)
	TACHYCARDIA	1 (0.2%)	1 (0.2%)	2 (0.2%)
	VENTRICULAR EXTRASYSTOLES	1 (0.2%)	0 .	1 (0.1%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED

CONFIDENTIAL

SB 207499

TABLE 15.7

ON-THERAPY ADVERSE EXPERIENCES THAT REQUIRED CORRECTIVE THERAPY BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
CARDIAC DISORDERS	VENTRICULAR TACHYCARDIA	0 .	1 (0.2%)	1 (0.1%)
EAR AND LABYRINTH DISORDERS	TOTAL	8 (1.8%)	2 (0.4%)	10 (1.1%)
	CERUMEN IMPACTION	1 (0.2%)	0 .	1 (0.1%)
	EAR PAIN	1 (0.2%)	1 (0.2%)	2 (0.2%)
	EAR PRURITUS	1 (0.2%)	0 .	1 (0.1%)
	MOTION SICKNESS	1 (0.2%)	0 .	1 (0.1%)
	TINNITUS	1 (0.2%)	0 .	1 (0.1%)
	VERTIGO	3 (0.7%)	1 (0.2%)	4 (0.4%)
EYE DISORDERS	TOTAL	8 (1.8%)	4 (0.9%)	12 (1.3%)
	CATARACT	1 (0.2%)	0 .	1 (0.1%)
	CHALAZION	0 .	1 (0.2%)	1 (0.1%)
	CONJUNCTIVAL HAEMORRHAGE	0 .	1 (0.2%)	1 (0.1%)
	CONJUNCTIVITIS	3 (0.7%)	1 (0.2%)	4 (0.4%)
	EYE ALLERGY	1 (0.2%)	0 .	1 (0.1%)
	EYE INFLAMMATION	2 (0.4%)	0 .	2 (0.2%)
	GLAUCOMA	1 (0.2%)	0 .	1 (0.1%)
	KERATOCONJUNCTIVITIS SICCA	0 .	1 (0.2%)	1 (0.1%)
GASTROINTESTINAL DISORDERS	TOTAL	29 (6.4%)	60 (13.2%)	89 (9.8%)
	ABDOMINAL DISCOMFORT	1 (0.2%)	1 (0.2%)	2 (0.2%)
	ABDOMINAL DISTENSION	0 .	1 (0.2%)	1 (0.1%)
	ABDOMINAL PAIN	4 (0.9%)	2 (0.4%)	6 (0.7%)
	ABDOMINAL PAIN UPPER	1 (0.2%)	5 (1.1%)	6 (0.7%)
	COLONIC HAEMORRHAGE	0 .	1 (0.2%)	1 (0.1%)
	COLONIC POLYP	0 .	1 (0.2%)	1 (0.1%)
	CONSTIPATION	2 (0.4%)	4 (0.9%)	6 (0.7%)
	DIARRHOEA	1 (0.2%)	8 (1.8%)	9 (1.0%)
	DIARRHOEA HAEMORRHAGIC	1 (0.2%)	0 .	1 (0.1%)
	DIVERTICULITIS	1 (0.2%)	1 (0.2%)	2 (0.2%)
	DIVERTICULUM	0 .	3 (0.7%)	3 (0.3%)
	DUODENAL ULCER	1 (0.2%)	2 (0.4%)	3 (0.3%)
	DYSPEPSIA	4 (0.9%)	14 (3.1%)	18 (2.0%)
	EPIGASTRIC DISCOMFORT	0 .	1 (0.2%)	1 (0.1%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED

CONFIDENTIAL

SB 207499

TABLE 15.7

ON-THERAPY ADVERSE EXPERIENCES THAT REQUIRED CORRECTIVE THERAPY BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
GASTROINTESTINAL DISORDERS	GASTRIC ULCER	1 (0.2%)	1 (0.2%)	2 (0.2%)
	GASTRITIS	3 (0.7%)	2 (0.4%)	5 (0.6%)
	GASTROINTESTINAL OBSTRUCTION	1 (0.2%)	0 .	1 (0.1%)
	GASTROINTESTINAL UPSET	0 .	1 (0.2%)	1 (0.1%)
	GASTROOESOPHAGEAL REFLUX DISEASE	2 (0.4%)	2 (0.4%)	4 (0.4%)
	GINGIVITIS	1 (0.2%)	0 .	1 (0.1%)
	GLOSSITIS	0 .	1 (0.2%)	1 (0.1%)
	ILEUS	0 .	1 (0.2%)	1 (0.1%)
	INGUINAL HERNIA	0 .	2 (0.4%)	2 (0.2%)
	INTESTINAL OBSTRUCTION	1 (0.2%)	0 .	1 (0.1%)
	INTESTINAL PERFORATION	1 (0.2%)	0 .	1 (0.1%)
	INTESTINAL POLYP	1 (0.2%)	0 .	1 (0.1%)
	MOUTH ULCERATION	2 (0.4%)	0 .	2 (0.2%)
	NAUSEA	4 (0.9%)	13 (2.9%)	17 (1.9%)
	OESOPHAGITIS	1 (0.2%)	1 (0.2%)	2 (0.2%)
	PANCREATITIS	1 (0.2%)	1 (0.2%)	2 (0.2%)
	PEPTIC ULCER	0 .	1 (0.2%)	1 (0.1%)
	REFLUX OESOPHAGITIS	1 (0.2%)	2 (0.4%)	3 (0.3%)
	TOOTH DISORDER	0 .	1 (0.2%)	1 (0.1%)
	TOOTHACHE	3 (0.7%)	2 (0.4%)	5 (0.6%)
	VOMITING	1 (0.2%)	4 (0.9%)	5 (0.6%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	TOTAL	15 (3.3%)	12 (2.6%)	27 (3.0%)
	CHEST DISCOMFORT	2 (0.4%)	3 (0.7%)	5 (0.6%)
	CHEST PAIN	6 (1.3%)	1 (0.2%)	7 (0.8%)
	INFLUENZA LIKE ILLNESS	0 .	3 (0.7%)	3 (0.3%)
	MALAISE	0 .	1 (0.2%)	1 (0.1%)
	OEDEMA PERIPHERAL	6 (1.3%)	2 (0.4%)	8 (0.9%)
	PAIN	1 (0.2%)	1 (0.2%)	2 (0.2%)
	PYREXIA	2 (0.4%)	1 (0.2%)	3 (0.3%)
HEPATOBILIARY DISORDERS	TOTAL	1 (0.2%)	4 (0.9%)	5 (0.6%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED

CONFIDENTIAL

SB 207499

TABLE 15.7

ON-THERAPY ADVERSE EXPERIENCES THAT REQUIRED CORRECTIVE THERAPY BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
HEPATOBILIARY DISORDERS	BILIARY COLIC	0 .	1 (0.2%)	1 (0.1%)
	CHOLELITHIASIS	1 (0.2%)	1 (0.2%)	2 (0.2%)
	CHRONIC HEPATITIS	0 .	1 (0.2%)	1 (0.1%)
	HEPATIC STEATOSIS	0 .	2 (0.4%)	2 (0.2%)
IMMUNE SYSTEM DISORDERS	TOTAL	3 (0.7%)	2 (0.4%)	5 (0.6%)
	ANAPHYLACTIC SHOCK	1 (0.2%)	0 .	1 (0.1%)
	HYPERSENSITIVITY	1 (0.2%)	1 (0.2%)	2 (0.2%)
	SEASONAL ALLERGY	1 (0.2%)	1 (0.2%)	2 (0.2%)
INFECTIONS AND INFESTATIONS	TOTAL	100 (22.1%)	104 (22.9%)	204 (22.5%)
	BACTERIAL INFECTION	1 (0.2%)	0 .	1 (0.1%)
	BLADDER INFECTION	0 .	1 (0.2%)	1 (0.1%)
	BRONCHITIS	6 (1.3%)	6 (1.3%)	12 (1.3%)
	BRONCHITIS ACUTE	1 (0.2%)	1 (0.2%)	2 (0.2%)
	BRONCHITIS ACUTE VIRAL	0 .	1 (0.2%)	1 (0.1%)
	BRONCHITIS VIRAL	0 .	1 (0.2%)	1 (0.1%)
	BRONCHOPNEUMONIA	3 (0.7%)	1 (0.2%)	4 (0.4%)
	CANDIDIASIS	1 (0.2%)	1 (0.2%)	2 (0.2%)
	CHRONIC SINUSITIS	0 .	1 (0.2%)	1 (0.1%)
	CYSTITIS	2 (0.4%)	2 (0.4%)	4 (0.4%)
	EAR INFECTION	5 (1.1%)	3 (0.7%)	8 (0.9%)
	ERYSIPELAS	1 (0.2%)	0 .	1 (0.1%)
	EYE INFECTION	0 .	2 (0.4%)	2 (0.2%)
	FOLLICULITIS	1 (0.2%)	0 .	1 (0.1%)
	FUNGAL INFECTION	1 (0.2%)	3 (0.7%)	4 (0.4%)
	FURUNCLE	0 .	1 (0.2%)	1 (0.1%)
	GASTROENTERITIS	2 (0.4%)	1 (0.2%)	3 (0.3%)
	GASTROENTERITIS VIRAL	0 .	2 (0.4%)	2 (0.2%)
	HELICOBACTER GASTRITIS	0 .	1 (0.2%)	1 (0.1%)
	HELICOBACTER INFECTION	0 .	1 (0.2%)	1 (0.1%)
	HERPES SIMPLEX	1 (0.2%)	0 .	1 (0.1%)
	HERPES ZOSTER	2 (0.4%)	2 (0.4%)	4 (0.4%)
	HORDEOLUM	0 .	1 (0.2%)	1 (0.1%)
	INFECTED INSECT BITE	1 (0.2%)	0 .	1 (0.1%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED

CONFIDENTIAL

SB 207499

TABLE 15.7

ON-THERAPY ADVERSE EXPERIENCES THAT REQUIRED CORRECTIVE THERAPY BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
INFECTIONS AND INFESTATIONS	INFECTED SEBACEOUS CYST	0 .	1 (0.2%)	1 (0.1%)
	INFECTED SKIN ULCER	1 (0.2%)	0 .	1 (0.1%)
	INFECTION	1 (0.2%)	0 .	1 (0.1%)
	INFLUENZA	12 (2.7%)	12 (2.6%)	24 (2.6%)
	JOINT ABSCESS	0 .	1 (0.2%)	1 (0.1%)
	LOBAR PNEUMONIA	1 (0.2%)	1 (0.2%)	2 (0.2%)
	LOCALISED INFECTION	2 (0.4%)	0 .	2 (0.2%)
	LOWER RESPIRATORY TRACT INFECTION	4 (0.9%)	6 (1.3%)	10 (1.1%)
	NASOPHARYNGITIS	29 (6.4%)	26 (5.7%)	55 (6.1%)
	ONYCHOMYCOSIS	1 (0.2%)	1 (0.2%)	2 (0.2%)
	ORAL CANDIDIASIS	1 (0.2%)	1 (0.2%)	2 (0.2%)
	ORAL FUNGAL INFECTION	0 .	1 (0.2%)	1 (0.1%)
	OROPHARYNGITIS FUNGAL	1 (0.2%)	0 .	1 (0.1%)
	OTITIS EXTERNA	0 .	1 (0.2%)	1 (0.1%)
	PHARYNGITIS	1 (0.2%)	4 (0.9%)	5 (0.6%)
	PNEUMONIA	3 (0.7%)	5 (1.1%)	8 (0.9%)
	PNEUMONIA BACTERIAL	1 (0.2%)	0 .	1 (0.1%)
	PNEUMONIA CHLAMYDIAL	0 .	1 (0.2%)	1 (0.1%)
	PULPITIS DENTAL	1 (0.2%)	0 .	1 (0.1%)
	RESPIRATORY TRACT INFECTION	4 (0.9%)	3 (0.7%)	7 (0.8%)
	RHINITIS INFECTIVE	0 .	1 (0.2%)	1 (0.1%)
	SALPINGITIS	0 .	1 (0.2%)	1 (0.1%)
	SINUSITIS	7 (1.5%)	4 (0.9%)	11 (1.2%)
	SKIN INFECTION	0 .	1 (0.2%)	1 (0.1%)
	STAPHYLOCOCCAL INFECTION	1 (0.2%)	0 .	1 (0.1%)
	TINEA INFECTION	1 (0.2%)	0 .	1 (0.1%)
	TINEA PEDIS	0 .	1 (0.2%)	1 (0.1%)
	TONSILLITIS	2 (0.4%)	0 .	2 (0.2%)
	TOOTH ABSCESS	2 (0.4%)	1 (0.2%)	3 (0.3%)
	TOOTH INFECTION	1 (0.2%)	1 (0.2%)	2 (0.2%)
	UPPER RESPIRATORY TRACT INFECTION	6 (1.3%)	10 (2.2%)	16 (1.8%)
	URINARY TRACT INFECTION	12 (2.7%)	2 (0.4%)	14 (1.5%)
	VAGINAL MYCOSIS	1 (0.2%)	0 .	1 (0.1%)
	VIRAL INFECTION	1 (0.2%)	0 .	1 (0.1%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED

CONFIDENTIAL

SB 207499

TABLE 15.7

ON-THERAPY ADVERSE EXPERIENCES THAT REQUIRED CORRECTIVE THERAPY BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
INFECTIONS AND INFESTATIONS	VIRAL UPPER RESPIRATORY TRACT INFECTION	1 (0.2%)	2 (0.4%)	3 (0.3%)
	VULVITIS	0 .	1 (0.2%)	1 (0.1%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	TOTAL	17 (3.8%)	12 (2.6%)	29 (3.2%)
	ALCOHOL POISONING	1 (0.2%)	0 .	1 (0.1%)
	ANIMAL BITE	1 (0.2%)	1 (0.2%)	2 (0.2%)
	ARTHROPOD BITE	1 (0.2%)	0 .	1 (0.1%)
	ARTHROPOD STING	1 (0.2%)	0 .	1 (0.1%)
	BACK INJURY	1 (0.2%)	1 (0.2%)	2 (0.2%)
	BLISTER	1 (0.2%)	1 (0.2%)	2 (0.2%)
	CHEST INJURY	0 .	1 (0.2%)	1 (0.1%)
	CONTUSION	0 .	2 (0.4%)	2 (0.2%)
	EPICONDYLITIS	1 (0.2%)	0 .	1 (0.1%)
	FALL	1 (0.2%)	0 .	1 (0.1%)
	FOOT FRACTURE	1 (0.2%)	0 .	1 (0.1%)
	HAND FRACTURE	1 (0.2%)	0 .	1 (0.1%)
	HIP FRACTURE	1 (0.2%)	0 .	1 (0.1%)
	HUMERUS FRACTURE	1 (0.2%)	0 .	1 (0.1%)
	JOINT INJURY	0 .	2 (0.4%)	2 (0.2%)
	LIMB INJURY	1 (0.2%)	2 (0.4%)	3 (0.3%)
	MUSCLE INJURY	1 (0.2%)	0 .	1 (0.1%)
	POST PROCEDURAL PAIN	0 .	1 (0.2%)	1 (0.1%)
	RADIATION ASSOCIATED PAIN	0 .	1 (0.2%)	1 (0.1%)
	RADIUS FRACTURE	0 .	1 (0.2%)	1 (0.1%)
	RIB FRACTURE	1 (0.2%)	1 (0.2%)	2 (0.2%)
	SKIN LACERATION	1 (0.2%)	0 .	1 (0.1%)
	THERMAL BURN	1 (0.2%)	0 .	1 (0.1%)
	TOOTH INJURY	0 .	1 (0.2%)	1 (0.1%)
	WOUND	1 (0.2%)	0 .	1 (0.1%)
	WRIST FRACTURE	1 (0.2%)	0 .	1 (0.1%)
INVESTIGATIONS	TOTAL	2 (0.4%)	9 (2.0%)	11 (1.2%)
	ASPARTATE AMINOTRANSFERASE INCREASED	0 .	1 (0.2%)	1 (0.1%)
	BLOOD HOMOCYSTEINE DECREASED	0 .	1 (0.2%)	1 (0.1%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED

CONFIDENTIAL

SB 207499

TABLE 15.7

ON-THERAPY ADVERSE EXPERIENCES THAT REQUIRED CORRECTIVE THERAPY BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
INVESTIGATIONS	BLOOD PRESSURE INCREASED	0 .	2 (0.4%)	2 (0.2%)
	BLOOD SODIUM DECREASED	0 .	1 (0.2%)	1 (0.1%)
	BODY TEMPERATURE INCREASED	0 .	1 (0.2%)	1 (0.1%)
	ELECTROCARDIOGRAM T WAVE INVERSION	0 .	1 (0.2%)	1 (0.1%)
	GAMMA-GLUTAMYLTRANSF ERASE INCREASED	1 (0.2%)	1 (0.2%)	2 (0.2%)
	HEART RATE INCREASED	0 .	1 (0.2%)	1 (0.1%)
	SPUTUM INCREASED	0 .	1 (0.2%)	1 (0.1%)
	SPUTUM TEST	0 .	1 (0.2%)	1 (0.1%)
	URINARY OCCULT BLOOD POSITIVE	1 (0.2%)	0 .	1 (0.1%)
METABOLISM AND NUTRITION DISORDERS	TOTAL	7 (1.5%)	18 (4.0%)	25 (2.8%)
	ANOREXIA	0 .	5 (1.1%)	5 (0.6%)
	DIABETES MELLITUS	5 (1.1%)	2 (0.4%)	7 (0.8%)
	GOUT	0 .	4 (0.9%)	4 (0.4%)
	HYPERCHOLESTEROLAEMI A	1 (0.2%)	1 (0.2%)	2 (0.2%)
	HYPERGLYCAEMIA	1 (0.2%)	3 (0.7%)	4 (0.4%)
	HYPOKALAEMIA	0 .	2 (0.4%)	2 (0.2%)
	VITAMIN B12 DEFICIENCY	0 .	2 (0.4%)	2 (0.2%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	TOTAL	33 (7.3%)	26 (5.7%)	59 (6.5%)
	ARTHRALGIA	4 (0.9%)	2 (0.4%)	6 (0.7%)
	ARTHRITIS	1 (0.2%)	0 .	1 (0.1%)
	BACK PAIN	14 (3.1%)	4 (0.9%)	18 (2.0%)
	BURSITIS	0 .	3 (0.7%)	3 (0.3%)
	FASCIITIS	0 .	1 (0.2%)	1 (0.1%)
	FIBROMYALGIA	1 (0.2%)	0 .	1 (0.1%)
	JOINT EFFUSION	0 .	1 (0.2%)	1 (0.1%)
	JOINT SWELLING	1 (0.2%)	0 .	1 (0.1%)
	LOCAL SWELLING	1 (0.2%)	0 .	1 (0.1%)
	LOCALISED OSTEOARTHRITIS	1 (0.2%)	0 .	1 (0.1%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED

CONFIDENTIAL

SB 207499

TABLE 15.7

ON-THERAPY ADVERSE EXPERIENCES THAT REQUIRED CORRECTIVE THERAPY BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	MONOARTHRITIS	1 (0.2%)	1 (0.2%)	2 (0.2%)
	MUSCLE CRAMP	0 .	1 (0.2%)	1 (0.1%)
	MUSCLE RIGIDITY	0 .	2 (0.4%)	2 (0.2%)
	MUSCLE TIGHTNESS	0 .	1 (0.2%)	1 (0.1%)
	MUSCULOSKELETAL DISCOMFORT	1 (0.2%)	0 .	1 (0.1%)
	MUSCULOSKELETAL PAIN	0 .	1 (0.2%)	1 (0.1%)
	MYALGIA	2 (0.4%)	2 (0.4%)	4 (0.4%)
	OSTEOARTHRITIS	3 (0.7%)	3 (0.7%)	6 (0.7%)
	OSTEOPOROSIS	1 (0.2%)	1 (0.2%)	2 (0.2%)
	PAIN IN EXTREMITY	1 (0.2%)	3 (0.7%)	4 (0.4%)
	PERIARTHRITIS	0 .	2 (0.4%)	2 (0.2%)
	RHEUMATOID ARTHRITIS	0 .	1 (0.2%)	1 (0.1%)
	SHOULDER BLADE PAIN	1 (0.2%)	0 .	1 (0.1%)
	SPINAL DISORDER	3 (0.7%)	2 (0.4%)	5 (0.6%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	TOTAL	6 (1.3%)	0 .	6 (0.7%)
	BASAL CELL CARCINOMA	1 (0.2%)	0 .	1 (0.1%)
	LUNG NEOPLASM MALIGNANT METASTASIS	1 (0.2%)	0 .	1 (0.1%)
	PROSTATE CANCER	1 (0.2%)	0 .	1 (0.1%)
	RENAL CELL CARCINOMA STAGE UNSPECIFIED	1 (0.2%)	0 .	1 (0.1%)
	SQUAMOUS CELL CARCINOMA OF SKIN	1 (0.2%)	0 .	1 (0.1%)
	THYROID GLAND CANCER	1 (0.2%)	0 .	1 (0.1%)
NERVOUS SYSTEM DISORDERS	TOTAL	24 (5.3%)	30 (6.6%)	54 (6.0%)
	CARPAL TUNNEL SYNDROME	1 (0.2%)	0 .	1 (0.1%)
	CEREBRAL THROMBOSIS	1 (0.2%)	0 .	1 (0.1%)
	CEREBROVASCULAR ACCIDENT	1 (0.2%)	1 (0.2%)	2 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED

CONFIDENTIAL

SB 207499

TABLE 15.7

ON-THERAPY ADVERSE EXPERIENCES THAT REQUIRED CORRECTIVE THERAPY BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
NERVOUS SYSTEM DISORDERS	CEREBROVASCULAR DISORDER	1 (0.2%)	1 (0.2%)	2 (0.2%)
	CONVULSION	0 .	1 (0.2%)	1 (0.1%)
	DIZZINESS	1 (0.2%)	4 (0.9%)	5 (0.6%)
	ENCEPHALOPATHY	1 (0.2%)	0 .	1 (0.1%)
	FACIAL PALSY	0 .	2 (0.4%)	2 (0.2%)
	HEADACHE	16 (3.5%)	21 (4.6%)	37 (4.1%)
	NEUROPATHY	1 (0.2%)	0 .	1 (0.1%)
	PARAESTHESIA	1 (0.2%)	0 .	1 (0.1%)
	PARKINSON'S DISEASE	0 .	1 (0.2%)	1 (0.1%)
	RADICULITIS LUMBOSACRAL	1 (0.2%)	0 .	1 (0.1%)
	SPINAL COLUMN STENOSIS	0 .	1 (0.2%)	1 (0.1%)
	SYNCOPE VASOVAGAL	1 (0.2%)	0 .	1 (0.1%)
	TORTICOLLIS	1 (0.2%)	0 .	1 (0.1%)
	TRANSIENT ISCHAEMIC ATTACK	0 .	1 (0.2%)	1 (0.1%)
	VERTEBRAL ARTERY OCCLUSION	0 .	1 (0.2%)	1 (0.1%)
PSYCHIATRIC DISORDERS	TOTAL	11 (2.4%)	14 (3.1%)	25 (2.8%)
	ANXIETY	1 (0.2%)	6 (1.3%)	7 (0.8%)
	DEPRESSION	5 (1.1%)	6 (1.3%)	11 (1.2%)
	INSOMNIA	3 (0.7%)	1 (0.2%)	4 (0.4%)
	MANIA	1 (0.2%)	0 .	1 (0.1%)
	NEUROSIS	1 (0.2%)	0 .	1 (0.1%)
	PANIC ATTACK	0 .	1 (0.2%)	1 (0.1%)
	SLEEP DISORDER	0 .	1 (0.2%)	1 (0.1%)
RENAL AND URINARY DISORDERS	TOTAL	7 (1.5%)	5 (1.1%)	12 (1.3%)
	CALCULUS BLADDER	1 (0.2%)	0 .	1 (0.1%)
	DYSURIA	1 (0.2%)	0 .	1 (0.1%)
	GLYCOSURIA	1 (0.2%)	0 .	1 (0.1%)
	HAEMATURIA	1 (0.2%)	0 .	1 (0.1%)
	HYPERTONIC BLADDER	0 .	1 (0.2%)	1 (0.1%)
	NEPHROLITHIASIS	1 (0.2%)	1 (0.2%)	2 (0.2%)
	POLLAKIURIA	1 (0.2%)	0 .	1 (0.1%)
	RENAL COLIC	1 (0.2%)	1 (0.2%)	2 (0.2%)
	RENAL IMPAIRMENT	0 .	1 (0.2%)	1 (0.1%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED

CONFIDENTIAL

SB 207499

TABLE 15.7

ON-THERAPY ADVERSE EXPERIENCES THAT REQUIRED CORRECTIVE THERAPY BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
RENAL AND URINARY DISORDERS	URINARY RETENTION	0 .	1 (0.2%)	1 (0.1%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	TOTAL	2 (0.4%)	5 (1.1%)	7 (0.8%)
	BENIGN PROSTATIC HYPERPLASIA	0 .	1 (0.2%)	1 (0.1%)
	EPIDIDYMITIS	0 .	1 (0.2%)	1 (0.1%)
	GENITAL RASH	1 (0.2%)	0 .	1 (0.1%)
	GYNAECOMASTIA	0 .	1 (0.2%)	1 (0.1%)
	PROSTATIC HYPERTROPHY	0 .	1 (0.2%)	1 (0.1%)
	PROSTATITIS	1 (0.2%)	1 (0.2%)	2 (0.2%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	TOTAL	191 (42.3%)	181 (39.8%)	372 (41.0%)
	ACUTE RESPIRATORY FAILURE	0 .	1 (0.2%)	1 (0.1%)
	CATARRH	0 .	1 (0.2%)	1 (0.1%)
	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE EXACERBATED	169 (37.4%)	161 (35.4%)	330 (36.4%)
	COUGH	6 (1.3%)	11 (2.4%)	17 (1.9%)
	DYSPHONIA	0 .	1 (0.2%)	1 (0.1%)
	DYSPNOEA	1 (0.2%)	2 (0.4%)	3 (0.3%)
	DYSPNOEA EXACERBATED	1 (0.2%)	3 (0.7%)	4 (0.4%)
	EPISTAXIS	2 (0.4%)	2 (0.4%)	4 (0.4%)
	HAEMOPTYSIS	1 (0.2%)	0 .	1 (0.1%)
	INCREASED BRONCHIAL SECRETION	0 .	1 (0.2%)	1 (0.1%)
	LUNG DISORDER	2 (0.4%)	0 .	2 (0.2%)
	NASAL CONGESTION	1 (0.2%)	2 (0.4%)	3 (0.3%)
	NASAL POLYPS	1 (0.2%)	0 .	1 (0.1%)
	NASAL SEPTUM DEVIATION	1 (0.2%)	1 (0.2%)	2 (0.2%)
	PHARYNGOLARYNGEAL PAIN	7 (1.5%)	3 (0.7%)	10 (1.1%)
	PLEURISY	0 .	1 (0.2%)	1 (0.1%)
	PLEURITIC PAIN	1 (0.2%)	0 .	1 (0.1%)
	PNEUMOTHORAX	1 (0.2%)	0 .	1 (0.1%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED

CONFIDENTIAL

SB 207499

TABLE 15.7

ON-THERAPY ADVERSE EXPERIENCES THAT REQUIRED CORRECTIVE THERAPY BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	POSTNASAL DRIP	1 (0.2%)	1 (0.2%)	2 (0.2%)
	RHINITIS	8 (1.8%)	11 (2.4%)	19 (2.1%)
	RHINITIS ALLERGIC	2 (0.4%)	4 (0.9%)	6 (0.7%)
	RHINITIS SEASONAL	1 (0.2%)	0 .	1 (0.1%)
	RHINORRHOEA	2 (0.4%)	2 (0.4%)	4 (0.4%)
	THROAT IRRITATION	1 (0.2%)	2 (0.4%)	3 (0.3%)
	WHEEZING	1 (0.2%)	0 .	1 (0.1%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	TOTAL	12 (2.7%)	13 (2.9%)	25 (2.8%)
	DECUBITUS ULCER	1 (0.2%)	0 .	1 (0.1%)
	DERMATITIS ALLERGIC	1 (0.2%)	0 .	1 (0.1%)
	DERMATITIS CONTACT	0 .	1 (0.2%)	1 (0.1%)
	DERMATITIS MEDICAMENTOSA	1 (0.2%)	0 .	1 (0.1%)
	DRY SKIN	0 .	1 (0.2%)	1 (0.1%)
	ECZEMA	2 (0.4%)	2 (0.4%)	4 (0.4%)
	LICHEN PLANUS	1 (0.2%)	0 .	1 (0.1%)
	NEURODERMATITIS	0 .	1 (0.2%)	1 (0.1%)
	PRURITUS	1 (0.2%)	1 (0.2%)	2 (0.2%)
	PSORIASIS	1 (0.2%)	0 .	1 (0.1%)
	RASH	1 (0.2%)	0 .	1 (0.1%)
	RASH PRURITIC	0 .	1 (0.2%)	1 (0.1%)
	SEBORRHOEIC DERMATITIS	1 (0.2%)	0 .	1 (0.1%)
	SKIN ATROPHY	0 .	1 (0.2%)	1 (0.1%)
	SKIN BURNING SENSATION	0 .	1 (0.2%)	1 (0.1%)
	SKIN HYPERTROPHY	0 .	1 (0.2%)	1 (0.1%)
	SKIN LESION	1 (0.2%)	1 (0.2%)	2 (0.2%)
	SKIN ULCER	1 (0.2%)	0 .	1 (0.1%)
	STASIS DERMATITIS	1 (0.2%)	0 .	1 (0.1%)
	URTICARIA	2 (0.4%)	3 (0.7%)	5 (0.6%)
	URTICARIA PAPULAR	0 .	1 (0.2%)	1 (0.1%)
	VASCULAR SKIN DISORDER	0 .	1 (0.2%)	1 (0.1%)
SOCIAL CIRCUMSTANCES	TOTAL	1 (0.2%)	1 (0.2%)	2 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED

CONFIDENTIAL

SB 207499

TABLE 15.7

ON-THERAPY ADVERSE EXPERIENCES THAT REQUIRED CORRECTIVE THERAPY BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
SOCIAL CIRCUMSTANCES	ABSTAINS FROM ALCOHOL	1 (0.2%)	0 .	1 (0.1%)
	ALCOHOL USE	0 .	1 (0.2%)	1 (0.1%)
SURGICAL AND MEDICAL PROCEDURES	TOTAL	2 (0.4%)	1 (0.2%)	3 (0.3%)
	CATARACT EXTRACTION	2 (0.4%)	0 .	2 (0.2%)
	TOOTH EXTRACTION	0 .	1 (0.2%)	1 (0.1%)
VASCULAR DISORDERS	TOTAL	17 (3.8%)	14 (3.1%)	31 (3.4%)
	AORTIC ANEURYSM	0 .	1 (0.2%)	1 (0.1%)
	AORTIC DISSECTION	0 .	1 (0.2%)	1 (0.1%)
	CIRCULATORY COLLAPSE	0 .	1 (0.2%)	1 (0.1%)
	HOT FLUSH	1 (0.2%)	0 .	1 (0.1%)
	HYPERTENSION	14 (3.1%)	10 (2.2%)	24 (2.6%)
	HYPERTENSIVE CRISIS	1 (0.2%)	0 .	1 (0.1%)
	HYPOTENSION	0 .	1 (0.2%)	1 (0.1%)
	PHLEBITIS	0 .	1 (0.2%)	1 (0.1%)
	THROMBOPHLEBITIS	1 (0.2%)	0 .	1 (0.1%)
	VARICOSE VEIN	0 .	1 (0.2%)	1 (0.1%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.8A

INCIDENCE OF RUN-IN SERIOUS ADVERSE EXPERIENCES BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP

PROTOCOL 157

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=454)	SB 207499 (N=456)	NON-RAND. (N=480)	Total (N=1390)
TOTAL	TOTAL	0 .	3 (0.7%)	11 (2.3%)	14 (1.0%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	TOTAL	0 .	1 (0.2%)	0 .	1 (0.1%)
	SECONDARY POLYCYTHAEMIA	0 .	1 (0.2%)	0 .	1 (0.1%)
GASTROINTESTINAL DISORDERS	TOTAL	0 .	1 (0.2%)	0 .	1 (0.1%)
	ABDOMINAL PAIN UPPER	0 .	1 (0.2%)	0 .	1 (0.1%)
PSYCHIATRIC DISORDERS	TOTAL	0 .	1 (0.2%)	0 .	1 (0.1%)
	DYSTHYMIC DISORDER	0 .	1 (0.2%)	0 .	1 (0.1%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	TOTAL	0 .	1 (0.2%)	11 (2.3%)	12 (0.9%)
	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE EXACERBATED	0 .	0 .	11 (2.3%)	11 (0.8%)
	CHRONIC RESPIRATORY FAILURE	0 .	1 (0.2%)	0 .	1 (0.1%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.8B

ON-THERAPY SERIOUS ADVERSE EXPERIENCES BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP

PROTOCOL 157

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
TOTAL	TOTAL	55 (12.2%)	53 (11.6%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	TOTAL	1 (0.2%)	0 .
	IRON DEFICIENCY ANAEMIA	1 (0.2%)	0 .
CARDIAC DISORDERS	TOTAL	7 (1.5%)	14 (3.1%)
	ACUTE MYOCARDIAL INFARCTION	0 .	1 (0.2%)
	ANGINA PECTORIS	0 .	1 (0.2%)
	ANGINA UNSTABLE	1 (0.2%)	0 .
	ATRIAL FIBRILLATION	1 (0.2%)	3 (0.7%)
	ATRIAL FLUTTER	0 .	2 (0.4%)
	BRADYARRHYTHMIA	0 .	1 (0.2%)
	CARDIAC FAILURE	0 .	1 (0.2%)
	CARDIAC FAILURE ACUTE	0 .	1 (0.2%)
	CORONARY ARTERY DISEASE	1 (0.2%)	2 (0.4%)
	MYOCARDIAL INFARCTION	1 (0.2%)	1 (0.2%)
	MYOCARDIAL ISCHAEMIA	2 (0.4%)	2 (0.4%)
	TACHYCARDIA	2 (0.4%)	0 .
	VENTRICULAR TACHYCARDIA	0 .	1 (0.2%)
EYE DISORDERS	TOTAL	1 (0.2%)	0 .
	CATARACT	1 (0.2%)	0 .
GASTROINTESTINAL DISORDERS	TOTAL	3 (0.7%)	9 (2.0%)
	COLONIC HAEMORRHAGE	0 .	1 (0.2%)
	DIARRHOEA	0 .	1 (0.2%)
	DIVERTICULUM	0 .	1 (0.2%)
	DUODENAL ULCER	0 .	2 (0.4%)
	GASTRITIS	0 .	1 (0.2%)
	ILEUS	1 (0.2%)	1 (0.2%)
	INGUINAL HERNIA	0 .	1 (0.2%)
	INTESTINAL OBSTRUCTION	1 (0.2%)	0 .

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED

CONFIDENTIAL

SB 207499

TABLE 15.8B

ON-THERAPY SERIOUS ADVERSE EXPERIENCES BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP

PROTOCOL 157

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
GASTROINTESTINAL DISORDERS	INTESTINAL PERFORATION	1 (0.2%)	0 .
	PANCREATITIS	0 .	1 (0.2%)
	REFLUX OESOPHAGITIS	0 .	1 (0.2%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	TOTAL	1 (0.2%)	0 .
	CHEST PAIN	1 (0.2%)	0 .
HEPATOBILIARY DISORDERS	TOTAL	0 .	1 (0.2%)
	CHOLELITHIASIS	0 .	1 (0.2%)
IMMUNE SYSTEM DISORDERS	TOTAL	2 (0.4%)	0 .
	ANAPHYLACTIC SHOCK	1 (0.2%)	0 .
	HYPERSENSITIVITY	1 (0.2%)	0 .
INFECTIONS AND INFESTATIONS	TOTAL	8 (1.8%)	2 (0.4%)
	BRONCHOPNEUMONIA	1 (0.2%)	0 .
	GASTROENTERITIS	1 (0.2%)	0 .
	HERPES ZOSTER	1 (0.2%)	0 .
	LOBAR PNEUMONIA	1 (0.2%)	0 .
	PNEUMONIA	2 (0.4%)	2 (0.4%)
	PNEUMONIA BACTERIAL	1 (0.2%)	0 .
	VIRAL LABYRINTHITIS	1 (0.2%)	0 .
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	TOTAL	4 (0.9%)	0 .
	ALCOHOL POISONING	1 (0.2%)	0 .
	HIP FRACTURE	1 (0.2%)	0 .
	RIB FRACTURE	1 (0.2%)	0 .
	THERMAL BURN	1 (0.2%)	0 .
INVESTIGATIONS	TOTAL	0 .	1 (0.2%)
	BLOOD IN STOOL	0 .	1 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED

CONFIDENTIAL

SB 207499

TABLE 15.8B

ON-THERAPY SERIOUS ADVERSE EXPERIENCES BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP

PROTOCOL 157

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	TOTAL	6 (1.3%)	2 (0.4%)
	BASAL CELL CARCINOMA	1 (0.2%)	0 .
	BLADDER CANCER	0 .	1 (0.2%)
	GASTRIC CANCER	1 (0.2%)	0 .
	LUNG NEOPLASM MALIGNANT	1 (0.2%)	1 (0.2%)
	METASTASIS	1 (0.2%)	0 .
	PROSTATE CANCER	1 (0.2%)	0 .
	RENAL CELL CARCINOMA STAGE UNSPECIFIED	1 (0.2%)	0 .
	THYROID GLAND CANCER	1 (0.2%)	0 .
NERVOUS SYSTEM DISORDERS	TOTAL	7 (1.5%)	4 (0.9%)
	CARPAL TUNNEL SYNDROME	1 (0.2%)	0 .
	CEREBRAL THROMBOSIS	1 (0.2%)	0 .
	CEREBROVASCULAR ACCIDENT	1 (0.2%)	0 .
	CONVULSION	0 .	1 (0.2%)
	ENCEPHALOPATHY	1 (0.2%)	0 .
	HEADACHE	0 .	1 (0.2%)
	LUMBAR SPINAL STENOSIS	0 .	1 (0.2%)
	NEUROPATHY	1 (0.2%)	0 .
	SYNCOPE	2 (0.4%)	1 (0.2%)
	SYNCOPE VASOVAGAL	1 (0.2%)	0 .
PSYCHIATRIC DISORDERS	TOTAL	2 (0.4%)	0 .
	DEPRESSION	1 (0.2%)	0 .
	MANIA	1 (0.2%)	0 .
RENAL AND URINARY DISORDERS	TOTAL	2 (0.4%)	0 .
	CALCULUS BLADDER	1 (0.2%)	0 .
	PROTEINURIA	1 (0.2%)	0 .

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED

CONFIDENTIAL

SB 207499

TABLE 15.8B

ON-THERAPY SERIOUS ADVERSE EXPERIENCES BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP

PROTOCOL 157

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	TOTAL	0 .	1 (0.2%)
	EPIDIDYMITIS	0 .	1 (0.2%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	TOTAL	20 (4.4%)	21 (4.6%)
	ACUTE RESPIRATORY FAILURE	0 .	1 (0.2%)
	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE EXACERBATED	18 (4.0%)	19 (4.2%)
	DYSPNOEA	0 .	1 (0.2%)
	PNEUMOTHORAX	1 (0.2%)	0 .
	PULMONARY FIBROSIS	1 (0.2%)	0 .
	RESPIRATORY ALKALOSIS	0 .	1 (0.2%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	TOTAL	1 (0.2%)	0 .
	DERMATITIS MEDICAMENTOSA	1 (0.2%)	0 .
VASCULAR DISORDERS	TOTAL	1 (0.2%)	1 (0.2%)
	AORTIC ANEURYSM	0 .	1 (0.2%)
	AORTIC DISSECTION	0 .	1 (0.2%)
	THROMBOPHLEBITIS	1 (0.2%)	0 .

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED

CONFIDENTIAL

SB 207499

TABLE 15.8C

POST-THERAPY SERIOUS ADVERSE EXPERIENCES BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP

PROTOCOL 157

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
TOTAL	TOTAL	15 (3.3%)	11 (2.4%)
CARDIAC DISORDERS	TOTAL	2 (0.4%)	1 (0.2%)
	ACUTE MYOCARDIAL INFARCTION	0 .	1 (0.2%)
	CARDIAC FAILURE	1 (0.2%)	0 .
	MYOCARDIAL INFARCTION	1 (0.2%)	0 .
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	TOTAL	0 .	1 (0.2%)
	DEATH	0 .	1 (0.2%)
HEPATOBILIARY DISORDERS	TOTAL	1 (0.2%)	0 .
	CHOLELITHIASIS	1 (0.2%)	0 .
INFECTIONS AND INFESTATIONS	TOTAL	3 (0.7%)	1 (0.2%)
	CELLULITIS	1 (0.2%)	0 .
	PNEUMONIA	3 (0.7%)	1 (0.2%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	TOTAL	2 (0.4%)	0 .
	ANKLE FRACTURE	1 (0.2%)	0 .
	POSTPERICARDIOTOMY SYNDROME	1 (0.2%)	0 .
METABOLISM AND NUTRITION DISORDERS	TOTAL	0 .	1 (0.2%)
	DIABETES MELLITUS	0 .	1 (0.2%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	TOTAL	1 (0.2%)	0 .
	BACK PAIN	1 (0.2%)	0 .

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.8C

POST-THERAPY SERIOUS ADVERSE EXPERIENCES BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP

PROTOCOL 157

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	TOTAL	1 (0.2%)	2 (0.4%)
	COLON CANCER	0 .	1 (0.2%)
	EYELID TUMOUR	0 .	1 (0.2%)
	PROSTATE CANCER	1 (0.2%)	0 .
NERVOUS SYSTEM DISORDERS	TOTAL	2 (0.4%)	1 (0.2%)
	CEREBROVASCULAR ACCIDENT	0 .	1 (0.2%)
	COMA	1 (0.2%)	0 .
	INTRACRANIAL ANEURYSM	1 (0.2%)	0 .
PSYCHIATRIC DISORDERS	TOTAL	0 .	1 (0.2%)
	ANXIETY	0 .	1 (0.2%)
RENAL AND URINARY DISORDERS	TOTAL	1 (0.2%)	0 .
	RENAL INSUFFICIENCY	1 (0.2%)	0 .
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	TOTAL	3 (0.7%)	3 (0.7%)
	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE EXACERBATED	2 (0.4%)	2 (0.4%)
	PULMONARY EMBOLISM	1 (0.2%)	0 .
	RESPIRATORY FAILURE	0 .	1 (0.2%)
VASCULAR DISORDERS	TOTAL	1 (0.2%)	0 .
	AORTIC ANEURYSM RUPTURE	1 (0.2%)	0 .

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED

CONFIDENTIAL

SB 207499

TABLE 15.9A

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES LEADING TO PATIENT WITHDRAWAL BY MEDDRA PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND TREATMENT GROUP
PROTOCOL 157

MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
TOTAL	40 (8.8%)	75 (16.5%)	115 (12.7%)
CHRONIC OBSTRUCTIVE AIRWAYS DISEASE EXACERBATED	17 (3.8%)	12 (2.6%)	29 (3.2%)
NAUSEA	1 (0.2%)	16 (3.5%)	17 (1.9%)
DIARRHOEA	2 (0.4%)	11 (2.4%)	13 (1.4%)
VOMITING	0 .	7 (1.5%)	7 (0.8%)
ABDOMINAL PAIN	0 .	5 (1.1%)	5 (0.6%)
DYSPEPSIA	0 .	5 (1.1%)	5 (0.6%)
ABDOMINAL PAIN UPPER	0 .	4 (0.9%)	4 (0.4%)
DIZZINESS	0 .	4 (0.9%)	4 (0.4%)
HEADACHE	1 (0.2%)	3 (0.7%)	4 (0.4%)
ANOREXIA	0 .	3 (0.7%)	3 (0.3%)
DYSPNOEA EXACERBATED	0 .	3 (0.7%)	3 (0.3%)
ATRIAL FIBRILLATION	0 .	2 (0.4%)	2 (0.2%)
DUODENAL ULCER	0 .	2 (0.4%)	2 (0.2%)
DYSPNOEA	2 (0.4%)	0 .	2 (0.2%)
FATIGUE	0 .	2 (0.4%)	2 (0.2%)
LUNG DISORDER	2 (0.4%)	0 .	2 (0.2%)
LUNG NEOPLASM MALIGNANT	1 (0.2%)	1 (0.2%)	2 (0.2%)
VENTRICULAR TACHYCARDIA	1 (0.2%)	1 (0.2%)	2 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AT LEAST ONE ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
4. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO SB 207499 TREATMENT GROUP

CONFIDENTIAL

SB 207499

TABLE 15.9A

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES LEADING TO PATIENT WITHDRAWAL BY MEDDRA PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND TREATMENT GROUP
PROTOCOL 157

MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
ABDOMINAL DISTENSION	1 (0.2%)	0 .	1 (0.1%)
ALCOHOLISM	1 (0.2%)	0 .	1 (0.1%)
AORTIC ANEURYSM	0 .	1 (0.2%)	1 (0.1%)
AORTIC DISSECTION	0 .	1 (0.2%)	1 (0.1%)
BLOOD IN STOOL	0 .	1 (0.2%)	1 (0.1%)
CARDIAC FAILURE ACUTE	0 .	1 (0.2%)	1 (0.1%)
CHEST DISCOMFORT	1 (0.2%)	0 .	1 (0.1%)
CONVULSION	0 .	1 (0.2%)	1 (0.1%)
DRY MOUTH	0 .	1 (0.2%)	1 (0.1%)
DYSGEUSIA	0 .	1 (0.2%)	1 (0.1%)
EMOTIONAL DISTRESS	0 .	1 (0.2%)	1 (0.1%)
EYELID OEDEMA	1 (0.2%)	0 .	1 (0.1%)
FEELING ABNORMAL	0 .	1 (0.2%)	1 (0.1%)
FORCED EXPIRATORY VOLUME DECREASED	1 (0.2%)	0 .	1 (0.1%)
GASTRIC CANCER	1 (0.2%)	0 .	1 (0.1%)
GASTRITIS	0 .	1 (0.2%)	1 (0.1%)
GASTROENTERITIS	0 .	1 (0.2%)	1 (0.1%)
HOT FLUSH	1 (0.2%)	0 .	1 (0.1%)
HYPOXIA	1 (0.2%)	0 .	1 (0.1%)
INSOMNIA	0 .	1 (0.2%)	1 (0.1%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AT LEAST ONE ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
4. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO SB 207499 TREATMENT GROUP

CONFIDENTIAL

SB 207499

TABLE 15.9A

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES LEADING TO PATIENT WITHDRAWAL BY MEDDRA PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND TREATMENT GROUP
PROTOCOL 157

MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
IRON DEFICIENCY ANAEMIA	1 (0.2%)	0 .	1 (0.1%)
LETHARGY	0 .	1 (0.2%)	1 (0.1%)
MANIA	1 (0.2%)	0 .	1 (0.1%)
METASTASIS	1 (0.2%)	0 .	1 (0.1%)
MUSCLE RIGIDITY	0 .	1 (0.2%)	1 (0.1%)
MYOCARDIAL INFARCTION	1 (0.2%)	0 .	1 (0.1%)
MYOCARDIAL ISCHAEMIA	0 .	1 (0.2%)	1 (0.1%)
PAIN IN EXTREMITY	1 (0.2%)	0 .	1 (0.1%)
PALPITATIONS	1 (0.2%)	0 .	1 (0.1%)
PANCREATITIS	0 .	1 (0.2%)	1 (0.1%)
PNEUMONIA BACTERIAL	1 (0.2%)	0 .	1 (0.1%)
PROSTATE CANCER	1 (0.2%)	0 .	1 (0.1%)
PULMONARY FIBROSIS	1 (0.2%)	0 .	1 (0.1%)
RECTAL HAEMORRHAGE	0 .	1 (0.2%)	1 (0.1%)
REFLUX OESOPHAGITIS	0 .	1 (0.2%)	1 (0.1%)
SLEEP DISORDER	0 .	1 (0.2%)	1 (0.1%)
SPUTUM INCREASED	0 .	1 (0.2%)	1 (0.1%)
SYNCOPE	1 (0.2%)	0 .	1 (0.1%)
THERMAL BURN	1 (0.2%)	0 .	1 (0.1%)
THYROID GLAND CANCER	1 (0.2%)	0 .	1 (0.1%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AT LEAST ONE ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
4. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO SB 207499 TREATMENT GROUP

CONFIDENTIAL

SB 207499

TABLE 15.9A

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES LEADING TO PATIENT WITHDRAWAL BY MEDDRA PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND TREATMENT GROUP
PROTOCOL 157

MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
URTICARIA	0 .	1 (0.2%)	1 (0.1%)
VENTRICULAR EXTRASYSTOLES	1 (0.2%)	0 .	1 (0.1%)
WEIGHT DECREASED	0 .	1 (0.2%)	1 (0.1%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AT LEAST ONE ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
4. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO SB 207499 TREATMENT GROUP

CONFIDENTIAL

SB 207499

TABLE 15.9B

ON-THERAPY ADVERSE EXPERIENCES LEADING TO PATIENT WITHDRAWAL BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
TOTAL	TOTAL	40 (8.8%)	75 (16.5%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	TOTAL	1 (0.2%)	0 .
	IRON DEFICIENCY ANAEMIA	1 (0.2%)	0 .
CARDIAC DISORDERS	TOTAL	3 (0.7%)	5 (1.1%)
	ATRIAL FIBRILLATION	0 .	2 (0.4%)
	CARDIAC FAILURE ACUTE	0 .	1 (0.2%)
	MYOCARDIAL INFARCTION	1 (0.2%)	0 .
	MYOCARDIAL ISCHAEMIA	0 .	1 (0.2%)
	PALPITATIONS	1 (0.2%)	0 .
	VENTRICULAR EXTRASYSTOLES	1 (0.2%)	0 .
	VENTRICULAR TACHYCARDIA	1 (0.2%)	1 (0.2%)
EYE DISORDERS	TOTAL	1 (0.2%)	0 .
	EYELID OEDEMA	1 (0.2%)	0 .
GASTROINTESTINAL DISORDERS	TOTAL	3 (0.7%)	43 (9.5%)
	ABDOMINAL DISTENSION	1 (0.2%)	0 .
	ABDOMINAL PAIN	0 .	5 (1.1%)
	ABDOMINAL PAIN UPPER	0 .	4 (0.9%)
	DIARRHOEA	2 (0.4%)	11 (2.4%)
	DRY MOUTH	0 .	1 (0.2%)
	DUODENAL ULCER	0 .	2 (0.4%)
	DYSPEPSIA	0 .	5 (1.1%)
	GASTRITIS	0 .	1 (0.2%)
	NAUSEA	1 (0.2%)	16 (3.5%)
	PANCREATITIS	0 .	1 (0.2%)
	RECTAL HAEMORRHAGE	0 .	1 (0.2%)
	REFLUX OESOPHAGITIS	0 .	1 (0.2%)
	VOMITING	0 .	7 (1.5%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	TOTAL	1 (0.2%)	4 (0.9%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED

CONFIDENTIAL

SB 207499

TABLE 15.9B

ON-THERAPY ADVERSE EXPERIENCES LEADING TO PATIENT WITHDRAWAL BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	CHEST DISCOMFORT	1 (0.2%)	0 .
	FATIGUE	0 .	2 (0.4%)
	FEELING ABNORMAL	0 .	1 (0.2%)
	LETHARGY	0 .	1 (0.2%)
INFECTIONS AND INFESTATIONS	TOTAL	1 (0.2%)	1 (0.2%)
	GASTROENTERITIS	0 .	1 (0.2%)
	PNEUMONIA BACTERIAL	1 (0.2%)	0 .
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	TOTAL	1 (0.2%)	0 .
	THERMAL BURN	1 (0.2%)	0 .
INVESTIGATIONS	TOTAL	1 (0.2%)	3 (0.7%)
	BLOOD IN STOOL	0 .	1 (0.2%)
	FORCED EXPIRATORY VOLUME DECREASED	1 (0.2%)	0 .
	SPUTUM INCREASED	0 .	1 (0.2%)
	WEIGHT DECREASED	0 .	1 (0.2%)
METABOLISM AND NUTRITION DISORDERS	TOTAL	0 .	3 (0.7%)
	ANOREXIA	0 .	3 (0.7%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	TOTAL	1 (0.2%)	1 (0.2%)
	MUSCLE RIGIDITY	0 .	1 (0.2%)
	PAIN IN EXTREMITY	1 (0.2%)	0 .
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	TOTAL	4 (0.9%)	1 (0.2%)
	GASTRIC CANCER	1 (0.2%)	0 .
	LUNG NEOPLASM MALIGNANT	1 (0.2%)	1 (0.2%)
	METASTASIS	1 (0.2%)	0 .

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED

CONFIDENTIAL

SB 207499

TABLE 15.9B

ON-THERAPY ADVERSE EXPERIENCES LEADING TO PATIENT WITHDRAWAL BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	PROSTATE CANCER	1 (0.2%)	0 .
	THYROID GLAND CANCER	1 (0.2%)	0 .
NERVOUS SYSTEM DISORDERS	TOTAL	2 (0.4%)	9 (2.0%)
	CONVULSION	0 .	1 (0.2%)
	DIZZINESS	0 .	4 (0.9%)
	DYSGEUSIA	0 .	1 (0.2%)
	HEADACHE	1 (0.2%)	3 (0.7%)
	SYNCOPE	1 (0.2%)	0 .
PSYCHIATRIC DISORDERS	TOTAL	2 (0.4%)	3 (0.7%)
	ALCOHOLISM	1 (0.2%)	0 .
	EMOTIONAL DISTRESS	0 .	1 (0.2%)
	INSOMNIA	0 .	1 (0.2%)
	MANIA	1 (0.2%)	0 .
	SLEEP DISORDER	0 .	1 (0.2%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	TOTAL	21 (4.6%)	14 (3.1%)
	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE EXACERBATED	17 (3.8%)	12 (2.6%)
	DYSPNOEA	2 (0.4%)	0 .
	DYSPNOEA EXACERBATED	0 .	3 (0.7%)
	HYPOXIA	1 (0.2%)	0 .
	LUNG DISORDER	2 (0.4%)	0 .
	PULMONARY FIBROSIS	1 (0.2%)	0 .
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	TOTAL	0 .	1 (0.2%)
	URTICARIA	0 .	1 (0.2%)
VASCULAR DISORDERS	TOTAL	1 (0.2%)	1 (0.2%)
	AORTIC ANEURYSM	0 .	1 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED

CONFIDENTIAL

SB 207499

TABLE 15.9B

ON-THERAPY ADVERSE EXPERIENCES LEADING TO PATIENT WITHDRAWAL BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 157

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
VASCULAR DISORDERS	AORTIC DISSECTION	0 .	1 (0.2%)
	HOT FLUSH	1 (0.2%)	0 .

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED

CONFIDENTIAL

SB 207499

TABLE 15.10

ALL POST-THERAPY ADVERSE EXPERIENCES BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP

PROTOCOL 157

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
TOTAL	TOTAL	55 (12.2%)	67 (14.7%)	122 (13.5%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	TOTAL	2 (0.4%)	1 (0.2%)	3 (0.3%)
	LEUKOCYTOSIS	2 (0.4%)	1 (0.2%)	3 (0.3%)
CARDIAC DISORDERS	TOTAL	4 (0.9%)	3 (0.7%)	7 (0.8%)
	ACUTE MYOCARDIAL INFARCTION	1 (0.2%)	1 (0.2%)	2 (0.2%)
	ANGINA PECTORIS	1 (0.2%)	0 .	1 (0.1%)
	ATRIAL FIBRILLATION	0 .	1 (0.2%)	1 (0.1%)
	CARDIAC FAILURE	1 (0.2%)	0 .	1 (0.1%)
	MYOCARDIAL INFARCTION	1 (0.2%)	0 .	1 (0.1%)
	SUPRAVENTRICULAR EXTRASYSTOLES	0 .	1 (0.2%)	1 (0.1%)
EAR AND LABYRINTH DISORDERS	TOTAL	0 .	2 (0.4%)	2 (0.2%)
	EAR PAIN	0 .	1 (0.2%)	1 (0.1%)
	VERTIGO	0 .	1 (0.2%)	1 (0.1%)
ENDOCRINE DISORDERS	TOTAL	0 .	1 (0.2%)	1 (0.1%)
	HYPOTHYROIDISM	0 .	1 (0.2%)	1 (0.1%)
EYE DISORDERS	TOTAL	0 .	1 (0.2%)	1 (0.1%)
	BLEPHARITIS	0 .	1 (0.2%)	1 (0.1%)
GASTROINTESTINAL DISORDERS	TOTAL	9 (2.0%)	6 (1.3%)	15 (1.7%)
	ABDOMINAL PAIN	1 (0.2%)	0 .	1 (0.1%)
	CONSTIPATION	2 (0.4%)	1 (0.2%)	3 (0.3%)
	DYSPEPSIA	2 (0.4%)	1 (0.2%)	3 (0.3%)
	GASTRITIS	1 (0.2%)	0 .	1 (0.1%)
	HIATUS HERNIA	1 (0.2%)	0 .	1 (0.1%)
	NAUSEA	2 (0.4%)	3 (0.7%)	5 (0.6%)
	RECTAL POLYP	1 (0.2%)	0 .	1 (0.1%)
	TOOTHACHE	1 (0.2%)	1 (0.2%)	2 (0.2%)
	VOMITING	1 (0.2%)	1 (0.2%)	2 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED

CONFIDENTIAL

SB 207499

TABLE 15.10

ALL POST-THERAPY ADVERSE EXPERIENCES BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP

PROTOCOL 157

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	TOTAL	2 (0.4%)	5 (1.1%)	7 (0.8%)
	CHEST PAIN	1 (0.2%)	1 (0.2%)	2 (0.2%)
	DEATH	0 .	1 (0.2%)	1 (0.1%)
	INFLUENZA LIKE ILLNESS	0 .	1 (0.2%)	1 (0.1%)
	LETHARGY	0 .	1 (0.2%)	1 (0.1%)
	MALAISE	0 .	1 (0.2%)	1 (0.1%)
	OEDEMA	1 (0.2%)	0 .	1 (0.1%)
HEPATOBILIARY DISORDERS	TOTAL	2 (0.4%)	0 .	2 (0.2%)
	CHOLELITHIASIS	1 (0.2%)	0 .	1 (0.1%)
	HEPATIC STEATOSIS	1 (0.2%)	0 .	1 (0.1%)
INFECTIONS AND INFESTATIONS	TOTAL	9 (2.0%)	18 (4.0%)	27 (3.0%)
	BRONCHITIS	0 .	2 (0.4%)	2 (0.2%)
	BRONCHITIS ACUTE	0 .	2 (0.4%)	2 (0.2%)
	CANDIDIASIS	0 .	1 (0.2%)	1 (0.1%)
	CELLULITIS	1 (0.2%)	0 .	1 (0.1%)
	CYSTITIS	1 (0.2%)	0 .	1 (0.1%)
	GASTROENTERITIS VIRAL	1 (0.2%)	0 .	1 (0.1%)
	HERPES ZOSTER	0 .	1 (0.2%)	1 (0.1%)
	INFLUENZA	1 (0.2%)	1 (0.2%)	2 (0.2%)
	LOWER RESPIRATORY TRACT INFECTION	1 (0.2%)	1 (0.2%)	2 (0.2%)
	NASOPHARYNGITIS	0 .	1 (0.2%)	1 (0.1%)
	PNEUMONIA	3 (0.7%)	4 (0.9%)	7 (0.8%)
	PYELONEPHRITIS CHRONIC	0 .	1 (0.2%)	1 (0.1%)
	RESPIRATORY TRACT INFECTION	1 (0.2%)	2 (0.4%)	3 (0.3%)
	SINUSITIS	0 .	1 (0.2%)	1 (0.1%)
	UPPER RESPIRATORY TRACT INFECTION	0 .	2 (0.4%)	2 (0.2%)
	URINARY TRACT INFECTION	1 (0.2%)	2 (0.4%)	3 (0.3%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED

CONFIDENTIAL

SB 207499

TABLE 15.10

ALL POST-THERAPY ADVERSE EXPERIENCES BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP

PROTOCOL 157

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	TOTAL	2 (0.4%)	2 (0.4%)	4 (0.4%)
	ANIMAL BITE	0 .	1 (0.2%)	1 (0.1%)
	ANKLE FRACTURE	1 (0.2%)	0 .	1 (0.1%)
	BLISTER	0 .	1 (0.2%)	1 (0.1%)
	POSTPERICARDIOTOMY SYNDROME	1 (0.2%)	0 .	1 (0.1%)
INVESTIGATIONS	TOTAL	5 (1.1%)	6 (1.3%)	11 (1.2%)
	ALANINE AMINOTRANSFERASE INCREASED	0 .	1 (0.2%)	1 (0.1%)
	ASPARTATE AMINOTRANSFERASE INCREASED	1 (0.2%)	1 (0.2%)	2 (0.2%)
	BLOOD IN STOOL	0 .	1 (0.2%)	1 (0.1%)
	BLOOD PRESSURE INCREASED	1 (0.2%)	0 .	1 (0.1%)
	C-REACTIVE PROTEIN INCREASED	1 (0.2%)	1 (0.2%)	2 (0.2%)
	FAECAL OCCULT BLOOD	0 .	1 (0.2%)	1 (0.1%)
	FAECAL OCCULT BLOOD POSITIVE	1 (0.2%)	1 (0.2%)	2 (0.2%)
	GAMMA-GLUTAMYLTRANSFERASE INCREASED	2 (0.4%)	1 (0.2%)	3 (0.3%)
	LIVER FUNCTION TEST ABNORMAL	0 .	1 (0.2%)	1 (0.1%)
	PROTEIN URINE PRESENT	0 .	1 (0.2%)	1 (0.1%)
METABOLISM AND NUTRITION DISORDERS	TOTAL	2 (0.4%)	2 (0.4%)	4 (0.4%)
	DIABETES MELLITUS	1 (0.2%)	1 (0.2%)	2 (0.2%)
	HYPOKALAEMIA	1 (0.2%)	0 .	1 (0.1%)
	VITAMIN B12 DEFICIENCY	0 .	1 (0.2%)	1 (0.1%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	TOTAL	3 (0.7%)	4 (0.9%)	7 (0.8%)
	ARTHRITIS	0 .	1 (0.2%)	1 (0.1%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED

CONFIDENTIAL

SB 207499

TABLE 15.10

ALL POST-THERAPY ADVERSE EXPERIENCES BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP

PROTOCOL 157

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	BACK PAIN	3 (0.7%)	0 .	3 (0.3%)
	BURSITIS	0 .	1 (0.2%)	1 (0.1%)
	LOCALISED OSTEOARTHRITIS	0 .	1 (0.2%)	1 (0.1%)
	MUSCLE CRAMP	0 .	1 (0.2%)	1 (0.1%)
	MUSCULOSKELETAL CHEST PAIN	0 .	1 (0.2%)	1 (0.1%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	TOTAL	1 (0.2%)	2 (0.4%)	3 (0.3%)
	COLON CANCER	0 .	1 (0.2%)	1 (0.1%)
	EYELID TUMOUR	0 .	1 (0.2%)	1 (0.1%)
	PROSTATE CANCER	1 (0.2%)	0 .	1 (0.1%)
NERVOUS SYSTEM DISORDERS	TOTAL	7 (1.5%)	4 (0.9%)	11 (1.2%)
	APHONIA	1 (0.2%)	0 .	1 (0.1%)
	CEREBROVASCULAR ACCIDENT	0 .	1 (0.2%)	1 (0.1%)
	COMA	1 (0.2%)	0 .	1 (0.1%)
	DIZZINESS	0 .	2 (0.4%)	2 (0.2%)
	HEADACHE	3 (0.7%)	1 (0.2%)	4 (0.4%)
	INTRACRANIAL ANEURYSM	1 (0.2%)	0 .	1 (0.1%)
	RADICULITIS LUMBOSACRAL	1 (0.2%)	0 .	1 (0.1%)
PSYCHIATRIC DISORDERS	TOTAL	1 (0.2%)	3 (0.7%)	4 (0.4%)
	ANXIETY	0 .	2 (0.4%)	2 (0.2%)
	DEPRESSION	0 .	1 (0.2%)	1 (0.1%)
	INSOMNIA	1 (0.2%)	0 .	1 (0.1%)
	PANIC ATTACK	0 .	1 (0.2%)	1 (0.1%)
RENAL AND URINARY DISORDERS	TOTAL	1 (0.2%)	0 .	1 (0.1%)
	RENAL INSUFFICIENCY	1 (0.2%)	0 .	1 (0.1%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED

CONFIDENTIAL

SB 207499

TABLE 15.10

ALL POST-THERAPY ADVERSE EXPERIENCES BY MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND TREATMENT GROUP

PROTOCOL 157

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)	Total (N=907)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	TOTAL	24 (5.3%)	28 (6.2%)	52 (5.7%)
	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE EXACERBATED	21 (4.6%)	26 (5.7%)	47 (5.2%)
	COUGH	1 (0.2%)	1 (0.2%)	2 (0.2%)
	DYSPNOEA	1 (0.2%)	2 (0.4%)	3 (0.3%)
	EPISTAXIS	1 (0.2%)	1 (0.2%)	2 (0.2%)
	HOARSENESS	0 .	1 (0.2%)	1 (0.1%)
	NASAL CONGESTION	0 .	1 (0.2%)	1 (0.1%)
	PULMONARY EMBOLISM	1 (0.2%)	0 .	1 (0.1%)
	RESPIRATORY FAILURE	0 .	1 (0.2%)	1 (0.1%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	TOTAL	1 (0.2%)	0 .	1 (0.1%)
	SKIN ULCER	1 (0.2%)	0 .	1 (0.1%)
VASCULAR DISORDERS	TOTAL	7 (1.5%)	1 (0.2%)	8 (0.9%)
	AORTIC ANEURYSM RUPTURE	1 (0.2%)	0 .	1 (0.1%)
	HYPERTENSION	5 (1.1%)	1 (0.2%)	6 (0.7%)
	HYPOTENSION	1 (0.2%)	0 .	1 (0.1%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED

CONFIDENTIAL

SB 207499

TABLE 15.11A

GASTROINTESTINAL ADVERSE EXPERIENCES OF CONCERN BY MEDDRA PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND TREATMENT GROUP
PROTOCOL 157

MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
TOTAL	11 (2.4%)	30 (6.6%)
DIARRHOEA	1 (0.2%)	10 (2.2%)
VOMITING	1 (0.2%)	6 (1.3%)
ABDOMINAL PAIN	1 (0.2%)	4 (0.9%)
NAUSEA	1 (0.2%)	4 (0.9%)
BLOOD IN STOOL	0 .	3 (0.7%)
ABDOMINAL PAIN UPPER	1 (0.2%)	2 (0.4%)
DYSPEPSIA	0 .	2 (0.4%)
GASTRITIS	0 .	2 (0.4%)
COLONIC HAEMORRHAGE	0 .	1 (0.2%)
DUODENAL ULCER	0 .	1 (0.2%)
FEELING ABNORMAL	0 .	1 (0.2%)
GASTRODUODENITIS	0 .	1 (0.2%)
GASTROENTERITIS	2 (0.4%)	1 (0.2%)
GASTROENTERITIS VIRAL	0 .	1 (0.2%)
HAEMORRHOIDAL HAEMORRHAGE	0 .	1 (0.2%)
ILEUS	0 .	1 (0.2%)
REFLUX OESOPHAGITIS	0 .	1 (0.2%)
FAECAL OCCULT BLOOD POSITIVE	2 (0.4%)	0 .
FAECES DISCOLOURED	1 (0.2%)	0 .
IRON DEFICIENCY ANAEMIA	1 (0.2%)	0 .

1. EACH PATIENT COUNTED ONCE PER MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AT LEAST ONE ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
4. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO SB 207499 TREATMENT GROUP

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.11A

GASTROINTESTINAL ADVERSE EXPERIENCES OF CONCERN BY MEDDRA PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND TREATMENT GROUP
PROTOCOL 157

MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
RECTAL HAEMORRHAGE	1 (0.2%)	0 .
SECONDARY ANAEMIA	1 (0.2%)	0 .

1. EACH PATIENT COUNTED ONCE PER MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AT LEAST ONE ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
4. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO SB 207499 TREATMENT GROUP

CONFIDENTIAL

SB 207499

TABLE 15.11B

GASTROINTESTINAL ADVERSE EXPERIENCES OF CONCERN THAT LED TO PATIENT WITHDRAWAL BY MEDDRA PREFERRED TERM, DESCENDING FREQUENCY OF OCC AND TREATMENT GROUP
PROTOCOL 157

MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=452)	SB 207499 (N=455)
TOTAL	1 (0.2%)	17 (3.7%)
DIARRHOEA	0 .	6 (1.3%)
NAUSEA	0 .	4 (0.9%)
ABDOMINAL PAIN	0 .	3 (0.7%)
VOMITING	0 .	3 (0.7%)
ABDOMINAL PAIN UPPER	0 .	2 (0.4%)
BLOOD IN STOOL	0 .	1 (0.2%)
DUODENAL ULCER	0 .	1 (0.2%)
DYSPEPSIA	0 .	1 (0.2%)
FEELING ABNORMAL	0 .	1 (0.2%)
GASTRITIS	0 .	1 (0.2%)
GASTROENTERITIS	0 .	1 (0.2%)
REFLUX OESOPHAGITIS	0 .	1 (0.2%)
IRON DEFICIENCY ANAEMIA	1 (0.2%)	0 .

1. EACH PATIENT COUNTED ONCE PER MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AT LEAST ONE ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
4. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO SB 207499 TREATMENT GROUP

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.11C

INCIDENCE OF ON-THERAPY GASTROINTESTINAL ADVERSE EXPERIENCES OF CONCERN BY TREATMENT GROUP, MEDDRA PREFERRED TERM, INVESTIGATOR-DETERMINED INTENSITY AND DESCENDING FREQUENCY OF OCCURRENCE
PROTOCOL 157

TREATMENT GROUP: PLACEBO (N=452)

MEDDRA PREFERRED TERM	Intensity			
	Mild	Moderate	Severe	Total
TOTAL	5 (1.1%)	4 (0.9%)	2 (0.4%)	11 (2.4%)
FAECAL OCCULT BLOOD POSITIVE	2 (0.4%)	0 .	0 .	2 (0.4%)
GASTROENTERITIS	1 (0.2%)	1 (0.2%)	0 .	2 (0.4%)
ABDOMINAL PAIN	0 .	1 (0.2%)	0 .	1 (0.2%)
ABDOMINAL PAIN UPPER	0 .	0 .	1 (0.2%)	1 (0.2%)
DIARRHOEA	0 .	1 (0.2%)	0 .	1 (0.2%)
FAECES DISCOLOURED	1 (0.2%)	0 .	0 .	1 (0.2%)
IRON DEFICIENCY ANAEMIA	0 .	0 .	1 (0.2%)	1 (0.2%)
NAUSEA	1 (0.2%)	0 .	0 .	1 (0.2%)
RECTAL HAEMORRHAGE	0 .	1 (0.2%)	0 .	1 (0.2%)
SECONDARY ANAEMIA	1 (0.2%)	0 .	0 .	1 (0.2%)
VOMITING	1 (0.2%)	0 .	0 .	1 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA PREFERRED TERM AND INTENSITY
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
3. MAXIMUM INTENSITY IS USED FOR EACH ADVERSE EVENT FOR EACH PATIENT

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.11C

INCIDENCE OF ON-THERAPY GASTROINTESTINAL ADVERSE EXPERIENCES OF CONCERN BY TREATMENT GROUP, MEDDRA PREFERRED TERM, INVESTIGATOR-DETERMINED INTENSITY AND DESCENDING FREQUENCY OF OCCURRENCE
PROTOCOL 157

TREATMENT GROUP: SB 207499 (N=455)

MEDDRA PREFERRED TERM	Intensity			
	Mild	Moderate	Severe	Total
TOTAL	8 (1.8%)	18 (4.0%)	6 (1.3%)	30 (7.0%)
DIARRHOEA	2 (0.4%)	6 (1.3%)	2 (0.4%)	10 (2.2%)
VOMITING	2 (0.4%)	4 (0.9%)	0 .	6 (1.3%)
ABDOMINAL PAIN	0 .	4 (0.9%)	0 .	4 (0.9%)
NAUSEA	0 .	3 (0.7%)	1 (0.2%)	4 (0.9%)
BLOOD IN STOOL	1 (0.2%)	1 (0.2%)	1 (0.2%)	3 (0.7%)
ABDOMINAL PAIN UPPER	0 .	1 (0.2%)	1 (0.2%)	2 (0.4%)
DYSPEPSIA	1 (0.2%)	1 (0.2%)	0 .	2 (0.4%)
GASTRITIS	0 .	1 (0.2%)	1 (0.2%)	2 (0.4%)
COLONIC HAEMORRHAGE	0 .	1 (0.2%)	0 .	1 (0.2%)
DUODENAL ULCER	0 .	1 (0.2%)	0 .	1 (0.2%)
FEELING ABNORMAL	0 .	1 (0.2%)	0 .	1 (0.2%)
GASTRODUODENITIS	0 .	1 (0.2%)	0 .	1 (0.2%)
GASTROENTERITIS	1 (0.2%)	0 .	0 .	1 (0.2%)
GASTROENTERITIS VIRAL	1 (0.2%)	0 .	0 .	1 (0.2%)
HAEMORRHOIDAL HAEMORRHAGE	1 (0.2%)	0 .	0 .	1 (0.2%)
ILEUS	0 .	0 .	1 (0.2%)	1 (0.2%)
REFLUX OESOPHAGITIS	0 .	0 .	1 (0.2%)	1 (0.2%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA PREFERRED TERM AND INTENSITY
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMIZED
3. MAXIMUM INTENSITY IS USED FOR EACH ADVERSE EVENT FOR EACH PATIENT

CONFIDENTIAL

SB 207499

TABLE 15.12A

TRANSITIONS FROM BASELINE IN FOB RESULTS FOR PATIENTS WITH GI AES OF CONCERN DURING DOUBLE-BLIND PERIOD

PROTOCOL 157

		------DOUBLE BLIND PHASE------ NEGATIVE		POSITIVE		
TREATMENT GROUP	BASELINE					TOTAL
PLACEBO	NEGATIVE	5	(62.5%)	3	(37.5%)	8
	POSITIVE	0		0		0
	TOTAL	5	(62.5%)	3	(37.5%)	8
SB 207499	NEGATIVE	11	(84.6%)	2	(15.4%)	13
	POSITIVE	0		0		0
	TOTAL	11	(84.6%)	2	(15.4%)	13

1. ONLY PATIENTS WITH GASTROINTESTINAL ADVERSE EXPERIENCES OF CONCERN ARE INCLUDED IN THE SUMMARY

CONFIDENTIAL

SB 207499

TABLE 15.12B

TRANSITIONS FROM BASELINE IN FOB RESULTS FOR ALL PATIENTS DURING DOUBLE-BLIND PERIOD

PROTOCOL 157

TREATMENT GROUP	BASELINE	------DOUBLE BLIND PHASE------ NEGATIVE		POSITIVE		TOTAL
PLACEBO	NEGATIVE	139	(96.5%)	5	(3.5%)	144
	POSITIVE	0		0		0
	MISSING	1	(100.0%)	0		1
	TOTAL	140	(96.6%)	5	(3.4%)	145
SB 207499	NEGATIVE	130	(97.0%)	4	(3.0%)	134
	POSITIVE	0		0		0
	MISSING	4	(100.0%)	0		4
	TOTAL	134	(97.1%)	4	(2.9%)	138

CONFIDENTIAL

SB 207499

TABLE 15.13A

TRANSITIONS FROM BASELINE IN ORTHOSTATIC VITAL SIGNS FOR PATIENTS WITH GASTROINTESTINAL ADVERSE EXPERIENCES OF CONCERN
PROTOCOL 157

PARAMETER: SYSTOLIC BP TIME POINT: TOTAL ON-THERAPY

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE NORMAL		HIGH		CONCERN
PLACEBO	NORMAL (DECREASE<10 MM HG)	10	7	(70.0%)	3	(30.0%)	0
	HIGH (DECREASE 10-19 MM HG)	1	0		1	(100.0%)	0
	CONCERN (DECREASE>=20 MM HG)	0	0		0		0
	TOTAL	11	7	(63.6%)	4	(36.4%)	0
SB 207499	NORMAL (DECREASE<10 MM HG)	20	19	(95.0%)	1	(5.0%)	0
	HIGH (DECREASE 10-19 MM HG)	3	1	(33.3%)	2	(66.7%)	0
	CONCERN (DECREASE>=20 MM HG)	0	0		0		0
	TOTAL	23	20	(87.0%)	3	(13.0%)	0

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 52 WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.13A

TRANSITIONS FROM BASELINE IN ORTHOSTATIC VITAL SIGNS FOR PATIENTS WITH GASTROINTESTINAL ADVERSE EXPERIENCES OF CONCERN
PROTOCOL 157

PARAMETER: SYSTOLIC BP TIME POINT: ENDPOINT

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE NORMAL		HIGH		CONCERN
PLACEBO	NORMAL (DECREASE<10 MM HG)	10	8	(80.0%)	2	(20.0%)	0
	HIGH (DECREASE 10-19 MM HG)	1	1	(100.0%)	0		0
	CONCERN (DECREASE>=20 MM HG)	0	0		0		0
	TOTAL	11	9	(81.8%)	2	(18.2%)	0
SB 207499	NORMAL (DECREASE<10 MM HG)	20	20	(100.0%)	0		0
	HIGH (DECREASE 10-19 MM HG)	3	2	(66.7%)	1	(33.3%)	0
	CONCERN (DECREASE>=20 MM HG)	0	0		0		0
	TOTAL	23	22	(95.7%)	1	(4.3%)	0

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 52 WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.13A

TRANSITIONS FROM BASELINE IN ORTHOSTATIC VITAL SIGNS FOR PATIENTS WITH GASTROINTESTINAL ADVERSE EXPERIENCES OF CONCERN
PROTOCOL 157

PARAMETER: DIASTOLIC BP TIME POINT: TOTAL ON-THERAPY

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE NORMAL		DOUBLE BLIND PHASE CONCERN	
PLACEBO	NORMAL (DECREASE<10 MM HG)	11	9	(81.8%)	2	(18.2%)
	CONCERN (DECREASE>=10 MM HG)	0	0		0	
	TOTAL	11	9	(81.8%)	2	(18.2%)
SB 207499	NORMAL (DECREASE<10 MM HG)	23	23	(100.0%)	0	
	CONCERN (DECREASE>=10 MM HG)	0	0		0	
	TOTAL	23	23	(100.0%)	0	

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 52 WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.13A

TRANSITIONS FROM BASELINE IN ORTHOSTATIC VITAL SIGNS FOR PATIENTS WITH GASTROINTESTINAL ADVERSE EXPERIENCES OF CONCERN
PROTOCOL 157

PARAMETER: DIASTOLIC BP TIME POINT: ENDPOINT

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE NORMAL		DOUBLE BLIND PHASE CONCERN	
PLACEBO	NORMAL (DECREASE<10 MM HG)	11	10	(90.9%)	1	(9.1%)
	CONCERN (DECREASE>=10 MM HG)	0	0		0	
	TOTAL	11	10	(90.9%)	1	(9.1%)
SB 207499	NORMAL (DECREASE<10 MM HG)	23	23	(100.0%)	0	
	CONCERN (DECREASE>=10 MM HG)	0	0		0	
	TOTAL	23	23	(100.0%)	0	

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 52 WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.13A

TRANSITIONS FROM BASELINE IN ORTHOSTATIC VITAL SIGNS FOR PATIENTS WITH GASTROINTESTINAL ADVERSE EXPERIENCES OF CONCERN
PROTOCOL 157

PARAMETER: HEART RATE TIME POINT: TOTAL ON-THERAPY

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE NORMAL		CONCERN	
PLACEBO	NORMAL (INCREASE<10 BPM)	11	8	(72.7%)	3	(27.3%)
	CONCERN (INCREASE>=10 BPM)	0	0		0	
	TOTAL	11	8	(72.7%)	3	(27.3%)
SB 207499	NORMAL (INCREASE<10 BPM)	20	19	(95.0%)	1	(5.0%)
	CONCERN (INCREASE>=10 BPM)	3	3	(100.0%)	0	
	TOTAL	23	22	(95.7%)	1	(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 52 WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.13A

TRANSITIONS FROM BASELINE IN ORTHOSTATIC VITAL SIGNS FOR PATIENTS WITH GASTROINTESTINAL ADVERSE EXPERIENCES OF CONCERN
PROTOCOL 157

PARAMETER: HEART RATE TIME POINT: ENDPOINT

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE NORMAL		CONCERN	
PLACEBO	NORMAL (INCREASE<10 BPM)	11	11	(100.0%)	0	
	CONCERN (INCREASE>=10 BPM)	0	0		0	
	TOTAL	11	11	(100.0%)	0	
SB 207499	NORMAL (INCREASE<10 BPM)	20	19	(95.0%)	1	(5.0%)
	CONCERN (INCREASE>=10 BPM)	3	3	(100.0%)	0	
	TOTAL	23	22	(95.7%)	1	(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 52 WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.13B

TRANSITIONS FROM BASELINE IN ORTHOSTATIC VITAL SIGNS

PROTOCOL 157

PARAMETER: SYSTOLIC BP TIME POINT: TOTAL ON-THERAPY

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL (DECREASE<10 MM HG)	386	320	(82.9%)	55	(14.2%)	11	(2.8%)
	HIGH (DECREASE 10-19 MM HG)	32	20	(62.5%)	11	(34.4%)	1	(3.1%)
	CONCERN (DECREASE>=20 MM HG)	0	0		0		0	
	TOTAL	418	340	(81.3%)	66	(15.8%)	12	(2.9%)
SB 207499	NORMAL (DECREASE<10 MM HG)	371	295	(79.5%)	65	(17.5%)	11	(3.0%)
	HIGH (DECREASE 10-19 MM HG)	22	14	(63.6%)	6	(27.3%)	2	(9.1%)
	CONCERN (DECREASE>=20 MM HG)	1	1	(100.0%)	0		0	
	TOTAL	394	310	(78.7%)	71	(18.0%)	13	(3.3%)

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 52 WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.13B

TRANSITIONS FROM BASELINE IN ORTHOSTATIC VITAL SIGNS

PROTOCOL 157

PARAMETER: SYSTOLIC BP TIME POINT: ENDPOINT

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL (DECREASE<10 MM HG)	386	361	(93.5%)	21	(5.4%)	4	(1.0%)
	HIGH (DECREASE 10-19 MM HG)	32	26	(81.3%)	6	(18.8%)	0	
	CONCERN (DECREASE>=20 MM HG)	0	0		0		0	
	TOTAL	418	387	(92.6%)	27	(6.5%)	4	(1.0%)
SB 207499	NORMAL (DECREASE<10 MM HG)	371	340	(91.6%)	27	(7.3%)	4	(1.1%)
	HIGH (DECREASE 10-19 MM HG)	22	20	(90.9%)	2	(9.1%)	0	
	CONCERN (DECREASE>=20 MM HG)	1	1	(100.0%)	0		0	
	TOTAL	394	361	(91.6%)	29	(7.4%)	4	(1.0%)

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 52 WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.13B

TRANSITIONS FROM BASELINE IN ORTHOSTATIC VITAL SIGNS

PROTOCOL 157

PARAMETER: DIASTOLIC BP TIME POINT: TOTAL ON-THERAPY

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE NORMAL		DOUBLE BLIND PHASE CONCERN	
PLACEBO	NORMAL (DECREASE<10 MM HG)	415	388	(93.5%)	27	(6.5%)
	CONCERN (DECREASE>=10 MM HG)	3	2	(66.7%)	1	(33.3%)
	TOTAL	418	390	(93.3%)	28	(6.7%)
SB 207499	NORMAL (DECREASE<10 MM HG)	387	355	(91.7%)	32	(8.3%)
	CONCERN (DECREASE>=10 MM HG)	7	6	(85.7%)	1	(14.3%)
	TOTAL	394	361	(91.6%)	33	(8.4%)

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 52 WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.13B

TRANSITIONS FROM BASELINE IN ORTHOSTATIC VITAL SIGNS

PROTOCOL 157

PARAMETER: DIASTOLIC BP TIME POINT: ENDPOINT

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: NORMAL		DOUBLE BLIND PHASE: CONCERN	
PLACEBO	NORMAL (DECREASE<10 MM HG)	415	408	(98.3%)	7	(1.7%)
	CONCERN (DECREASE>=10 MM HG)	3	2	(66.7%)	1	(33.3%)
	TOTAL	418	410	(98.1%)	8	(1.9%)
SB 207499	NORMAL (DECREASE<10 MM HG)	387	376	(97.2%)	11	(2.8%)
	CONCERN (DECREASE>=10 MM HG)	7	7	(100.0%)	0	
	TOTAL	394	383	(97.2%)	11	(2.8%)

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 52 WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.13B

TRANSITIONS FROM BASELINE IN ORTHOSTATIC VITAL SIGNS

PROTOCOL 157

PARAMETER: HEART RATE TIME POINT: TOTAL ON-THERAPY

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE NORMAL		DOUBLE BLIND PHASE CONCERN	
PLACEBO	NORMAL (INCREASE<10 BPM)	389	345	(88.7%)	44	(11.3%)
	CONCERN (INCREASE>=10 BPM)	29	20	(69.0%)	9	(31.0%)
	TOTAL	418	365	(87.3%)	53	(12.7%)
SB 207499	NORMAL (INCREASE<10 BPM)	382	343	(89.8%)	39	(10.2%)
	CONCERN (INCREASE>=10 BPM)	12	9	(75.0%)	3	(25.0%)
	TOTAL	394	352	(89.3%)	42	(10.7%)

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 52 WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.13B

TRANSITIONS FROM BASELINE IN ORTHOSTATIC VITAL SIGNS

PROTOCOL 157

PARAMETER: HEART RATE TIME POINT: ENDPOINT

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE NORMAL		DOUBLE BLIND PHASE CONCERN	
PLACEBO	NORMAL (INCREASE<10 BPM)	389	376	(96.7%)	13	(3.3%)
	CONCERN (INCREASE>=10 BPM)	29	25	(86.2%)	4	(13.8%)
	TOTAL	418	401	(95.9%)	17	(4.1%)
SB 207499	NORMAL (INCREASE<10 BPM)	382	369	(96.6%)	13	(3.4%)
	CONCERN (INCREASE>=10 BPM)	12	9	(75.0%)	3	(25.0%)
	TOTAL	394	378	(95.9%)	16	(4.1%)

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 52 WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND TREATMENT GROUP

PROTOCOL 157

PARAMETER	VISIT/WEEK	TREATMENT GROUP	RESULT N	RESULT MEAN	RESULT STD	RESULT MIN	RESULT MAX	CHANGE FROM BASELINE N	CHANGE FROM BASELINE MEAN	CHANGE FROM BASELINE STD	CHANGE FROM BASELINE MIN	CHANGE FROM BASELINE MAX
Alanine Aminotransferase (IU/L)	VISIT 3/BASELINE	PLACEBO	442	21.45	17.30	5.0	291.0	0	.	.	.	.
		SB 207499	442	21.89	16.71	4.0	176.0	0	.	.	.	.
	VISIT 4/WEEK 2	PLACEBO	7	60.71	123.7	4.0	341.0	7	1.00	22.02	-16.0	50.0
		SB 207499	11	16.45	2.98	12.0	22.0	11	0.36	4.11	-8.0	5.0
	VISIT 5/WEEK 4	PLACEBO	424	23.03	22.75	5.0	353.0	424	1.35	12.01	-29.0	133.0
		SB 207499	397	21.40	17.06	4.0	166.0	396	-0.54	12.39	-81.0	99.0
	VISIT 6/WEEK 8	PLACEBO	400	22.60	17.46	5.0	241.0	400	1.09	10.17	-50.0	102.0
		SB 207499	383	21.07	14.65	4.0	178.0	382	-1.13	11.59	-93.0	74.0
	VISIT 7/WEEK 12	PLACEBO	402	23.64	21.42	6.0	298.0	402	1.98	11.61	-46.0	139.0
		SB 207499	362	23.08	18.55	5.0	163.0	361	0.59	14.28	-92.0	98.0
	VISIT 8/WEEK 20	PLACEBO	386	23.38	16.81	6.0	192.0	386	1.94	11.97	-99.0	80.0
		SB 207499	336	22.22	15.60	4.0	132.0	336	-0.41	12.99	-102.0	61.0
	VISIT 9/WEEK 28	PLACEBO	376	22.70	14.54	5.0	138.0	376	1.40	12.96	-153.0	63.0
		SB 207499	326	21.83	15.74	5.0	180.0	326	-1.02	13.77	-81.0	76.0
	VISIT 10/WEEK 36	PLACEBO	355	22.65	16.43	5.0	151.0	355	1.16	18.55	-227.0	128.0
		SB 207499	307	20.78	13.74	6.0	102.0	307	-2.08	13.46	-86.0	64.0
	VISIT 11/WEEK 44	PLACEBO	333	22.78	17.66	6.0	188.0	333	1.45	18.36	-213.0	134.0
		SB 207499	283	20.36	11.90	5.0	90.0	283	-2.28	13.29	-113.0	42.0
	VISIT 12/WEEK 52	PLACEBO	325	22.82	19.60	4.0	263.0	325	1.09	20.41	-199.0	239.0
		SB 207499	282	20.52	14.36	4.0	112.0	281	-2.28	13.92	-91.0	70.0
	SAFETY FOLLOW-UP	PLACEBO	53	29.02	23.19	9.0	147.0	53	5.30	20.05	-53.0	82.0
		SB 207499	50	23.36	24.04	4.0	159.0	50	0.00	24.91	-79.0	145.0
Albumin (G/L)	VISIT 3/BASELINE	PLACEBO	442	42.83	2.56	31.0	52.0	0	.	.	.	.
		SB 207499	443	42.60	2.37	35.0	51.0	0	.	.	.	.
	VISIT 4/WEEK 2	PLACEBO	7	42.14	2.48	38.0	45.0	7	-0.14	2.12	-3.0	2.0
		SB 207499	11	42.73	1.95	40.0	47.0	11	-0.36	1.50	-3.0	1.0
	VISIT 5/WEEK 4	PLACEBO	423	42.75	2.61	34.0	51.0	423	-0.01	2.34	-9.0	12.0
		SB 207499	399	42.58	2.41	34.0	49.0	399	-0.14	1.86	-6.0	8.0
	VISIT 6/WEEK 8	PLACEBO	400	42.78	2.43	35.0	52.0	400	-0.07	2.24	-7.0	14.0
		SB 207499	385	42.82	2.52	34.0	49.0	385	0.14	2.13	-8.0	7.0
	VISIT 7/WEEK 12	PLACEBO	402	42.80	2.51	35.0	50.0	402	0.00	2.20	-6.0	11.0

CONFIDENTIAL

SB 207499

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND TREATMENT GROUP

PROTOCOL 157

PARAMETER	VISIT/WEEK	TREATMENT GROUP	RESULT N	RESULT MEAN	RESULT STD	RESULT MIN	RESULT MAX	CHANGE FROM BASELINE N	CHANGE FROM BASELINE MEAN	CHANGE FROM BASELINE STD	CHANGE FROM BASELINE MIN	CHANGE FROM BASELINE MAX
Albumin (G/L)	VISIT 7/WEEK 12	SB 207499	362	42.76	2.69	33.0	53.0	362	0.08	2.33	-7.0	7.0
	VISIT 8/WEEK 20	PLACEBO	386	43.06	2.72	35.0	53.0	386	0.26	2.37	-6.0	15.0
		SB 207499	336	43.13	2.69	33.0	51.0	336	0.50	2.26	-5.0	9.0
	VISIT 9/WEEK 28	PLACEBO	376	43.19	2.79	32.0	53.0	376	0.40	2.41	-6.0	11.0
		SB 207499	327	43.32	2.57	36.0	50.0	327	0.61	2.44	-6.0	11.0
	VISIT 10/WEEK 36	PLACEBO	355	43.47	2.80	35.0	52.0	355	0.61	2.41	-8.0	8.0
		SB 207499	307	43.45	2.64	34.0	52.0	307	0.68	2.25	-7.0	10.0
	VISIT 11/WEEK 44	PLACEBO	334	43.58	3.04	33.0	52.0	334	0.70	2.49	-7.0	10.0
		SB 207499	283	43.72	2.74	34.0	51.0	283	0.87	2.38	-7.0	10.0
	VISIT 12/WEEK 52	PLACEBO	325	44.37	3.03	35.0	55.0	325	1.50	2.61	-7.0	12.0
		SB 207499	282	44.22	3.15	31.0	52.0	281	1.47	2.58	-8.0	9.0
	SAFETY FOLLOW-UP	PLACEBO	53	43.58	3.42	36.0	52.0	53	0.70	2.42	-6.0	7.0
		SB 207499	50	43.32	3.55	36.0	49.0	50	0.78	2.64	-7.0	9.0
Alkaline Phosphatase (IU/L)	VISIT 3/BASELINE	PLACEBO	441	79.05	23.16	26.0	196.0	0	.	.	.	.
		SB 207499	443	80.09	24.70	9.0	327.0	0	.	.	.	.
	VISIT 4/WEEK 2	PLACEBO	7	92.71	20.58	66.0	125.0	7	-3.86	6.74	-11.0	8.0
		SB 207499	11	73.64	17.69	48.0	98.0	11	-0.91	6.17	-14.0	7.0
	VISIT 5/WEEK 4	PLACEBO	423	79.39	26.88	25.0	346.0	423	0.33	18.38	-65.0	274.0
		SB 207499	397	78.11	21.55	23.0	185.0	397	-1.25	14.83	-190.0	81.0
	VISIT 6/WEEK 8	PLACEBO	400	78.94	24.38	24.0	221.0	400	0.26	15.35	-89.0	100.0
		SB 207499	383	79.17	21.23	31.0	169.0	383	0.02	15.35	-202.0	76.0
	VISIT 7/WEEK 12	PLACEBO	400	80.01	24.25	24.0	211.0	400	1.54	13.32	-57.0	88.0
		SB 207499	362	79.60	22.05	30.0	155.0	362	0.41	17.17	-218.0	70.0
	VISIT 8/WEEK 20	PLACEBO	386	80.41	24.36	21.0	222.0	386	1.97	15.82	-77.0	99.0
		SB 207499	336	80.62	22.90	32.0	175.0	336	1.65	18.45	-209.0	79.0
	VISIT 9/WEEK 28	PLACEBO	376	79.54	22.64	22.0	200.0	376	1.24	16.38	-93.0	99.0
		SB 207499	326	79.59	22.31	35.0	183.0	326	0.62	19.42	-202.0	79.0
	VISIT 10/WEEK 36	PLACEBO	355	77.81	22.95	23.0	221.0	355	-0.80	17.31	-103.0	91.0
		SB 207499	307	76.86	22.34	34.0	157.0	307	-2.09	18.94	-197.0	82.0
	VISIT 11/WEEK 44	PLACEBO	334	76.17	22.99	24.0	215.0	334	-2.58	16.86	-96.0	96.0
		SB 207499	283	75.81	20.84	34.0	154.0	283	-3.23	18.63	-214.0	75.0

CONFIDENTIAL

SB 207499

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND TREATMENT GROUP

PROTOCOL 157

PARAMETER	VISIT/WEEK	TREATMENT GROUP	RESULT N	RESULT MEAN	RESULT STD	RESULT MIN	RESULT MAX	CHANGE FROM BASELINE N	CHANGE FROM BASELINE MEAN	CHANGE FROM BASELINE STD	CHANGE FROM BASELINE MIN	CHANGE FROM BASELINE MAX
Alkaline Phosphatase (IU/L)	VISIT 12/WEEK 52	PLACEBO	326	74.71	22.53	23.0	172.0	326	-3.52	15.92	-76.0	73.0
		SB 207499	282	76.14	23.90	31.0	250.0	281	-3.19	22.64	-197.0	187.0
	SAFETY FOLLOW-UP	PLACEBO	53	78.43	24.83	29.0	158.0	53	-2.21	16.22	-60.0	43.0
		SB 207499	50	78.48	22.45	45.0	143.0	50	-3.98	32.74	-199.0	54.0
Amylase ()	SAFETY FOLLOW-UP	SB 207499	0	.	.	.	.	0	.	.	.	.
Amylase (IU/L)	SAFETY FOLLOW-UP	PLACEBO	1	102.00	.	102.0	102.0	1	-13.00	.	-13.0	-13.0
		SB 207499	3	94.00	26.89	63.0	111.0	3	21.00	9.00	12.0	30.0
Aspartate Aminotransferase (IU/L)	VISIT 3/BASELINE	PLACEBO	442	22.49	11.65	9.0	134.0	0	.	.	.	.
		SB 207499	443	23.45	21.75	8.0	372.0	0	.	.	.	.
	VISIT 4/WEEK 2	PLACEBO	7	43.29	63.62	13.0	187.0	7	4.57	24.60	-15.0	58.0
		SB 207499	11	19.36	4.20	11.0	26.0	11	-0.36	3.04	-6.0	4.0
	VISIT 5/WEEK 4	PLACEBO	423	23.50	18.04	9.0	204.0	423	1.00	12.43	-45.0	158.0
		SB 207499	397	21.78	13.58	7.0	164.0	397	-1.05	10.64	-115.0	78.0
	VISIT 6/WEEK 8	PLACEBO	400	23.15	16.10	8.0	182.0	400	0.79	11.57	-46.0	136.0
		SB 207499	383	21.92	13.19	8.0	190.0	383	-0.80	11.45	-138.0	88.0
	VISIT 7/WEEK 12	PLACEBO	401	23.28	16.30	8.0	204.0	401	0.72	11.44	-52.0	128.0
		SB 207499	362	22.42	15.50	8.0	172.0	362	-0.45	13.16	-132.0	105.0
	VISIT 8/WEEK 20	PLACEBO	385	23.15	14.43	10.0	177.0	385	0.84	10.12	-32.0	131.0
		SB 207499	335	22.19	13.44	10.0	143.0	335	-0.80	11.90	-143.0	76.0
	VISIT 9/WEEK 28	PLACEBO	375	22.71	10.86	10.0	111.0	375	0.35	8.69	-60.0	65.0
		SB 207499	325	22.35	13.98	8.0	151.0	325	-0.88	12.27	-121.0	84.0
	VISIT 10/WEEK 36	PLACEBO	355	23.59	15.78	9.0	147.0	355	1.19	14.54	-93.0	120.0
		SB 207499	307	21.78	11.64	6.0	98.0	307	-1.33	12.02	-148.0	65.0
	VISIT 11/WEEK 44	PLACEBO	332	23.67	16.24	9.0	155.0	332	1.38	14.23	-82.0	118.0
		SB 207499	283	21.58	12.63	8.0	148.0	283	-1.23	13.77	-157.0	126.0
	VISIT 12/WEEK 52	PLACEBO	326	23.81	13.87	10.0	137.0	326	1.19	12.00	-65.0	119.0
		SB 207499	281	22.02	11.63	6.0	106.0	280	-1.15	12.18	-132.0	68.0
	SAFETY FOLLOW-UP	PLACEBO	53	30.47	25.07	11.0	154.0	53	3.96	21.09	-43.0	100.0
		SB 207499	50	25.78	29.32	2.0	205.0	50	0.60	28.04	-38.0	186.0

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND TREATMENT GROUP

PROTOCOL 157

PARAMETER	VISIT/WEEK	TREATMENT GROUP	RESULT N	RESULT MEAN	RESULT STD	RESULT MIN	RESULT MAX	CHANGE FROM BASELINE N	CHANGE FROM BASELINE MEAN	CHANGE FROM BASELINE STD	CHANGE FROM BASELINE MIN	CHANGE FROM BASELINE MAX
Blood Urea Nitrogen (MMOL/L)	VISIT 3/BASELINE	PLACEBO	441	5.43	1.66	1.8	12.3	0	.	.	.	.
		SB 207499	443	5.69	1.90	1.7	13.5	0	.	.	.	.
	VISIT 4/WEEK 2	PLACEBO	7	6.43	2.77	3.9	11.5	7	1.17	2.37	-0.4	5.6
		SB 207499	11	5.78	1.95	3.7	10.2	11	-0.49	1.34	-2.9	1.1
	VISIT 5/WEEK 4	PLACEBO	423	5.64	1.76	1.7	14.9	423	0.18	1.32	-5.7	7.9
		SB 207499	399	5.63	1.89	1.8	12.0	399	-0.07	1.31	-4.6	4.8
	VISIT 6/WEEK 8	PLACEBO	400	5.56	1.80	1.3	15.2	400	0.13	1.35	-5.9	9.3
		SB 207499	385	5.75	1.85	1.5	12.9	385	0.02	1.27	-3.7	3.9
	VISIT 7/WEEK 12	PLACEBO	402	5.61	1.67	1.6	13.2	402	0.17	1.36	-5.2	5.9
		SB 207499	362	5.62	1.89	1.7	14.9	362	-0.08	1.46	-7.6	5.3
	VISIT 8/WEEK 20	PLACEBO	386	5.58	1.77	1.5	13.3	386	0.12	1.42	-4.1	6.6
		SB 207499	336	5.70	1.92	1.7	15.6	336	-0.05	1.37	-4.8	6.1
	VISIT 9/WEEK 28	PLACEBO	376	5.73	1.75	1.9	11.9	376	0.28	1.38	-4.9	5.5
		SB 207499	327	5.75	1.81	1.7	17.1	327	0.08	1.44	-4.7	5.3
	VISIT 10/WEEK 36	PLACEBO	355	5.65	1.68	1.5	12.1	355	0.23	1.39	-6.3	5.4
		SB 207499	307	5.63	1.81	1.0	16.6	307	-0.05	1.43	-5.2	5.1
	VISIT 11/WEEK 44	PLACEBO	334	5.69	1.93	1.6	17.1	334	0.27	1.53	-5.3	11.0
		SB 207499	283	5.76	1.81	2.0	12.2	283	0.06	1.36	-6.7	5.9
	VISIT 12/WEEK 52	PLACEBO	326	5.68	1.78	2.1	12.1	326	0.29	1.44	-5.1	5.4
		SB 207499	282	5.73	1.94	1.8	18.0	281	0.09	1.49	-5.0	6.7
	SAFETY FOLLOW-UP	PLACEBO	53	5.37	1.76	2.2	9.7	53	0.33	1.40	-2.7	4.2
		SB 207499	50	6.16	2.68	1.8	16.5	50	0.43	1.91	-6.5	5.6
C-Reactive Protein ()	SAFETY FOLLOW-UP	PLACEBO	0	.	.	.	.	0	.	.	.	.
		SB 207499	0	.	.	.	.	0	.	.	.	.
C-Reactive Protein (G/L)	VISIT 3/BASELINE	PLACEBO	135	0.01	0.02	0.0	0.1	0	.	.	.	.
		SB 207499	150	0.01	0.02	0.0	0.2	0	.	.	.	.
	VISIT 4/WEEK 2	PLACEBO	2	0.00	0.00	0.0	0.0	1	-0.07	.	-0.1	-0.1
		SB 207499	2	0.02	0.03	0.0	0.0	1	-0.02	.	-0.0	-0.0
	VISIT 5/WEEK 4	PLACEBO	1	0.00	.	0.0	0.0	0	.	.	.	.
	VISIT 6/WEEK 8	PLACEBO	1	0.01	.	0.0	0.0	1	-0.07	.	-0.1	-0.1

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND TREATMENT GROUP

PROTOCOL 157

PARAMETER	VISIT/WEEK	TREATMENT GROUP	RESULT N	RESULT MEAN	RESULT STD	RESULT MIN	RESULT MAX	CHANGE FROM BASELINE N	CHANGE FROM BASELINE MEAN	CHANGE FROM BASELINE STD	CHANGE FROM BASELINE MIN	CHANGE FROM BASELINE MAX
C-Reactive Protein (G/L)	VISIT 6/WEEK 8	SB 207499	4	0.01	0.00	0.0	0.0	2	-0.08	0.11	-0.2	0.0
	VISIT 8/WEEK 20	SB 207499	3	0.01	0.00	0.0	0.0	1	-0.01	.	-0.0	-0.0
	VISIT 9/WEEK 28	PLACEBO	1	0.01	.	0.0	0.0	1	0.00	.	0.0	0.0
	VISIT 10/WEEK 36	PLACEBO	3	0.03	0.05	0.0	0.1	0	.	.	.	.
	VISIT 11/WEEK 44	PLACEBO	3	0.01	0.01	0.0	0.0	1	0.00	.	0.0	0.0
		SB 207499	1	0.01	.	0.0	0.0	1	0.01	.	0.0	0.0
	VISIT 12/WEEK 52	PLACEBO	71	0.02	0.03	0.0	0.2	34	0.01	0.03	-0.1	0.1
		SB 207499	59	0.02	0.03	0.0	0.2	34	0.01	0.03	-0.0	0.2
	SAFETY FOLLOW-UP	PLACEBO	1	0.09	.	0.1	0.1	1	0.06	.	0.1	0.1
		SB 207499	6	0.01	0.00	0.0	0.0	3	0.00	0.00	-0.0	0.0
CD4 Percent ()	SAFETY FOLLOW-UP	PLACEBO	0	.	.	.	.	0	.	.	.	.
		SB 207499	0	.	.	.	.	0	.	.	.	.
CD8 Percent ()	SAFETY FOLLOW-UP	PLACEBO	0	.	.	.	.	0	.	.	.	.
		SB 207499	0	.	.	.	.	0	.	.	.	.
Chloride (MMOL/L)	VISIT 3/BASELINE	PLACEBO	442	103.61	3.53	73.0	112.0	0	.	.	.	.
		SB 207499	443	103.66	3.38	81.0	114.0	0	.	.	.	.
	VISIT 4/WEEK 2	PLACEBO	7	105.43	1.99	103.0	108.0	7	1.29	2.63	-4.0	4.0
		SB 207499	11	105.82	3.12	102.0	111.0	11	1.27	3.88	-6.0	7.0
	VISIT 5/WEEK 4	PLACEBO	423	103.81	3.17	85.0	113.0	423	0.25	3.47	-9.0	29.0
		SB 207499	399	104.24	3.20	94.0	114.0	399	0.46	2.90	-14.0	14.0
	VISIT 6/WEEK 8	PLACEBO	400	103.90	3.23	89.0	112.0	400	0.24	3.31	-12.0	28.0
		SB 207499	385	103.95	3.17	93.0	114.0	385	0.20	2.90	-8.0	14.0
	VISIT 7/WEEK 12	PLACEBO	402	103.68	3.32	85.0	111.0	402	0.00	3.17	-11.0	28.0
		SB 207499	362	103.81	3.16	92.0	113.0	362	0.09	3.13	-11.0	16.0
	VISIT 8/WEEK 20	PLACEBO	385	103.85	2.94	92.0	114.0	385	0.12	3.20	-7.0	31.0
		SB 207499	336	104.06	3.15	89.0	113.0	336	0.24	2.60	-8.0	9.0
	VISIT 9/WEEK 28	PLACEBO	376	103.66	2.86	91.0	111.0	376	-0.17	3.07	-11.0	29.0
		SB 207499	327	103.92	3.18	88.0	110.0	327	0.09	3.01	-11.0	13.0

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND TREATMENT GROUP

PROTOCOL 157

PARAMETER	VISIT/WEEK	TREATMENT GROUP	RESULT N	RESULT MEAN	RESULT STD	RESULT MIN	RESULT MAX	CHANGE FROM BASELINE N	CHANGE FROM BASELINE MEAN	CHANGE FROM BASELINE STD	CHANGE FROM BASELINE MIN	CHANGE FROM BASELINE MAX
Chloride (MMOL/L)	VISIT 10/WEEK 36	PLACEBO	355	103.65	3.04	92.0	110.0	355	-0.21	3.52	-12.0	33.0
		SB 207499	307	104.01	3.04	88.0	112.0	307	0.12	2.96	-10.0	10.0
	VISIT 11/WEEK 44	PLACEBO	334	103.56	3.01	92.0	112.0	334	-0.30	3.33	-12.0	31.0
		SB 207499	283	104.07	2.82	95.0	110.0	283	0.15	2.92	-9.0	12.0
	VISIT 12/WEEK 52	PLACEBO	326	103.80	2.98	94.0	114.0	326	-0.09	3.29	-10.0	28.0
		SB 207499	282	103.81	3.09	90.0	111.0	281	-0.12	3.08	-17.0	11.0
	SAFETY FOLLOW-UP	PLACEBO	53	103.49	3.22	97.0	110.0	53	-0.47	3.07	-10.0	7.0
		SB 207499	50	104.76	3.42	99.0	117.0	50	0.50	2.57	-6.0	6.0
Creatinine (UMOL/L)	VISIT 3/BASELINE	PLACEBO	442	73.86	19.28	32.0	181.0	0	.	.	.	.
		SB 207499	443	76.74	29.22	32.0	468.0	0	.	.	.	.
	VISIT 4/WEEK 2	PLACEBO	7	76.57	33.83	55.0	152.0	7	8.71	21.01	-4.0	55.0
		SB 207499	11	78.18	28.12	42.0	132.0	11	-2.64	20.40	-51.0	30.0
	VISIT 5/WEEK 4	PLACEBO	423	74.78	22.54	31.0	288.0	423	0.53	15.54	-49.0	239.0
		SB 207499	398	74.70	23.52	30.0	230.0	398	-1.77	19.58	-283.0	138.0
	VISIT 6/WEEK 8	PLACEBO	400	72.97	19.73	30.0	161.0	400	-0.85	11.61	-54.0	55.0
		SB 207499	383	73.75	21.23	27.0	212.0	383	-2.77	20.30	-331.0	40.0
	VISIT 7/WEEK 12	PLACEBO	402	73.61	24.64	26.0	379.0	402	-0.33	18.88	-46.0	308.0
		SB 207499	362	72.94	21.57	29.0	207.0	362	-3.65	23.89	-393.0	57.0
	VISIT 8/WEEK 20	PLACEBO	386	71.58	20.80	31.0	239.0	386	-2.32	14.38	-54.0	161.0
		SB 207499	336	72.38	22.30	29.0	229.0	336	-4.63	20.72	-316.0	37.0
	VISIT 9/WEEK 28	PLACEBO	376	69.55	20.36	29.0	242.0	376	-4.26	12.23	-90.0	61.0
		SB 207499	326	70.94	20.62	29.0	232.0	326	-5.76	21.41	-325.0	47.0
	VISIT 10/WEEK 36	PLACEBO	355	69.41	19.40	31.0	147.0	355	-4.14	12.91	-57.0	65.0
		SB 207499	307	69.68	21.50	30.0	247.0	307	-6.76	21.00	-317.0	37.0
	VISIT 11/WEEK 44	PLACEBO	334	68.23	19.73	27.0	197.0	334	-5.27	13.46	-52.0	140.0
		SB 207499	283	68.56	19.05	25.0	142.0	283	-7.82	22.02	-329.0	30.0
	VISIT 12/WEEK 52	PLACEBO	326	67.98	17.77	27.0	125.0	326	-5.09	11.00	-48.0	36.0
		SB 207499	282	69.54	22.01	24.0	257.0	281	-7.00	23.22	-341.0	30.0
	SAFETY FOLLOW-UP	PLACEBO	53	64.25	16.42	42.0	105.0	53	-3.83	9.27	-18.0	20.0
		SB 207499	50	74.96	37.34	39.0	241.0	50	-10.54	49.52	-340.0	51.0

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND TREATMENT GROUP

PROTOCOL 157

PARAMETER	VISIT/WEEK	TREATMENT GROUP	RESULT N	RESULT MEAN	RESULT STD	RESULT MIN	RESULT MAX	CHANGE FROM BASELINE N	CHANGE FROM BASELINE MEAN	CHANGE FROM BASELINE STD	CHANGE FROM BASELINE MIN	CHANGE FROM BASELINE MAX
Gamma Glutamyl Transferase (IU/L)	VISIT 3/BASELINE	PLACEBO	442	41.15	38.06	9.0	376.0	0	.	.	.	.
		SB 207499	443	44.65	82.15	9.0	1365.0	0	.	.	.	.
	VISIT 4/WEEK 2	PLACEBO	7	71.29	81.64	15.0	242.0	7	-11.29	14.75	-33.0	9.0
		SB 207499	11	28.91	10.48	16.0	45.0	11	-1.45	5.61	-9.0	9.0
	VISIT 5/WEEK 4	PLACEBO	423	42.73	51.17	1.0	500.0	423	1.54	30.88	-76.0	398.0
		SB 207499	398	38.22	41.10	5.0	470.0	398	-4.47	30.28	-312.0	81.0
	VISIT 6/WEEK 8	PLACEBO	400	42.51	58.19	10.0	774.0	400	0.99	39.04	-102.0	591.0
		SB 207499	384	38.48	40.35	6.0	442.0	384	-4.05	36.44	-438.0	105.0
	VISIT 7/WEEK 12	PLACEBO	402	43.96	52.33	10.0	675.0	402	2.19	37.36	-98.0	615.0
		SB 207499	362	40.94	61.96	6.0	929.0	362	-2.04	53.24	-434.0	668.0
	VISIT 8/WEEK 20	PLACEBO	386	45.69	84.30	1.0	1484.0	386	4.58	64.13	-137.0	1108
		SB 207499	336	38.66	40.54	7.0	415.0	336	-4.67	43.66	-447.0	236.0
	VISIT 9/WEEK 28	PLACEBO	376	40.90	38.94	1.0	357.0	376	0.49	28.72	-157.0	297.0
		SB 207499	326	39.50	47.07	7.0	476.0	326	-4.63	47.45	-423.0	319.0
	VISIT 10/WEEK 36	PLACEBO	355	43.00	53.83	8.0	675.0	355	2.47	45.59	-183.0	615.0
		SB 207499	307	38.53	37.38	8.0	318.0	307	-4.61	46.14	-534.0	146.0
	VISIT 11/WEEK 44	PLACEBO	333	44.18	55.96	9.0	740.0	333	3.82	48.26	-158.0	680.0
		SB 207499	283	36.46	35.43	9.0	365.0	283	-6.71	47.24	-539.0	120.0
	VISIT 12/WEEK 52	PLACEBO	326	42.94	39.21	10.0	297.0	326	1.41	30.82	-193.0	196.0
		SB 207499	282	41.04	52.29	8.0	564.0	281	-2.91	49.64	-493.0	289.0
	SAFETY FOLLOW-UP	PLACEBO	53	65.62	71.07	11.0	409.0	53	10.34	54.02	-107.0	259.0
		SB 207499	50	57.08	87.65	13.0	554.0	50	4.90	61.01	-331.0	184.0
Glucose - Fasting (MMOL/L)	VISIT 3/BASELINE	PLACEBO	131	6.22	2.13	4.2	19.4	0	.	.	.	.
		SB 207499	128	5.85	1.53	3.3	15.8	0	.	.	.	.
	VISIT 4/WEEK 2	PLACEBO	3	5.10	0.60	4.5	5.7	1	-0.60	.	-0.6	-0.6
		SB 207499	3	6.00	0.87	5.5	7.0	2	-0.60	0.28	-0.8	-0.4
	VISIT 5/WEEK 4	PLACEBO	134	6.15	1.65	4.1	15.6	103	-0.08	1.33	-6.1	3.5
		SB 207499	131	5.93	1.67	3.4	16.6	111	0.01	0.88	-4.1	2.9
	VISIT 6/WEEK 8	PLACEBO	113	6.43	2.44	3.0	19.8	88	0.09	1.44	-6.0	4.3
		SB 207499	114	5.82	1.64	3.4	19.0	96	-0.01	0.87	-1.9	3.6
	VISIT 7/WEEK 12	PLACEBO	120	6.35	2.38	3.6	21.1	102	0.20	1.45	-5.9	9.6

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND TREATMENT GROUP

PROTOCOL 157

PARAMETER	VISIT/WEEK	TREATMENT GROUP	RESULT N	RESULT MEAN	RESULT STD	RESULT MIN	RESULT MAX	CHANGE FROM BASELINE N	CHANGE FROM BASELINE MEAN	CHANGE FROM BASELINE STD	CHANGE FROM BASELINE MIN	CHANGE FROM BASELINE MAX
Glucose - Fasting (MMOL/L)	VISIT 7/WEEK 12	SB 207499	118	5.74	1.47	3.4	16.5	96	-0.12	1.34	-8.3	4.2
	VISIT 8/WEEK 20	PLACEBO	108	6.50	2.50	3.7	18.5	87	0.24	1.97	-7.7	11.6
		SB 207499	109	5.87	1.73	3.5	18.7	90	-0.05	1.19	-8.1	3.4
	VISIT 9/WEEK 28	PLACEBO	112	6.25	1.98	2.9	15.5	87	0.17	2.10	-13.5	9.0
		SB 207499	99	5.69	1.07	3.9	11.6	89	-0.20	1.29	-8.6	4.5
	VISIT 10/WEEK 36	PLACEBO	105	6.32	2.21	4.1	19.0	84	0.21	1.81	-10.4	7.5
		SB 207499	91	5.70	0.94	3.7	9.5	81	-0.19	1.16	-8.4	1.9
	VISIT 11/WEEK 44	PLACEBO	97	6.34	1.83	3.7	15.4	78	0.22	1.91	-9.3	6.4
		SB 207499	95	5.71	0.92	3.7	10.2	79	-0.11	1.28	-9.4	2.0
	VISIT 12/WEEK 52	PLACEBO	107	6.28	1.88	2.9	14.3	85	0.20	1.69	-11.7	4.2
		SB 207499	85	5.75	0.83	4.4	8.4	77	-0.10	1.38	-9.3	2.3
	SAFETY FOLLOW-UP	PLACEBO	19	6.03	1.82	4.5	13.0	17	0.19	0.90	-0.7	3.1
		SB 207499	18	5.30	0.67	3.9	6.4	16	-0.54	0.60	-1.4	0.5
Glucose - Random (MMOL/L)	VISIT 3/BASELINE	PLACEBO	310	5.98	1.65	3.3	16.7	0	.	.	.	.
		SB 207499	315	6.00	1.84	2.8	17.5	0	.	.	.	.
	VISIT 4/WEEK 2	PLACEBO	4	6.00	1.00	5.4	7.5	4	0.38	1.00	-0.4	1.7
		SB 207499	8	5.89	1.23	4.3	8.4	7	-0.07	0.81	-1.7	0.9
	VISIT 5/WEEK 4	PLACEBO	287	6.07	1.96	3.2	21.1	268	0.01	1.51	-6.5	4.9
		SB 207499	267	5.96	1.61	1.8	15.4	259	0.04	1.35	-6.6	4.9
	VISIT 6/WEEK 8	PLACEBO	287	6.06	1.67	2.7	17.5	271	0.13	1.48	-4.9	6.6
		SB 207499	271	5.95	1.58	2.3	14.7	256	-0.08	1.40	-5.4	4.9
	VISIT 7/WEEK 12	PLACEBO	282	6.00	1.69	3.8	16.8	272	0.04	1.24	-4.8	3.9
		SB 207499	244	5.84	1.65	2.8	15.3	233	-0.14	1.40	-5.3	4.9
	VISIT 8/WEEK 20	PLACEBO	278	6.03	1.64	1.3	14.9	264	0.03	1.44	-4.9	5.0
		SB 207499	227	5.96	1.53	3.2	14.7	215	-0.04	1.92	-9.9	9.3
	VISIT 9/WEEK 28	PLACEBO	264	5.97	1.84	2.2	17.8	252	-0.02	1.62	-4.8	6.4
		SB 207499	228	6.07	1.85	2.1	15.5	215	0.03	1.76	-6.1	10.0
	VISIT 10/WEEK 36	PLACEBO	250	6.22	1.89	3.6	16.9	235	0.23	1.71	-4.7	10.2
		SB 207499	216	6.12	1.93	2.0	16.8	200	0.07	1.70	-8.0	11.2
	VISIT 11/WEEK 44	PLACEBO	236	6.20	1.75	3.7	17.2	221	0.24	1.74	-5.6	12.4
		SB 207499	188	6.03	1.76	2.2	15.2	173	-0.02	1.65	-9.8	5.5

CONFIDENTIAL

SB 207499

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND TREATMENT GROUP

PROTOCOL 157

PARAMETER	VISIT/WEEK	TREATMENT GROUP	RESULT N	RESULT MEAN	RESULT STD	RESULT MIN	RESULT MAX	CHANGE FROM BASELINE N	CHANGE FROM BASELINE MEAN	CHANGE FROM BASELINE STD	CHANGE FROM BASELINE MIN	CHANGE FROM BASELINE MAX
Glucose - Random (MMOL/L)	VISIT 12/WEEK 52	PLACEBO	219	6.18	1.94	3.2	17.2	208	0.14	1.68	-7.8	8.5
		SB 207499	197	6.15	1.85	2.0	15.4	186	0.08	1.69	-6.6	6.9
	SAFETY FOLLOW-UP	PLACEBO	34	6.39	2.03	4.3	11.7	32	0.00	1.66	-2.8	4.8
		SB 207499	32	6.46	2.49	3.4	14.9	30	0.59	2.13	-2.5	7.6
Helper / Suppressor Ratio Percent in Blood (%)	VISIT 3/BASELINE	PLACEBO	428	2.13	1.30	0.3	8.5	0	.	.	.	.
		SB 207499	426	2.18	1.39	0.2	12.6	0	.	.	.	.
	VISIT 4/WEEK 2	PLACEBO	6	1.82	1.15	0.7	3.9	2	0.26	0.20	0.1	0.4
		SB 207499	8	1.83	0.64	1.1	2.9	4	-0.02	0.36	-0.5	0.4
	VISIT 5/WEEK 4	PLACEBO	3	1.76	0.44	1.3	2.2	3	-0.06	0.01	-0.1	-0.0
		SB 207499	2	1.74	0.18	1.6	1.9	2	-0.03	0.28	-0.2	0.2
	VISIT 6/WEEK 8	PLACEBO	2	1.79	0.69	1.3	2.3	2	-0.36	0.60	-0.8	0.1
		SB 207499	7	2.16	1.39	0.7	4.4	7	-0.29	0.51	-1.0	0.7
	VISIT 7/WEEK 12	PLACEBO	2	1.88	0.44	1.6	2.2	2	-0.04	0.49	-0.4	0.3
		SB 207499	2	1.13	0.81	0.6	1.7	2	-0.17	0.03	-0.2	-0.1
	VISIT 8/WEEK 20	PLACEBO	2	2.63	0.83	2.0	3.2	2	-0.27	0.12	-0.4	-0.2
		SB 207499	4	1.77	0.81	0.9	2.8	4	0.21	0.23	-0.1	0.4
	VISIT 9/WEEK 28	PLACEBO	5	1.90	0.85	1.1	3.3	5	0.11	0.24	-0.2	0.4
		SB 207499	6	2.54	1.23	0.9	4.6	6	-0.04	0.26	-0.5	0.3
	VISIT 10/WEEK 36	PLACEBO	4	1.70	0.69	1.1	2.5	4	0.00	0.23	-0.3	0.2
		SB 207499	1	0.74	.	0.7	0.7	1	-0.37	.	-0.4	-0.4
	VISIT 11/WEEK 44	PLACEBO	4	2.04	0.67	1.3	3.0	4	-0.37	0.45	-0.8	0.3
		SB 207499	1	1.33	.	1.3	1.3	1	-0.43	.	-0.4	-0.4
	VISIT 12/WEEK 52	PLACEBO	315	2.19	1.41	0.5	9.0	304	0.02	0.63	-3.5	6.1
		SB 207499	275	2.14	1.16	0.4	6.6	259	-0.02	0.58	-3.5	3.1
	SAFETY FOLLOW-UP	PLACEBO	12	2.35	1.28	0.9	5.6	11	-0.16	0.56	-1.3	0.6
		SB 207499	11	1.49	0.76	0.5	2.9	11	0.04	0.27	-0.4	0.4
Hematocrit (%)	VISIT 3/BASELINE	PLACEBO	432	44.05	4.05	17.0	60.0	0	.	.	.	.
		SB 207499	426	44.04	3.92	30.0	57.4	0	.	.	.	.
	VISIT 4/WEEK 2	PLACEBO	7	42.29	3.73	37.3	46.7	7	1.59	8.30	-3.2	20.3
		SB 207499	11	45.09	3.32	40.2	51.7	11	0.00	3.08	-4.5	6.0

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND TREATMENT GROUP

PROTOCOL 157

PARAMETER	VISIT/WEEK	TREATMENT GROUP	RESULT N	RESULT MEAN	RESULT STD	RESULT MIN	RESULT MAX	CHANGE FROM BASELINE N	CHANGE FROM BASELINE MEAN	CHANGE FROM BASELINE STD	CHANGE FROM BASELINE MIN	CHANGE FROM BASELINE MAX
Hematocrit (%)	VISIT 5/WEEK 4	PLACEBO	410	43.97	3.95	31.0	58.0	408	-0.04	2.55	-8.0	21.0
		SB 207499	382	43.99	3.94	32.0	55.0	381	-0.14	2.34	-16.5	8.0
	VISIT 6/WEEK 8	PLACEBO	391	43.73	3.76	30.0	57.0	389	-0.30	2.39	-16.0	7.0
		SB 207499	382	43.84	3.94	32.0	57.0	382	-0.29	2.68	-15.7	9.0
	VISIT 7/WEEK 12	PLACEBO	396	43.83	3.93	31.0	57.0	394	-0.25	2.80	-11.0	19.0
		SB 207499	355	43.70	3.66	32.3	55.6	354	-0.46	2.56	-11.8	7.0
	VISIT 8/WEEK 20	PLACEBO	375	43.73	3.71	30.6	55.0	373	-0.27	3.01	-12.0	30.0
		SB 207499	333	43.72	3.80	33.0	55.0	332	-0.45	2.69	-14.8	11.0
	VISIT 9/WEEK 28	PLACEBO	367	43.75	3.92	24.6	57.0	365	-0.26	2.70	-14.8	11.0
		SB 207499	323	43.80	3.98	33.7	58.0	322	-0.35	2.84	-15.9	11.0
	VISIT 10/WEEK 36	PLACEBO	349	44.02	3.99	31.5	56.0	348	-0.07	2.71	-12.0	9.0
		SB 207499	303	43.89	3.75	32.0	55.0	302	-0.22	2.61	-13.5	7.6
	VISIT 11/WEEK 44	PLACEBO	335	44.05	4.12	33.9	64.9	334	-0.01	2.88	-8.0	21.4
		SB 207499	284	43.94	3.84	33.0	58.0	284	-0.33	3.07	-12.1	15.5
	VISIT 12/WEEK 52	PLACEBO	314	44.28	4.03	33.3	56.1	314	0.28	3.15	-6.6	30.7
		SB 207499	277	43.73	3.89	31.2	57.0	275	-0.47	2.65	-13.8	10.9
	SAFETY FOLLOW-UP	PLACEBO	46	43.53	4.22	35.6	55.0	46	-0.38	3.07	-5.0	12.0
		SB 207499	48	44.10	3.89	36.1	53.8	48	-0.38	2.35	-6.5	5.2
Hemoglobin (G/L)	VISIT 3/BASELINE	PLACEBO	432	146.82	12.86	61.0	188.0	0	.	.	.	.
		SB 207499	426	146.91	13.35	86.0	194.0	0	.	.	.	.
	VISIT 4/WEEK 2	PLACEBO	7	143.29	13.83	122.0	157.0	7	5.00	26.73	-10.0	65.0
		SB 207499	11	150.55	11.24	128.0	169.0	11	-1.18	9.35	-15.0	19.0
	VISIT 5/WEEK 4	PLACEBO	410	146.31	12.70	100.0	183.0	408	-0.33	7.21	-25.0	65.0
		SB 207499	382	146.55	12.86	106.0	184.0	381	-0.77	7.06	-61.0	31.0
	VISIT 6/WEEK 8	PLACEBO	391	145.92	12.19	102.0	184.0	389	-0.87	6.78	-45.0	23.0
		SB 207499	382	146.46	12.76	106.0	186.0	382	-0.79	8.06	-39.0	35.0
	VISIT 7/WEEK 12	PLACEBO	396	146.50	13.03	105.0	183.0	394	-0.39	8.16	-37.0	62.0
		SB 207499	355	146.32	12.34	108.0	185.0	354	-1.13	7.92	-47.0	21.0
	VISIT 8/WEEK 20	PLACEBO	375	146.18	12.51	95.0	181.0	373	-0.56	9.08	-38.0	103.0
		SB 207499	333	146.13	12.61	106.0	182.0	332	-1.21	8.22	-51.0	40.0
	VISIT 9/WEEK 28	PLACEBO	367	145.62	13.33	79.0	186.0	365	-1.06	7.39	-31.0	33.0

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND TREATMENT GROUP

PROTOCOL 157

PARAMETER	VISIT/WEEK	TREATMENT GROUP	RESULT N	RESULT MEAN	RESULT STD	RESULT MIN	RESULT MAX	CHANGE FROM BASELINE N	CHANGE FROM BASELINE MEAN	CHANGE FROM BASELINE STD	CHANGE FROM BASELINE MIN	CHANGE FROM BASELINE MAX
Hemoglobin (G/L)	VISIT 9/WEEK 28	SB 207499	323	145.84	12.67	114.0	185.0	322	-1.41	8.34	-50.0	41.0
	VISIT 10/WEEK 36	PLACEBO	349	146.12	13.34	104.0	180.0	348	-0.99	8.29	-37.0	27.0
		SB 207499	303	145.78	11.98	106.0	183.0	302	-1.25	7.96	-46.0	29.0
	VISIT 11/WEEK 44	PLACEBO	335	146.16	13.49	109.0	217.0	334	-0.78	9.00	-26.0	73.0
		SB 207499	284	145.85	12.25	111.0	189.0	284	-1.83	9.05	-43.0	44.0
	VISIT 12/WEEK 52	PLACEBO	314	146.89	12.94	110.0	183.0	314	0.04	9.81	-24.0	98.0
		SB 207499	277	145.43	12.56	104.0	189.0	275	-2.03	8.60	-46.0	41.0
	SAFETY FOLLOW-UP	PLACEBO	46	143.85	13.65	114.0	176.0	46	-2.28	9.43	-23.0	33.0
		SB 207499	48	145.40	13.64	114.0	174.0	48	-2.02	7.54	-20.0	11.0
Platelets (10^9/L)	VISIT 3/BASELINE	PLACEBO	431	256.81	71.23	6.0	588.0	0	.	.	.	.
		SB 207499	426	250.84	65.70	55.0	554.0	0	.	.	.	.
	VISIT 4/WEEK 2	PLACEBO	7	235.71	33.47	194.0	282.0	7	35.57	104.5	-48.0	256.0
		SB 207499	11	235.73	44.80	166.0	307.0	11	-10.73	27.96	-65.0	25.0
	VISIT 5/WEEK 4	PLACEBO	410	253.71	64.10	75.0	476.0	408	-3.92	45.07	-242.0	215.0
		SB 207499	381	250.81	62.71	74.0	434.0	380	1.21	38.36	-218.0	188.0
	VISIT 6/WEEK 8	PLACEBO	391	253.20	68.61	24.0	489.0	389	-7.46	43.76	-309.0	126.0
		SB 207499	381	249.94	60.49	72.0	486.0	381	0.70	41.50	-196.0	214.0
	VISIT 7/WEEK 12	PLACEBO	395	251.84	65.03	24.0	562.0	393	-6.50	42.98	-221.0	242.0
		SB 207499	354	248.97	62.48	65.0	439.0	353	1.37	39.16	-175.0	124.0
	VISIT 8/WEEK 20	PLACEBO	375	252.44	66.42	44.0	621.0	373	-6.92	45.69	-241.0	230.0
		SB 207499	333	250.42	65.94	59.0	489.0	332	3.29	47.33	-207.0	253.0
	VISIT 9/WEEK 28	PLACEBO	366	255.49	69.63	37.0	648.0	364	-3.31	47.40	-201.0	337.0
		SB 207499	322	244.15	59.98	43.0	616.0	321	-2.02	46.54	-211.0	255.0
	VISIT 10/WEEK 36	PLACEBO	349	254.30	68.67	21.0	589.0	348	-4.26	49.21	-206.0	278.0
		SB 207499	302	243.35	59.49	55.0	482.0	301	-3.69	39.98	-195.0	205.0
	VISIT 11/WEEK 44	PLACEBO	331	254.11	71.95	58.0	587.0	330	-6.78	49.93	-213.0	208.0
		SB 207499	283	245.99	61.23	45.0	450.0	283	0.17	40.33	-197.0	143.0
	VISIT 12/WEEK 52	PLACEBO	312	254.75	63.46	91.0	566.0	312	-5.09	49.03	-242.0	191.0
		SB 207499	275	252.17	60.39	85.0	459.0	273	2.51	46.69	-166.0	233.0
	SAFETY FOLLOW-UP	PLACEBO	45	250.31	59.77	152.0	434.0	45	0.78	37.89	-90.0	96.0
		SB 207499	48	258.79	82.64	81.0	492.0	48	15.10	55.42	-146.0	198.0

CONFIDENTIAL

SB 207499

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND TREATMENT GROUP

PROTOCOL 157

PARAMETER	VISIT/WEEK	TREATMENT GROUP	RESULT N	RESULT MEAN	RESULT STD	RESULT MIN	RESULT MAX	CHANGE FROM BASELINE N	CHANGE FROM BASELINE MEAN	CHANGE FROM BASELINE STD	CHANGE FROM BASELINE MIN	CHANGE FROM BASELINE MAX
Potassium (MMOL/L)	VISIT 3/BASELINE	PLACEBO	441	4.48	0.39	3.1	5.8	0	.	.	.	.
		SB 207499	443	4.48	0.64	3.3	13.6	0	.	.	.	.
	VISIT 4/WEEK 2	PLACEBO	7	4.40	0.29	3.9	4.8	7	-0.06	0.28	-0.5	0.4
		SB 207499	11	4.48	0.54	3.8	5.5	11	-0.05	0.52	-0.8	1.2
	VISIT 5/WEEK 4	PLACEBO	423	4.48	0.41	3.4	7.6	423	-0.01	0.45	-1.3	2.8
		SB 207499	396	4.44	0.43	3.0	6.0	396	-0.05	0.69	-9.8	1.8
	VISIT 6/WEEK 8	PLACEBO	400	4.46	0.39	3.4	5.9	400	-0.02	0.40	-1.3	1.7
		SB 207499	383	4.46	0.45	3.3	7.3	383	-0.04	0.69	-9.9	1.9
	VISIT 7/WEEK 12	PLACEBO	399	4.42	0.38	2.8	5.9	399	-0.06	0.40	-1.3	1.6
		SB 207499	362	4.42	0.39	3.4	5.8	362	-0.07	0.69	-9.9	1.4
	VISIT 8/WEEK 20	PLACEBO	385	4.51	0.41	3.3	6.4	385	0.02	0.42	-1.7	2.0
		SB 207499	335	4.45	0.41	3.0	6.0	335	-0.03	0.69	-9.4	1.9
	VISIT 9/WEEK 28	PLACEBO	375	4.47	0.40	3.5	7.1	375	-0.02	0.42	-1.3	1.8
		SB 207499	325	4.41	0.42	3.4	7.4	325	-0.07	0.76	-9.7	3.1
	VISIT 10/WEEK 36	PLACEBO	355	4.45	0.41	3.5	6.4	355	-0.04	0.42	-1.5	1.6
		SB 207499	307	4.44	0.46	3.4	8.3	307	-0.06	0.73	-9.2	4.1
	VISIT 11/WEEK 44	PLACEBO	331	4.44	0.38	3.5	5.9	331	-0.06	0.40	-1.3	1.6
		SB 207499	283	4.41	0.41	3.2	6.5	283	-0.08	0.76	-9.8	2.4
	VISIT 12/WEEK 52	PLACEBO	326	4.45	0.36	3.3	5.5	326	-0.04	0.42	-1.5	1.6
		SB 207499	281	4.44	0.37	3.3	5.7	280	-0.06	0.74	-9.7	1.5
	SAFETY FOLLOW-UP	PLACEBO	53	4.49	0.41	3.7	5.5	53	-0.04	0.38	-0.8	1.0
		SB 207499	50	4.47	0.48	3.4	6.6	50	-0.01	0.63	-3.2	0.8
Red Blood Cell Count (10^12/L)	VISIT 3/BASELINE	PLACEBO	432	4.74	0.46	2.0	6.8	0	.	.	.	.
		SB 207499	426	4.70	0.46	3.2	6.9	0	.	.	.	.
	VISIT 4/WEEK 2	PLACEBO	7	4.46	0.30	4.2	5.0	7	0.17	0.90	-0.3	2.2
		SB 207499	11	4.83	0.40	4.1	5.5	11	-0.01	0.32	-0.5	0.6
	VISIT 5/WEEK 4	PLACEBO	410	4.71	0.44	3.5	6.8	408	-0.02	0.25	-0.7	2.2
		SB 207499	382	4.70	0.44	3.2	6.7	381	-0.01	0.22	-1.4	0.9
	VISIT 6/WEEK 8	PLACEBO	391	4.70	0.43	3.1	6.6	389	-0.04	0.25	-1.9	0.9
		SB 207499	382	4.68	0.44	3.4	6.6	382	-0.02	0.28	-2.2	1.1
	VISIT 7/WEEK 12	PLACEBO	396	4.72	0.46	3.5	6.8	394	-0.01	0.29	-1.2	2.1

CONFIDENTIAL

SB 207499

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND TREATMENT GROUP

PROTOCOL 157

PARAMETER	VISIT/WEEK	TREATMENT GROUP	RESULT N	RESULT MEAN	RESULT STD	RESULT MIN	RESULT MAX	CHANGE FROM BASELINE N	CHANGE FROM BASELINE MEAN	CHANGE FROM BASELINE STD	CHANGE FROM BASELINE MIN	CHANGE FROM BASELINE MAX
Red Blood Cell Count (10^12/L)	VISIT 7/WEEK 12	SB 207499	355	4.68	0.42	3.4	6.4	354	-0.03	0.26	-0.9	0.8
	VISIT 8/WEEK 20	PLACEBO	375	4.72	0.43	3.5	6.3	373	-0.01	0.30	-1.4	3.1
		SB 207499	333	4.68	0.43	3.3	6.5	332	-0.03	0.27	-1.5	0.9
	VISIT 9/WEEK 28	PLACEBO	367	4.70	0.43	3.5	6.1	365	-0.03	0.26	-1.5	1.3
		SB 207499	323	4.67	0.43	3.4	6.3	322	-0.03	0.27	-1.6	0.9
	VISIT 10/WEEK 36	PLACEBO	349	4.73	0.44	3.4	6.2	348	-0.01	0.27	-1.1	1.3
		SB 207499	303	4.67	0.42	3.5	6.3	302	-0.02	0.26	-1.3	0.9
	VISIT 11/WEEK 44	PLACEBO	335	4.71	0.45	3.4	7.0	334	-0.02	0.29	-0.7	2.3
		SB 207499	284	4.66	0.42	3.6	6.2	284	-0.05	0.29	-1.1	1.7
	VISIT 12/WEEK 52	PLACEBO	314	4.72	0.44	3.5	6.3	314	0.00	0.32	-0.8	2.9
		SB 207499	277	4.65	0.41	3.4	6.0	275	-0.05	0.25	-1.4	0.6
	SAFETY FOLLOW-UP	PLACEBO	46	4.68	0.45	3.8	5.7	46	-0.05	0.31	-0.6	1.2
		SB 207499	48	4.73	0.46	3.7	5.8	48	-0.05	0.26	-0.5	0.5
Sodium (MMOL/L)	VISIT 3/BASELINE	PLACEBO	441	140.80	3.29	103.0	149.0	0	.	.	.	.
		SB 207499	443	140.77	2.85	128.0	153.0	0	.	.	.	.
	VISIT 4/WEEK 2	PLACEBO	7	142.29	1.11	141.0	144.0	7	0.86	1.95	-3.0	3.0
		SB 207499	11	141.64	3.32	137.0	149.0	11	0.36	2.80	-4.0	6.0
	VISIT 5/WEEK 4	PLACEBO	424	140.83	2.74	128.0	153.0	424	0.13	3.79	-8.0	39.0
		SB 207499	399	140.94	2.64	131.0	151.0	399	0.11	2.89	-15.0	9.0
	VISIT 6/WEEK 8	PLACEBO	400	140.94	2.83	130.0	154.0	400	0.11	3.33	-9.0	36.0
		SB 207499	385	140.75	2.91	129.0	151.0	385	-0.08	3.07	-13.0	8.0
	VISIT 7/WEEK 12	PLACEBO	402	140.70	2.78	129.0	149.0	402	-0.10	3.36	-11.0	35.0
		SB 207499	362	140.76	2.65	131.0	149.0	362	0.02	2.86	-13.0	8.0
	VISIT 8/WEEK 20	PLACEBO	385	140.79	2.70	128.0	149.0	385	0.00	3.52	-11.0	41.0
		SB 207499	336	141.04	2.62	129.0	150.0	336	0.17	2.59	-9.0	11.0
	VISIT 9/WEEK 28	PLACEBO	376	140.67	2.37	130.0	148.0	376	-0.20	3.30	-10.0	38.0
		SB 207499	327	140.82	2.56	129.0	148.0	327	-0.08	2.81	-12.0	9.0
	VISIT 10/WEEK 36	PLACEBO	355	140.70	2.55	130.0	148.0	355	-0.09	3.54	-9.0	40.0
		SB 207499	307	141.00	2.59	128.0	148.0	307	0.06	3.00	-13.0	8.0
	VISIT 11/WEEK 44	PLACEBO	334	140.73	2.48	130.0	148.0	334	-0.06	3.39	-11.0	37.0
		SB 207499	283	141.16	2.31	132.0	148.0	283	0.12	2.77	-11.0	8.0

CONFIDENTIAL

SB 207499

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND TREATMENT GROUP

PROTOCOL 157

PARAMETER	VISIT/WEEK	TREATMENT GROUP	RESULT N	RESULT MEAN	RESULT STD	RESULT MIN	RESULT MAX	CHANGE FROM BASELINE N	CHANGE FROM BASELINE MEAN	CHANGE FROM BASELINE STD	CHANGE FROM BASELINE MIN	CHANGE FROM BASELINE MAX
Sodium (MMOL/L)	VISIT 12/WEEK 52	PLACEBO	326	141.21	2.59	132.0	151.0	326	0.39	3.49	-13.0	37.0
		SB 207499	282	141.21	2.46	132.0	149.0	281	0.19	2.76	-11.0	7.0
	SAFETY FOLLOW-UP	PLACEBO	53	141.26	2.31	135.0	146.0	53	0.34	2.63	-6.0	6.0
		SB 207499	50	141.84	3.06	136.0	150.0	50	0.46	2.73	-4.0	9.0
Total Bilirubin (UMOL/L)	VISIT 3/BASELINE	PLACEBO	441	9.98	4.87	0.0	35.0	0	.	.	.	.
		SB 207499	443	10.12	4.89	2.0	35.0	0	.	.	.	.
	VISIT 4/WEEK 2	PLACEBO	7	7.86	3.08	4.0	14.0	7	-2.14	4.06	-9.0	4.0
		SB 207499	11	11.55	5.05	5.0	24.0	11	-0.82	3.97	-8.0	4.0
	VISIT 5/WEEK 4	PLACEBO	424	10.49	4.97	1.0	37.0	424	0.62	4.26	-21.0	14.0
		SB 207499	398	10.54	4.69	2.0	31.0	398	0.39	4.09	-20.0	16.0
	VISIT 6/WEEK 8	PLACEBO	400	10.29	4.45	2.0	30.0	400	0.44	4.21	-19.0	18.0
		SB 207499	383	10.63	4.34	2.0	31.0	383	0.38	4.16	-19.0	17.0
	VISIT 7/WEEK 12	PLACEBO	402	10.12	4.21	1.0	33.0	402	0.18	3.89	-18.0	13.0
		SB 207499	362	10.43	4.17	1.0	33.0	362	0.15	4.00	-24.0	12.0
	VISIT 8/WEEK 20	PLACEBO	386	10.47	4.47	2.0	31.0	386	0.48	4.12	-17.0	20.0
		SB 207499	336	10.46	4.43	1.0	30.0	336	0.19	4.43	-24.0	17.0
	VISIT 9/WEEK 28	PLACEBO	376	10.24	4.24	2.0	34.0	376	0.28	4.18	-23.0	13.0
		SB 207499	326	10.39	4.22	3.0	31.0	326	0.21	4.55	-25.0	18.0
	VISIT 10/WEEK 36	PLACEBO	355	10.49	4.51	3.0	32.0	355	0.55	4.33	-19.0	18.0
		SB 207499	307	10.99	4.28	4.0	37.0	307	0.82	4.27	-21.0	14.0
	VISIT 11/WEEK 44	PLACEBO	334	10.26	4.08	3.0	38.0	334	0.44	4.00	-17.0	15.0
		SB 207499	283	10.80	3.88	4.0	26.0	283	0.49	4.71	-24.0	16.0
	VISIT 12/WEEK 52	PLACEBO	326	10.69	4.27	3.0	34.0	326	0.98	4.12	-23.0	19.0
		SB 207499	282	10.73	4.27	3.0	33.0	281	0.70	4.01	-22.0	13.0
	SAFETY FOLLOW-UP	PLACEBO	53	10.34	4.80	5.0	31.0	52	0.10	3.83	-8.0	13.0
		SB 207499	50	10.52	3.94	5.0	23.0	50	-0.64	4.73	-22.0	10.0
Total Protein (G/L)	VISIT 3/BASELINE	PLACEBO	441	71.41	5.20	54.0	89.0	0	.	.	.	.
		SB 207499	443	70.65	4.64	55.0	87.0	0	.	.	.	.
	VISIT 4/WEEK 2	PLACEBO	7	71.00	2.94	68.0	76.0	7	-1.00	5.32	-9.0	5.0
		SB 207499	11	69.82	2.99	66.0	75.0	11	-0.82	3.06	-5.0	4.0

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND TREATMENT GROUP

PROTOCOL 157

PARAMETER	VISIT/WEEK	TREATMENT GROUP	RESULT N	RESULT MEAN	RESULT STD	RESULT MIN	RESULT MAX	CHANGE FROM BASELINE N	CHANGE FROM BASELINE MEAN	CHANGE FROM BASELINE STD	CHANGE FROM BASELINE MIN	CHANGE FROM BASELINE MAX
Total Protein (G/L)	VISIT 5/WEEK 4	PLACEBO	423	70.78	4.73	59.0	85.0	423	-0.67	4.48	-23.0	22.0
		SB 207499	399	70.26	4.49	58.0	88.0	399	-0.46	3.75	-12.0	24.0
	VISIT 6/WEEK 8	PLACEBO	400	70.93	4.58	57.0	85.0	400	-0.55	4.39	-18.0	20.0
		SB 207499	385	70.55	4.68	57.0	91.0	385	-0.16	4.12	-12.0	24.0
	VISIT 7/WEEK 12	PLACEBO	402	71.24	4.99	60.0	89.0	402	-0.25	4.41	-23.0	21.0
		SB 207499	362	70.38	4.42	56.0	87.0	362	-0.33	4.12	-18.0	23.0
	VISIT 8/WEEK 20	PLACEBO	386	71.44	4.95	60.0	91.0	386	-0.05	4.79	-22.0	18.0
		SB 207499	336	70.97	4.37	58.0	83.0	336	0.38	4.01	-18.0	23.0
	VISIT 9/WEEK 28	PLACEBO	376	71.77	4.65	59.0	93.0	376	0.34	4.55	-22.0	22.0
		SB 207499	327	71.41	4.61	58.0	87.0	327	0.65	4.16	-11.0	23.0
	VISIT 10/WEEK 36	PLACEBO	355	72.23	4.78	55.0	86.0	355	0.80	4.36	-20.0	14.0
		SB 207499	307	71.80	4.65	60.0	90.0	307	1.04	4.05	-11.0	25.0
	VISIT 11/WEEK 44	PLACEBO	334	72.16	4.54	58.0	88.0	334	0.73	4.46	-20.0	22.0
		SB 207499	283	71.64	4.53	59.0	84.0	283	0.84	4.40	-15.0	23.0
	VISIT 12/WEEK 52	PLACEBO	325	73.02	4.86	62.0	90.0	325	1.73	4.33	-18.0	19.0
		SB 207499	282	72.21	4.59	59.0	84.0	281	1.48	4.30	-9.0	29.0
	SAFETY FOLLOW-UP	PLACEBO	53	72.38	5.77	60.0	87.0	53	0.19	5.51	-24.0	11.0
		SB 207499	50	71.58	5.08	62.0	83.0	50	0.52	5.16	-13.0	16.0
Uric Acid (UMOL/L)	VISIT 3/BASELINE	PLACEBO	441	328.53	86.36	125.0	633.0	0	.	.	.	.
		SB 207499	443	336.09	86.80	131.0	651.0	0	.	.	.	.
	VISIT 4/WEEK 2	PLACEBO	7	330.00	54.42	243.0	376.0	7	15.71	52.37	-94.0	70.0
		SB 207499	11	319.36	82.64	197.0	505.0	11	-0.55	68.33	-160.0	115.0
	VISIT 5/WEEK 4	PLACEBO	424	337.79	89.03	90.0	651.0	424	8.72	52.05	-371.0	210.0
		SB 207499	399	335.13	86.66	109.0	640.0	399	-0.70	51.67	-158.0	287.0
	VISIT 6/WEEK 8	PLACEBO	399	330.10	87.37	110.0	656.0	399	0.07	59.04	-328.0	284.0
		SB 207499	385	333.27	84.84	140.0	612.0	385	-2.30	50.89	-165.0	262.0
	VISIT 7/WEEK 12	PLACEBO	401	331.48	88.92	91.0	694.0	401	1.96	50.07	-195.0	245.0
		SB 207499	362	324.50	82.88	128.0	582.0	362	-12.96	59.20	-319.0	217.0
	VISIT 8/WEEK 20	PLACEBO	384	332.31	87.46	126.0	716.0	384	2.60	58.65	-326.0	261.0
		SB 207499	336	333.76	84.42	97.0	651.0	336	-3.59	58.59	-379.0	281.0
	VISIT 9/WEEK 28	PLACEBO	375	344.79	92.06	91.0	740.0	375	15.27	57.88	-151.0	286.0

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND TREATMENT GROUP

PROTOCOL 157

PARAMETER	VISIT/WEEK	TREATMENT GROUP	RESULT N	RESULT MEAN	RESULT STD	RESULT MIN	RESULT MAX	CHANGE FROM BASELINE N	CHANGE FROM BASELINE MEAN	CHANGE FROM BASELINE STD	CHANGE FROM BASELINE MIN	CHANGE FROM BASELINE MAX
Uric Acid (UMOL/L)	VISIT 9/WEEK 28	SB 207499	327	338.42	86.91	125.0	597.0	327	1.08	63.31	-370.0	296.0
	VISIT 10/WEEK 36	PLACEBO	354	345.10	93.71	123.0	744.0	354	17.10	60.59	-251.0	361.0
		SB 207499	307	343.75	86.94	163.0	639.0	307	6.62	61.33	-191.0	251.0
	VISIT 11/WEEK 44	PLACEBO	332	339.91	90.06	116.0	622.0	332	13.62	54.68	-246.0	262.0
		SB 207499	283	338.97	86.79	155.0	668.0	283	0.88	57.17	-210.0	163.0
	VISIT 12/WEEK 52	PLACEBO	324	344.32	89.59	164.0	736.0	324	16.73	55.89	-230.0	227.0
		SB 207499	282	346.29	92.36	150.0	667.0	281	6.36	63.65	-218.0	269.0
	SAFETY FOLLOW-UP	PLACEBO	53	359.36	106.1	116.0	601.0	53	19.15	84.00	-231.0	323.0
		SB 207499	50	342.42	88.76	127.0	520.0	50	14.10	62.28	-168.0	127.0
Urine Blood - Dipstick ()	SAFETY FOLLOW-UP	PLACEBO	0	.	.	.	.	0	.	.	.	.
		SB 207499	0	.	.	.	.	0	.	.	.	.
Urine Glucose - Dipstick ()	SAFETY FOLLOW-UP	PLACEBO	0	.	.	.	.	0	.	.	.	.
		SB 207499	0	.	.	.	.	0	.	.	.	.
Urine Ketones - Dipstick ()	SAFETY FOLLOW-UP	PLACEBO	0	.	.	.	.	0	.	.	.	.
		SB 207499	0	.	.	.	.	0	.	.	.	.
Urine Protein - Dipstick ()	SAFETY FOLLOW-UP	PLACEBO	0	.	.	.	.	0	.	.	.	.
		SB 207499	0	.	.	.	.	0	.	.	.	.
White Blood Cell Count (10^9/L)	VISIT 3/BASELINE	PLACEBO	432	7.50	2.01	1.9	15.5	0	.	.	.	.
		SB 207499	426	7.44	1.94	2.7	24.5	0	.	.	.	.
	VISIT 4/WEEK 2	PLACEBO	7	6.90	1.27	5.7	9.0	7	-0.71	4.57	-10.0	3.8
		SB 207499	11	7.84	1.91	4.1	9.9	11	0.12	1.66	-2.5	2.7
	VISIT 5/WEEK 4	PLACEBO	410	7.48	2.01	2.9	18.2	408	-0.04	1.72	-7.0	7.0
		SB 207499	382	7.38	1.85	3.1	14.3	381	-0.03	1.44	-4.9	6.2
	VISIT 6/WEEK 8	PLACEBO	391	7.58	1.98	2.7	17.2	389	-0.01	1.84	-8.0	9.3
		SB 207499	382	7.52	1.87	2.8	15.7	382	0.08	1.51	-5.1	7.3
	VISIT 7/WEEK 12	PLACEBO	396	7.60	2.00	3.8	15.2	394	0.03	1.72	-6.8	8.6
		SB 207499	355	7.69	2.02	3.0	16.9	354	0.26	1.80	-5.9	9.0
	VISIT 8/WEEK 20	PLACEBO	375	7.57	2.05	2.9	16.5	373	0.03	1.90	-8.2	7.6

CONFIDENTIAL

SB 207499

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND TREATMENT GROUP

PROTOCOL 157

PARAMETER	VISIT/WEEK	TREATMENT GROUP	RESULT N	RESULT MEAN	RESULT STD	RESULT MIN	RESULT MAX	CHANGE FROM BASELINE N	CHANGE FROM BASELINE MEAN	CHANGE FROM BASELINE STD	CHANGE FROM BASELINE MIN	CHANGE FROM BASELINE MAX
White Blood Cell Count (10^9/L)	VISIT 8/WEEK 20	SB 207499	333	7.46	1.80	2.5	14.0	332	0.04	1.51	-5.2	8.5
	VISIT 9/WEEK 28	PLACEBO	366	7.57	1.89	3.3	14.3	365	0.08	1.68	-6.8	6.8
		SB 207499	322	7.59	1.99	3.1	15.2	321	0.23	1.79	-6.0	8.0
	VISIT 10/WEEK 36	PLACEBO	348	7.73	1.92	2.9	13.8	347	0.16	1.83	-7.0	6.3
		SB 207499	303	7.52	1.79	2.7	14.4	302	0.17	1.56	-6.7	6.0
	VISIT 11/WEEK 44	PLACEBO	335	7.77	2.04	3.1	16.3	334	0.22	1.89	-6.4	8.2
		SB 207499	284	7.51	1.87	2.7	16.8	284	0.14	1.50	-4.6	6.1
	VISIT 12/WEEK 52	PLACEBO	313	7.62	1.91	3.8	14.7	313	0.09	1.67	-6.6	7.3
		SB 207499	275	7.51	1.92	0.6	14.8	273	0.09	1.81	-6.2	9.0
	SAFETY FOLLOW-UP	PLACEBO	46	7.55	1.99	3.1	12.2	46	-0.14	1.98	-6.3	4.7
		SB 207499	48	7.52	1.94	4.5	13.9	48	0.24	1.88	-4.2	7.5

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE

PROTOCOL 157

PARAMETER: HEMOGLOBIN TIME POINT: TOTAL ON-THERAPY

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<0.8xLLN)	1	0	0	0	1 (100.0%)	0
	LOW (0.8xLLN -<1xLLN)	18	3 (16.7%)	12 (66.7%)	3 (16.7%)	0	0
	NORMAL (1xLLN-1xULN)	393	1 (0.3%)	30 (7.6%)	332 (84.5%)	29 (7.4%)	1 (0.3%)
	HIGH (>1xULN-1.2xULN)	21	0	0	4 (19.0%)	17 (81.0%)	0
	HIGH CONCERN (>1.2xULN)	0	0	0	0	0	0
	MISSING	2	0	1 (50.0%)	1 (50.0%)	0	0
	TOTAL	435	4 (0.9%)	43 (9.9%)	340 (78.2%)	47 (10.8%)	1 (0.2%)
SB 207499	LOW CONCERN (<0.8xLLN)	0	0	0	0	0	0
	LOW (0.8xLLN -<1xLLN)	19	1 (5.3%)	17 (89.5%)	1 (5.3%)	0	0
	NORMAL (1xLLN-1xULN)	378	1 (0.3%)	35 (9.3%)	319 (84.4%)	24 (6.3%)	0
	HIGH (>1xULN-1.2xULN)	19	0	1 (5.3%)	5 (26.3%)	13 (68.4%)	0
	HIGH CONCERN (>1.2xULN)	0	0	0	0	0	0
	MISSING	2	0	1 (50.0%)	1 (50.0%)	0	0
	TOTAL	418	2 (0.5%)	54 (12.9%)	326 (78.0%)	37 (8.9%)	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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: ENDPOINT
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE

PROTOCOL 157

PARAMETER: HEMOGLOBIN TIME POINT: ENDPOINT

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<0.8xLLN)	1	0	0	0	1 (100.0%)	0
	LOW (0.8xLLN -<1xLLN)	18	1 (5.6%)	8 (44.4%)	9 (50.0%)	0	0
	NORMAL (1xLLN-1xULN)	393	0	16 (4.1%)	363 (92.4%)	14 (3.6%)	0
	HIGH (>1xULN-1.2xULN)	21	0	0	7 (33.3%)	14 (66.7%)	0
	HIGH CONCERN (>1.2xULN)	0	0	0	0	0	0
	MISSING	2	0	0	2 (100.0%)	0	0
	TOTAL	435	1 (0.2%)	24 (5.5%)	381 (87.6%)	29 (6.7%)	0
SB 207499	LOW CONCERN (<0.8xLLN)	0	0	0	0	0	0
	LOW (0.8xLLN -<1xLLN)	19	0	8 (42.1%)	11 (57.9%)	0	0
	NORMAL (1xLLN-1xULN)	378	0	9 (2.4%)	363 (96.0%)	6 (1.6%)	0
	HIGH (>1xULN-1.2xULN)	19	0	0	8 (42.1%)	11 (57.9%)	0
	HIGH CONCERN (>1.2xULN)	0	0	0	0	0	0
	MISSING	2	0	1 (50.0%)	1 (50.0%)	0	0
	TOTAL	418	0	18 (4.3%)	383 (91.6%)	17 (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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: ENDPOINT
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE

PROTOCOL 157

PARAMETER: HEMATOCRIT TIME POINT: TOTAL ON-THERAPY

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<0.8xLLN)	1	0	0	0	1 (100.0%)	0
	LOW (0.8xLLN -<1xLLN)	14	1 (7.1%)	10 (71.4%)	3 (21.4%)	0	0
	NORMAL (1xLLN-1xULN)	382	2 (0.5%)	36 (9.4%)	293 (76.7%)	50 (13.1%)	1 (0.3%)
	HIGH (>1xULN-1.2xULN)	36	0	0	7 (19.4%)	29 (80.6%)	0
	HIGH CONCERN (>1.2xULN)	0	0	0	0	0	0
	MISSING	2	0	1 (50.0%)	1 (50.0%)	0	0
	TOTAL	435	3 (0.7%)	47 (10.8%)	304 (69.9%)	80 (18.4%)	1 (0.2%)
SB 207499	LOW CONCERN (<0.8xLLN)	0	0	0	0	0	0
	LOW (0.8xLLN -<1xLLN)	12	0	12 (100.0%)	0	1 (8.3%)	0
	NORMAL (1xLLN-1xULN)	372	1 (0.3%)	41 (11.0%)	277 (74.5%)	53 (14.2%)	1 (0.3%)
	HIGH (>1xULN-1.2xULN)	31	0	1 (3.2%)	8 (25.8%)	22 (71.0%)	0
	HIGH CONCERN (>1.2xULN)	1	0	0	0	1 (100.0%)	0
	MISSING	2	0	0	2 (100.0%)	0	0
	TOTAL	418	1 (0.2%)	54 (12.9%)	287 (68.7%)	77 (18.4%)	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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: ENDPOINT
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE

PROTOCOL 157

PARAMETER: HEMATOCRIT TIME POINT: ENDPOINT

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<0.8xLLN)	1	0	0	0	1 (100.0%)	0
	LOW (0.8xLLN -<1xLLN)	14	0	7 (50.0%)	7 (50.0%)	0	0
	NORMAL (1xLLN-1xULN)	382	1 (0.3%)	15 (3.9%)	344 (90.1%)	22 (5.8%)	0
	HIGH (>1xULN-1.2xULN)	36	0	0	11 (30.6%)	25 (69.4%)	0
	HIGH CONCERN (>1.2xULN)	0	0	0	0	0	0
	MISSING	2	0	0	2 (100.0%)	0	0
	TOTAL	435	1 (0.2%)	22 (5.1%)	364 (83.7%)	48 (11.0%)	0
SB 207499	LOW CONCERN (<0.8xLLN)	0	0	0	0	0	0
	LOW (0.8xLLN -<1xLLN)	12	0	9 (75.0%)	3 (25.0%)	0	0
	NORMAL (1xLLN-1xULN)	372	0	14 (3.8%)	341 (91.7%)	17 (4.6%)	0
	HIGH (>1xULN-1.2xULN)	31	0	0	13 (41.9%)	18 (58.1%)	0
	HIGH CONCERN (>1.2xULN)	1	0	0	0	1 (100.0%)	0
	MISSING	2	0	0	2 (100.0%)	0	0
	TOTAL	418	0	23 (5.5%)	359 (85.9%)	36 (8.6%)	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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: ENDPOINT
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE

PROTOCOL 157

PARAMETER: RED BLOOD CELL COUNT TIME POINT: TOTAL ON-THERAPY

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE LOW		NORMAL		HIGH	
PLACEBO	LOW (<1xLLN)	14	13	(92.9%)	1	(7.1%)	0	
	NORMAL (1xLLN-1xULN)	402	30	(7.5%)	347	(86.3%)	26	(6.5%)
	HIGH (>1xULN)	17	0		3	(17.6%)	14	(82.4%)
	MISSING	2	1	(50.0%)	1	(50.0%)	0	
	TOTAL	435	44	(10.1%)	352	(80.9%)	40	(9.2%)
SB 207499	LOW (<1xLLN)	24	22	(91.7%)	2	(8.3%)	0	
	NORMAL (1xLLN-1xULN)	379	30	(7.9%)	340	(89.7%)	9	(2.4%)
	HIGH (>1xULN)	13	0		4	(30.8%)	9	(69.2%)
	MISSING	2	0		2	(100.0%)	0	
	TOTAL	418	52	(12.4%)	348	(83.3%)	18	(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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: ENDPOINT
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE

PROTOCOL 157

PARAMETER: RED BLOOD CELL COUNT TIME POINT: ENDPOINT

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE LOW		DOUBLE BLIND PHASE NORMAL		DOUBLE BLIND PHASE HIGH	
PLACEBO	LOW (<1xLLN)	14	8	(57.1%)	6	(42.9%)	0	
	NORMAL (1xLLN-1xULN)	402	7	(1.7%)	387	(96.3%)	8	(2.0%)
	HIGH (>1xULN)	17	0		9	(52.9%)	8	(47.1%)
	MISSING	2	0		2	(100.0%)	0	
	TOTAL	435	15	(3.4%)	404	(92.9%)	16	(3.7%)
SB 207499	LOW (<1xLLN)	24	16	(66.7%)	8	(33.3%)	0	
	NORMAL (1xLLN-1xULN)	379	8	(2.1%)	368	(97.1%)	3	(0.8%)
	HIGH (>1xULN)	13	0		10	(76.9%)	3	(23.1%)
	MISSING	2	0		2	(100.0%)	0	
	TOTAL	418	24	(5.7%)	388	(92.8%)	6	(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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: ENDPOINT
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE

PROTOCOL 157

PARAMETER: WHITE BLOOD CELL COUNT TIME POINT: TOTAL ON-THERAPY

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: LOW CONCERN		LOW		NORMAL		HIGH		HIGH CONCERN
PLACEBO	LOW CONCERN (<=3000/mm3)	1	0		0		1	(100.0%)	0		0
	LOW (>3000/mm3-<1xLLN)	3	0		3	(100.0%)	0		0		0
	NORMAL (1xLLN-1xULN)	401	5	(1.2%)	6	(1.5%)	323	(80.5%)	67	(16.7%)	0
	HIGH (>1xULN-<20000/mm3)	28	0		0		7	(25.0%)	21	(75.0%)	0
	HIGH CONCERN (>=20000/mm3)	0	0		0		0		0		0
	MISSING	2	0		0		1	(50.0%)	1	(50.0%)	0
	TOTAL	435	5	(1.1%)	9	(2.1%)	332	(76.3%)	89	(20.5%)	0
SB 207499	LOW CONCERN (<=3000/mm3)	1	1	(100.0%)	0		0		0		0
	LOW (>3000/mm3-<1xLLN)	2	0		1	(50.0%)	1	(50.0%)	0		0
	NORMAL (1xLLN-1xULN)	400	1	(0.3%)	7	(1.8%)	307	(76.8%)	86	(21.5%)	0
	HIGH (>1xULN-<20000/mm3)	13	0		0		7	(53.8%)	6	(46.2%)	0
	HIGH CONCERN (>=20000/mm3)	0	0		0		0		0		0
	MISSING	2	0		0		2	(100.0%)	0		0
	TOTAL	418	2	(0.5%)	8	(1.9%)	317	(75.8%)	92	(22.0%)	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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: ENDPOINT
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE

PROTOCOL 157

PARAMETER: WHITE BLOOD CELL COUNT TIME POINT: ENDPOINT

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<=3000/mm3)	1	0	0	1 (100.0%)	0	0
	LOW (>3000/mm3-<1xLLN)	3	0	0	3 (100.0%)	0	0
	NORMAL (1xLLN-1xULN)	401	1 (0.2%)	2 (0.5%)	378 (94.3%)	20 (5.0%)	0
	HIGH (>1xULN-<20000/mm3)	28	0	0	21 (75.0%)	7 (25.0%)	0
	HIGH CONCERN (>=20000/mm3)	0	0	0	0	0	0
	MISSING	2	0	0	2 (100.0%)	0	0
	TOTAL	435	1 (0.2%)	2 (0.5%)	405 (93.1%)	27 (6.2%)	0
SB 207499	LOW CONCERN (<=3000/mm3)	1	1 (100.0%)	0	0	0	0
	LOW (>3000/mm3-<1xLLN)	2	0	0	2 (100.0%)	0	0
	NORMAL (1xLLN-1xULN)	400	1 (0.3%)	1 (0.3%)	370 (92.5%)	28 (7.0%)	0
	HIGH (>1xULN-<20000/mm3)	13	0	0	11 (84.6%)	2 (15.4%)	0
	HIGH CONCERN (>=20000/mm3)	0	0	0	0	0	0
	MISSING	2	0	0	2 (100.0%)	0	0
	TOTAL	418	2 (0.5%)	1 (0.2%)	385 (92.1%)	30 (7.2%)	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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: ENDPOINT
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE

PROTOCOL 157

PARAMETER: PLATELETS TIME POINT: TOTAL ON-THERAPY

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: LOW CONCERN		LOW		NORMAL		HIGH		HIGH CONCERN	
PLACEBO	LOW CONCERN (<100 BILLION/L)	3	2	(66.7%)	0		1	(33.3%)	0		0	
	LOW (100 BILLION/L-<1xLLN)	2	2	(100.0%)	0		0		0		0	
	NORMAL (1xLLN-1xULN)	411	1	(0.2%)	9	(2.2%)	376	(91.5%)	20	(4.9%)	5	(1.2%)
	HIGH (>1xULN-500 BILLION/L)	15	0		0		4	(26.7%)	9	(60.0%)	2	(13.3%)
	HIGH CONCERN (>500 BILLION/L)	2	0		0		0		1	(50.0%)	1	(50.0%)
	MISSING	2	0		0		2	(100.0%)	0		0	
	TOTAL	435	5	(1.1%)	9	(2.1%)	383	(88.0%)	30	(6.9%)	8	(1.8%)
SB 207499	LOW CONCERN (<100 BILLION/L)	3	2	(66.7%)	1	(33.3%)	0		0		0	
	LOW (100 BILLION/L-<1xLLN)	7	2	(28.6%)	3	(42.9%)	2	(28.6%)	0		0	
	NORMAL (1xLLN-1xULN)	401	2	(0.5%)	5	(1.2%)	367	(91.5%)	26	(6.5%)	1	(0.2%)
	HIGH (>1xULN-500 BILLION/L)	3	0		0		2	(66.7%)	1	(33.3%)	0	
	HIGH CONCERN (>500 BILLION/L)	2	0		0		0		2	(100.0%)	0	
	MISSING	2	0		0		2	(100.0%)	0		0	
	TOTAL	418	6	(1.4%)	9	(2.2%)	373	(89.2%)	29	(6.9%)	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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: ENDPOINT
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE

PROTOCOL 157

PARAMETER: PLATELETS TIME POINT: ENDPOINT

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<100 BILLION/L)	3	2 (66.7%)	0	1 (33.3%)	0	0
	LOW (100 BILLION/L-<1xLLN)	2	1 (50.0%)	1 (50.0%)	0	0	0
	NORMAL (1xLLN-1xULN)	411	0	3 (0.7%)	403 (98.1%)	4 (1.0%)	1 (0.2%)
	HIGH (>1xULN-500 BILLION/L)	15	0	0	10 (66.7%)	4 (26.7%)	1 (6.7%)
	HIGH CONCERN (>500 BILLION/L)	2	0	0	1 (50.0%)	1 (50.0%)	0
	MISSING	2	0	0	2 (100.0%)	0	0
	TOTAL	435	3 (0.7%)	4 (0.9%)	417 (95.9%)	9 (2.1%)	2 (0.5%)
SB 207499	LOW CONCERN (<100 BILLION/L)	3	1 (33.3%)	2 (66.7%)	0	0	0
	LOW (100 BILLION/L-<1xLLN)	7	2 (28.6%)	2 (28.6%)	3 (42.9%)	0	0
	NORMAL (1xLLN-1xULN)	401	0	1 (0.2%)	389 (97.0%)	11 (2.7%)	0
	HIGH (>1xULN-500 BILLION/L)	3	0	0	3 (100.0%)	0	0
	HIGH CONCERN (>500 BILLION/L)	2	0	0	1 (50.0%)	1 (50.0%)	0
	MISSING	2	0	0	2 (100.0%)	0	0
	TOTAL	418	3 (0.7%)	5 (1.2%)	398 (95.2%)	12 (2.9%)	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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: ENDPOINT
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE

PROTOCOL 157

PARAMETER: SODIUM TIME POINT: TOTAL ON-THERAPY

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<=130 MMOL/L)	3	1 (33.3%)	1 (33.3%)	1 (33.3%)	0	0
	LOW (>130 MMOL/L-<1xLLN)	8	2 (25.0%)	5 (62.5%)	1 (12.5%)	0	0
	NORMAL (1xLLN-1xULN)	418	5 (1.2%)	12 (2.9%)	367 (87.8%)	29 (6.9%)	5 (1.2%)
	HIGH (>1xULN-<150 MMOL/L)	6	0	0	5 (83.3%)	1 (16.7%)	0
	HIGH CONCERN (>=150 MMOL/L)	0	0	0	0	0	0
	MISSING	0	0	0	0	0	0
	TOTAL	435	8 (1.8%)	18 (4.1%)	374 (86.0%)	30 (6.9%)	5 (1.1%)
SB 207499	LOW CONCERN (<=130 MMOL/L)	1	1 (100.0%)	0	0	0	0
	LOW (>130 MMOL/L-<1xLLN)	7	3 (42.9%)	1 (14.3%)	3 (42.9%)	0	0
	NORMAL (1xLLN-1xULN)	400	1 (0.3%)	14 (3.5%)	362 (90.5%)	21 (5.3%)	2 (0.5%)
	HIGH (>1xULN-<150 MMOL/L)	8	0	0	4 (50.0%)	4 (50.0%)	0
	HIGH CONCERN (>=150 MMOL/L)	2	0	0	1 (50.0%)	0	1 (50.0%)
	MISSING	1	0	0	1 (100.0%)	0	0
	TOTAL	419	5 (1.2%)	15 (3.6%)	371 (88.5%)	25 (6.0%)	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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: ENDPOINT
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE

PROTOCOL 157

PARAMETER: SODIUM TIME POINT: ENDPOINT

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<=130 MMOL/L)	3	0	1 (33.3%)	2 (66.7%)	0	0
	LOW (>130 MMOL/L-<1xLLN)	8	0	3 (37.5%)	5 (62.5%)	0	0
	NORMAL (1xLLN-1xULN)	418	1 (0.2%)	5 (1.2%)	403 (96.4%)	7 (1.7%)	2 (0.5%)
	HIGH (>1xULN-<150 MMOL/L)	6	0	0	6 (100.0%)	0	0
	HIGH CONCERN (>=150 MMOL/L)	0	0	0	0	0	0
	MISSING	0	0	0	0	0	0
	TOTAL	435	1 (0.2%)	9 (2.1%)	416 (95.6%)	7 (1.6%)	2 (0.5%)
SB 207499	LOW CONCERN (<=130 MMOL/L)	1	1 (100.0%)	0	0	0	0
	LOW (>130 MMOL/L-<1xLLN)	7	1 (14.3%)	2 (28.6%)	4 (57.1%)	0	0
	NORMAL (1xLLN-1xULN)	400	1 (0.3%)	2 (0.5%)	391 (97.8%)	6 (1.5%)	0
	HIGH (>1xULN-<150 MMOL/L)	8	0	0	5 (62.5%)	3 (37.5%)	0
	HIGH CONCERN (>=150 MMOL/L)	2	0	0	2 (100.0%)	0	0
	MISSING	1	0	0	1 (100.0%)	0	0
	TOTAL	419	3 (0.7%)	4 (1.0%)	403 (96.2%)	9 (2.1%)	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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: ENDPOINT
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE

PROTOCOL 157

PARAMETER: POTASSIUM TIME POINT: TOTAL ON-THERAPY

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: 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-<1xLLN)	2	0	0	2 (100.0%)	0	0
	NORMAL (1xLLN-1xULN)	424	1 (0.2%)	7 (1.7%)	366 (86.3%)	17 (4.0%)	33 (7.8%)
	HIGH (>1xULN-<5.5 MMOL/L)	2	0	0	2 (100.0%)	0	0
	HIGH CONCERN (>=5.5 MMOL/L)	7	0	0	3 (42.9%)	1 (14.3%)	3 (42.9%)
	MISSING	0	0	0	0	0	0
	TOTAL	435	1 (0.2%)	7 (1.6%)	373 (85.7%)	18 (4.1%)	36 (8.3%)
SB 207499	LOW CONCERN (<=3.0 MMOL/L)	0	0	0	0	0	0
	LOW (>3.0 MMOL/L-<1xLLN)	3	1 (33.3%)	0	2 (66.7%)	0	0
	NORMAL (1xLLN-1xULN)	399	1 (0.3%)	12 (3.0%)	344 (86.2%)	15 (3.8%)	27 (6.8%)
	HIGH (>1xULN-<5.5 MMOL/L)	6	0	0	3 (50.0%)	1 (16.7%)	2 (33.3%)
	HIGH CONCERN (>=5.5 MMOL/L)	10	0	0	6 (60.0%)	0	4 (40.0%)
	MISSING	1	0	0	0	0	1 (100.0%)
	TOTAL	419	2 (0.5%)	12 (2.9%)	355 (84.7%)	16 (3.8%)	34 (8.1%)

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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: ENDPOINT
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE

PROTOCOL 157

PARAMETER: POTASSIUM TIME POINT: ENDPOINT

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: 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-<1xLLN)	2	0	0	2 (100.0%)	0	0
	NORMAL (1xLLN-1xULN)	424	0	2 (0.5%)	417 (98.3%)	3 (0.7%)	2 (0.5%)
	HIGH (>1xULN-<5.5 MMOL/L)	2	0	0	2 (100.0%)	0	0
	HIGH CONCERN (>=5.5 MMOL/L)	7	0	0	6 (85.7%)	0	1 (14.3%)
	MISSING	0	0	0	0	0	0
	TOTAL	435	0	2 (0.5%)	427 (98.2%)	3 (0.7%)	3 (0.7%)
SB 207499	LOW CONCERN (<=3.0 MMOL/L)	0	0	0	0	0	0
	LOW (>3.0 MMOL/L-<1xLLN)	3	0	0	3 (100.0%)	0	0
	NORMAL (1xLLN-1xULN)	399	0	5 (1.3%)	382 (95.7%)	6 (1.5%)	6 (1.5%)
	HIGH (>1xULN-<5.5 MMOL/L)	6	0	0	5 (83.3%)	1 (16.7%)	0
	HIGH CONCERN (>=5.5 MMOL/L)	10	0	0	8 (80.0%)	0	2 (20.0%)
	MISSING	1	0	0	0	0	1 (100.0%)
	TOTAL	419	0	5 (1.2%)	398 (95.0%)	7 (1.7%)	9 (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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: ENDPOINT
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE

PROTOCOL 157

PARAMETER: CHLORIDE TIME POINT: TOTAL ON-THERAPY

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE LOW		NORMAL		HIGH	
PLACEBO	LOW (<1xLLN)	5	4	(80.0%)	1	(20.0%)	0	
	NORMAL (1xLLN-1xULN)	404	6	(1.5%)	330	(81.7%)	68	(16.8%)
	HIGH (>1xULN)	25	0		9	(36.0%)	16	(64.0%)
	MISSING	0	0		0		0	
	TOTAL	434	10	(2.3%)	340	(78.3%)	84	(19.4%)
SB 207499	LOW (<1xLLN)	3	3	(100.0%)	0		0	
	NORMAL (1xLLN-1xULN)	393	9	(2.3%)	328	(83.5%)	57	(14.5%)
	HIGH (>1xULN)	22	0		7	(31.8%)	15	(68.2%)
	MISSING	1	0		1	(100.0%)	0	
	TOTAL	419	12	(2.9%)	336	(80.2%)	72	(17.2%)

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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: ENDPOINT
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE

PROTOCOL 157

PARAMETER: CHLORIDE TIME POINT: ENDPOINT

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE LOW		NORMAL		HIGH	
PLACEBO	LOW (<1xLLN)	5	2	(40.0%)	3	(60.0%)	0	
	NORMAL (1xLLN-1xULN)	404	1	(0.2%)	394	(97.5%)	9	(2.2%)
	HIGH (>1xULN)	25	0		19	(76.0%)	6	(24.0%)
	MISSING	0	0		0		0	
	TOTAL	434	3	(0.7%)	416	(95.9%)	15	(3.5%)
SB 207499	LOW (<1xLLN)	3	1	(33.3%)	2	(66.7%)	0	
	NORMAL (1xLLN-1xULN)	393	4	(1.0%)	373	(94.9%)	16	(4.1%)
	HIGH (>1xULN)	22	0		14	(63.6%)	8	(36.4%)
	MISSING	1	0		1	(100.0%)	0	
	TOTAL	419	5	(1.2%)	390	(93.1%)	24	(5.7%)

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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: ENDPOINT
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE

PROTOCOL 157

PARAMETER: BLOOD UREA NITROGEN TIME POINT: TOTAL ON-THERAPY

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL (<=1xULN)	431	399	(92.6%)	32	(7.4%)	0	
	HIGH (>1xULN-17.85 MMOL/L)	4	2	(50.0%)	2	(50.0%)	0	
	CONCERN (>17.85 MMOL/L)	0	0		0		0	
	MISSING	0	0		0		0	
	TOTAL	435	401	(92.2%)	34	(7.8%)	0	
SB 207499	NORMAL (<=1xULN)	405	378	(93.3%)	27	(6.7%)	0	
	HIGH (>1xULN-17.85 MMOL/L)	13	2	(15.4%)	10	(76.9%)	1	(7.7%)
	CONCERN (>17.85 MMOL/L)	0	0		0		0	
	MISSING	1	1	(100.0%)	0		0	
	TOTAL	419	381	(90.9%)	37	(8.8%)	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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: ENDPOINT
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE

PROTOCOL 157

PARAMETER: BLOOD UREA NITROGEN TIME POINT: ENDPOINT

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL (<=1xULN)	431	423	(98.1%)	8	(1.9%)	0	
	HIGH (>1xULN-17.85 MMOL/L)	4	3	(75.0%)	1	(25.0%)	0	
	CONCERN (>17.85 MMOL/L)	0	0		0		0	
	MISSING	0	0		0		0	
	TOTAL	435	426	(97.9%)	9	(2.1%)	0	
SB 207499	NORMAL (<=1xULN)	405	399	(98.5%)	6	(1.5%)	0	
	HIGH (>1xULN-17.85 MMOL/L)	13	7	(53.8%)	5	(38.5%)	1	(7.7%)
	CONCERN (>17.85 MMOL/L)	0	0		0		0	
	MISSING	1	1	(100.0%)	0		0	
	TOTAL	419	407	(97.1%)	11	(2.6%)	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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: ENDPOINT
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE

PROTOCOL 157

PARAMETER: CREATININE TIME POINT: TOTAL ON-THERAPY

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<0.5xLLN)	0	0	0	0	0	0
	LOW (0.5xLLN-<1xLLN)	11	0	11 (100.0%)	0	0	0
	NORMAL (1xLLN-1xULN)	419	0	40 (9.5%)	361 (86.2%)	15 (3.6%)	4 (1.0%)
	HIGH (>1xULN-1.5xULN)	5	0	0	1 (20.0%)	3 (60.0%)	1 (20.0%)
	HIGH CONCERN (>1.5xULN)	0	0	0	0	0	0
	MISSING	0	0	0	0	0	0
	TOTAL	435	0	51 (11.7%)	362 (83.2%)	18 (4.1%)	5 (1.1%)
SB 207499	LOW CONCERN (<0.5xLLN)	0	0	0	0	0	0
	LOW (0.5xLLN-<1xLLN)	8	0	5 (62.5%)	3 (37.5%)	0	0
	NORMAL (1xLLN-1xULN)	398	0	34 (8.5%)	349 (87.7%)	12 (3.0%)	3 (0.8%)
	HIGH (>1xULN-1.5xULN)	10	0	0	1 (10.0%)	9 (90.0%)	0
	HIGH CONCERN (>1.5xULN)	2	0	0	0	1 (50.0%)	1 (50.0%)
	MISSING	1	0	0	1 (100.0%)	0	0
	TOTAL	419	0	39 (9.3%)	354 (84.5%)	22 (5.3%)	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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: ENDPOINT
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE

PROTOCOL 157

PARAMETER: CREATININE TIME POINT: ENDPOINT

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<0.5xLLN)	0	0	0	0	0	0
	LOW (0.5xLLN-<1xLLN)	11	0	7 (63.6%)	4 (36.4%)	0	0
	NORMAL (1xLLN-1xULN)	419	0	13 (3.1%)	403 (96.2%)	3 (0.7%)	0
	HIGH (>1xULN-1.5xULN)	5	0	0	4 (80.0%)	0	1 (20.0%)
	HIGH CONCERN (>1.5xULN)	0	0	0	0	0	0
	MISSING	0	0	0	0	0	0
	TOTAL	435	0	20 (4.6%)	411 (94.5%)	3 (0.7%)	1 (0.2%)
SB 207499	LOW CONCERN (<0.5xLLN)	0	0	0	0	0	0
	LOW (0.5xLLN-<1xLLN)	8	0	5 (62.5%)	3 (37.5%)	0	0
	NORMAL (1xLLN-1xULN)	398	0	11 (2.8%)	384 (96.5%)	3 (0.8%)	0
	HIGH (>1xULN-1.5xULN)	10	0	0	4 (40.0%)	6 (60.0%)	0
	HIGH CONCERN (>1.5xULN)	2	0	0	0	1 (50.0%)	1 (50.0%)
	MISSING	1	0	0	1 (100.0%)	0	0
	TOTAL	419	0	16 (3.8%)	392 (93.6%)	10 (2.4%)	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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: ENDPOINT
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE

PROTOCOL 157

PARAMETER: URIC ACID TIME POINT: TOTAL ON-THERAPY

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL (<=1xULN)	415	379	(91.3%)	36	(8.7%)	0	
	HIGH (>1xULN-1.4xULN)	20	2	(10.0%)	14	(70.0%)	4	(20.0%)
	CONCERN (>1.4xULN)	0	0		0		0	
	MISSING	0	0		0		0	
	TOTAL	435	381	(87.6%)	50	(11.5%)	4	(0.9%)
SB 207499	NORMAL (<=1xULN)	405	368	(90.9%)	37	(9.1%)	0	
	HIGH (>1xULN-1.4xULN)	13	3	(23.1%)	8	(61.5%)	2	(15.4%)
	CONCERN (>1.4xULN)	0	0		0		0	
	MISSING	1	1	(100.0%)	0		0	
	TOTAL	419	372	(88.8%)	45	(10.7%)	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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: ENDPOINT
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE

PROTOCOL 157

PARAMETER: URIC ACID TIME POINT: ENDPOINT

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL (<=1xULN)	415	404	(97.3%)	11	(2.7%)	0	
	HIGH (>1xULN-1.4xULN)	20	7	(35.0%)	11	(55.0%)	2	(10.0%)
	CONCERN (>1.4xULN)	0	0		0		0	
	MISSING	0	0		0		0	
	TOTAL	435	411	(94.5%)	22	(5.1%)	2	(0.5%)
SB 207499	NORMAL (<=1xULN)	405	389	(96.0%)	16	(4.0%)	0	
	HIGH (>1xULN-1.4xULN)	13	6	(46.2%)	6	(46.2%)	1	(7.7%)
	CONCERN (>1.4xULN)	0	0		0		0	
	MISSING	1	1	(100.0%)	0		0	
	TOTAL	419	396	(94.5%)	22	(5.3%)	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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: ENDPOINT
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE

PROTOCOL 157

PARAMETER: ALKALINE PHOSPHATASE TIME POINT: TOTAL ON-THERAPY

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL (<=1xULN)	418	385	(92.1%)	32	(7.7%)	1	(0.2%)
	HIGH (>1xULN-2xULN)	17	5	(29.4%)	12	(70.6%)	0	
	CONCERN (>2xULN)	0	0		0		0	
	MISSING	0	0		0		0	
	TOTAL	435	390	(89.7%)	44	(10.1%)	1	(0.2%)
SB 207499	NORMAL (<=1xULN)	400	378	(94.5%)	22	(5.5%)	0	
	HIGH (>1xULN-2xULN)	17	4	(23.5%)	13	(76.5%)	0	
	CONCERN (>2xULN)	1	0		1	(100.0%)	0	
	MISSING	1	1	(100.0%)	0		0	
	TOTAL	419	383	(91.4%)	36	(8.6%)	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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: ENDPOINT
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE

PROTOCOL 157

PARAMETER: ALKALINE PHOSPHATASE TIME POINT: ENDPOINT

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE NORMAL		HIGH		CONCERN
PLACEBO	NORMAL (<=1xULN)	418	409	(97.8%)	9	(2.2%)	0
	HIGH (>1xULN-2xULN)	17	10	(58.8%)	7	(41.2%)	0
	CONCERN (>2xULN)	0	0		0		0
	MISSING	0	0		0		0
	TOTAL	435	419	(96.3%)	16	(3.7%)	0
SB 207499	NORMAL (<=1xULN)	400	393	(98.3%)	7	(1.8%)	0
	HIGH (>1xULN-2xULN)	17	11	(64.7%)	6	(35.3%)	0
	CONCERN (>2xULN)	1	0		1	(100.0%)	0
	MISSING	1	1	(100.0%)	0		0
	TOTAL	419	405	(96.7%)	14	(3.3%)	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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: ENDPOINT
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE

PROTOCOL 157

PARAMETER: ASPARTATE AMINOTRANSFERASE TIME POINT: TOTAL ON-THERAPY

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL (<=1xULN)	421	383	(91.0%)	33	(7.8%)	5	(1.2%)
	HIGH (>1xULN-2xULN)	12	4	(33.3%)	4	(33.3%)	4	(33.3%)
	CONCERN (>2xULN)	2	0		0		2	(100.0%)
	MISSING	0	0		0		0	
	TOTAL	435	387	(89.0%)	37	(8.5%)	11	(2.5%)
SB 207499	NORMAL (<=1xULN)	401	382	(95.3%)	17	(4.2%)	2	(0.5%)
	HIGH (>1xULN-2xULN)	15	4	(26.7%)	7	(46.7%)	4	(26.7%)
	CONCERN (>2xULN)	2	1	(50.0%)	1	(50.0%)	0	
	MISSING	1	1	(100.0%)	0		0	
	TOTAL	419	388	(92.6%)	25	(6.0%)	6	(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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: ENDPOINT
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE

PROTOCOL 157

PARAMETER: ASPARTATE AMINOTRANSFERASE TIME POINT: ENDPOINT

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL (<=1xULN)	421	406	(96.4%)	14	(3.3%)	1	(0.2%)
	HIGH (>1xULN-2xULN)	12	7	(58.3%)	2	(16.7%)	3	(25.0%)
	CONCERN (>2xULN)	2	0		2	(100.0%)	0	
	MISSING	0	0		0		0	
	TOTAL	435	413	(94.9%)	18	(4.1%)	4	(0.9%)
SB 207499	NORMAL (<=1xULN)	401	394	(98.3%)	7	(1.7%)	0	
	HIGH (>1xULN-2xULN)	15	9	(60.0%)	6	(40.0%)	0	
	CONCERN (>2xULN)	2	1	(50.0%)	1	(50.0%)	0	
	MISSING	1	1	(100.0%)	0		0	
	TOTAL	419	405	(96.7%)	14	(3.3%)	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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: ENDPOINT
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE

PROTOCOL 157

PARAMETER: ALANINE AMINOTRANSFERASE TIME POINT: TOTAL ON-THERAPY

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL (<=1xULN)	420	375	(89.3%)	37	(8.8%)	8	(1.9%)
	HIGH (>1xULN-2xULN)	13	5	(38.5%)	4	(30.8%)	4	(30.8%)
	CONCERN (>2xULN)	2	0		0		2	(100.0%)
	MISSING	0	0		0		0	
	TOTAL	435	380	(87.4%)	41	(9.4%)	14	(3.2%)
SB 207499	NORMAL (<=1xULN)	393	367	(93.4%)	26	(6.6%)	0	
	HIGH (>1xULN-2xULN)	22	9	(40.9%)	8	(36.4%)	5	(22.7%)
	CONCERN (>2xULN)	2	0		0		2	(100.0%)
	MISSING	2	1	(50.0%)	1	(50.0%)	0	
	TOTAL	419	377	(90.0%)	35	(8.4%)	7	(1.7%)

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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: ENDPOINT
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE

PROTOCOL 157

PARAMETER: ALANINE AMINOTRANSFERASE TIME POINT: ENDPOINT

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL (<=1xULN)	420	405	(96.4%)	14	(3.3%)	1	(0.2%)
	HIGH (>1xULN-2xULN)	13	8	(61.5%)	3	(23.1%)	2	(15.4%)
	CONCERN (>2xULN)	2	0		1	(50.0%)	1	(50.0%)
	MISSING	0	0		0		0	
	TOTAL	435	413	(94.9%)	18	(4.1%)	4	(0.9%)
SB 207499	NORMAL (<=1xULN)	393	388	(98.7%)	5	(1.3%)	0	
	HIGH (>1xULN-2xULN)	22	15	(68.2%)	6	(27.3%)	1	(4.5%)
	CONCERN (>2xULN)	2	0		1	(50.0%)	1	(50.0%)
	MISSING	2	1	(50.0%)	1	(50.0%)	0	
	TOTAL	419	404	(96.4%)	13	(3.1%)	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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: ENDPOINT
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE

PROTOCOL 157

PARAMETER: TOTAL BILIRUBIN TIME POINT: TOTAL ON-THERAPY

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL (<=1xULN)	421	402	(95.5%)	17	(4.0%)	2	(0.5%)
	HIGH (>1xULN-1.5xULN)	13	3	(23.1%)	8	(61.5%)	2	(15.4%)
	CONCERN (>1.5xULN)	1	0		0		1	(100.0%)
	MISSING	0	0		0		0	
	TOTAL	435	405	(93.1%)	25	(5.7%)	5	(1.1%)
SB 207499	NORMAL (<=1xULN)	406	388	(95.6%)	18	(4.4%)	0	
	HIGH (>1xULN-1.5xULN)	10	4	(40.0%)	5	(50.0%)	1	(10.0%)
	CONCERN (>1.5xULN)	2	0		2	(100.0%)	0	
	MISSING	1	1	(100.0%)	0		0	
	TOTAL	419	393	(93.8%)	25	(6.0%)	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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: ENDPOINT
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE

PROTOCOL 157

PARAMETER: TOTAL BILIRUBIN TIME POINT: ENDPOINT

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL (<=1xULN)	421	414	(98.3%)	5	(1.2%)	2	(0.5%)
	HIGH (>1xULN-1.5xULN)	13	10	(76.9%)	3	(23.1%)	0	
	CONCERN (>1.5xULN)	1	0		0		1	(100.0%)
	MISSING	0	0		0		0	
	TOTAL	435	424	(97.5%)	8	(1.8%)	3	(0.7%)
SB 207499	NORMAL (<=1xULN)	406	403	(99.3%)	3	(0.7%)	0	
	HIGH (>1xULN-1.5xULN)	10	8	(80.0%)	2	(20.0%)	0	
	CONCERN (>1.5xULN)	2	1	(50.0%)	1	(50.0%)	0	
	MISSING	1	1	(100.0%)	0		0	
	TOTAL	419	413	(98.6%)	6	(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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: ENDPOINT
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE

PROTOCOL 157

PARAMETER: TOTAL PROTEIN TIME POINT: TOTAL ON-THERAPY

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE LOW		DOUBLE BLIND PHASE NORMAL		DOUBLE BLIND PHASE HIGH	
PLACEBO	LOW (<1xLLN)	2	0		2	(100.0%)	0	
	NORMAL (1xLLN-1xULN)	422	3	(0.7%)	396	(93.8%)	23	(5.5%)
	HIGH (>1xULN)	11	0		4	(36.4%)	7	(63.6%)
	MISSING	0	0		0		0	
	TOTAL	435	3	(0.7%)	402	(92.4%)	30	(6.9%)
SB 207499	LOW (<1xLLN)	1	0		1	(100.0%)	0	
	NORMAL (1xLLN-1xULN)	412	3	(0.7%)	399	(96.8%)	10	(2.4%)
	HIGH (>1xULN)	5	0		3	(60.0%)	2	(40.0%)
	MISSING	1	0		1	(100.0%)	0	
	TOTAL	419	3	(0.7%)	404	(96.4%)	12	(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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: ENDPOINT
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE

PROTOCOL 157

PARAMETER: TOTAL PROTEIN TIME POINT: ENDPOINT

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE LOW		DOUBLE BLIND PHASE NORMAL		DOUBLE BLIND PHASE HIGH	
PLACEBO	LOW (<1xLLN)	2	0		2	(100.0%)	0	
	NORMAL (1xLLN-1xULN)	422	0		416	(98.6%)	6	(1.4%)
	HIGH (>1xULN)	11	0		5	(45.5%)	6	(54.5%)
	MISSING	0	0		0		0	
	TOTAL	435	0		423	(97.2%)	12	(2.8%)
SB 207499	LOW (<1xLLN)	1	0		1	(100.0%)	0	
	NORMAL (1xLLN-1xULN)	412	1	(0.2%)	410	(99.5%)	1	(0.2%)
	HIGH (>1xULN)	5	0		3	(60.0%)	2	(40.0%)
	MISSING	1	0		1	(100.0%)	0	
	TOTAL	419	1	(0.2%)	415	(99.0%)	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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: ENDPOINT
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE

PROTOCOL 157

PARAMETER: ALBUMIN TIME POINT: TOTAL ON-THERAPY

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE LOW		DOUBLE BLIND PHASE NORMAL		DOUBLE BLIND PHASE HIGH	
PLACEBO	LOW (<1xLLN)	1	0		1	(100.0%)	0	
	NORMAL (1xLLN-1xULN)	432	0		420	(97.2%)	12	(2.8%)
	HIGH (>1xULN)	2	0		0		2	(100.0%)
	MISSING	0	0		0		0	
	TOTAL	435	0		421	(96.8%)	14	(3.2%)
SB 207499	LOW (<1xLLN)	0	0		0		0	
	NORMAL (1xLLN-1xULN)	417	2	(0.5%)	406	(97.4%)	9	(2.2%)
	HIGH (>1xULN)	1	0		0		1	(100.0%)
	MISSING	1	0		1	(100.0%)	0	
	TOTAL	419	2	(0.5%)	407	(97.1%)	10	(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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: ENDPOINT
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE

PROTOCOL 157

PARAMETER: ALBUMIN TIME POINT: ENDPOINT

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE LOW		DOUBLE BLIND PHASE NORMAL		DOUBLE BLIND PHASE HIGH	
PLACEBO	LOW (<1xLLN)	1	0		1	(100.0%)	0	
	NORMAL (1xLLN-1xULN)	432	0		425	(98.4%)	7	(1.6%)
	HIGH (>1xULN)	2	0		1	(50.0%)	1	(50.0%)
	MISSING	0	0		0		0	
	TOTAL	435	0		427	(98.2%)	8	(1.8%)
SB 207499	LOW (<1xLLN)	0	0		0		0	
	NORMAL (1xLLN-1xULN)	417	1	(0.2%)	409	(98.1%)	7	(1.7%)
	HIGH (>1xULN)	1	0		1	(100.0%)	0	
	MISSING	1	0		1	(100.0%)	0	
	TOTAL	419	1	(0.2%)	411	(98.1%)	7	(1.7%)

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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: ENDPOINT
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE

PROTOCOL 157

PARAMETER: GLUCOSE - FASTING TIME POINT: TOTAL ON-THERAPY

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<2.0 MMOL/L)	0	0	0	0	0	0
	LOW (2.0 MMOL/L-<1xLLN)	0	0	0	0	0	0
	NORMAL (1xLLN-1xULN)	106	0	5 (4.7%)	76 (71.7%)	19 (17.9%)	6 (5.7%)
	HIGH (>1xULN-8.0 MMOL/L)	8	0	0	2 (25.0%)	2 (25.0%)	4 (50.0%)
	HIGH CONCERN (>8.0 MMOL/L)	18	0	0	3 (16.7%)	1 (5.6%)	14 (77.8%)
	MISSING	67	0	1 (1.5%)	51 (76.1%)	7 (10.4%)	8 (11.9%)
	TOTAL	199	0	6 (3.0%)	132 (66.3%)	29 (14.6%)	32 (16.1%)
SB 207499	LOW CONCERN (<2.0 MMOL/L)	0	0	0	0	0	0
	LOW (2.0 MMOL/L-<1xLLN)	2	0	1 (50.0%)	1 (50.0%)	0	0
	NORMAL (1xLLN-1xULN)	118	0	5 (4.2%)	100 (84.7%)	8 (6.8%)	5 (4.2%)
	HIGH (>1xULN-8.0 MMOL/L)	9	0	0	0	5 (55.6%)	4 (44.4%)
	HIGH CONCERN (>8.0 MMOL/L)	4	0	0	1 (25.0%)	0	3 (75.0%)
	MISSING	61	0	4 (6.6%)	46 (75.4%)	7 (11.5%)	5 (8.2%)
	TOTAL	194	0	10 (5.2%)	148 (76.3%)	20 (10.3%)	17 (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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: ENDPOINT
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE

PROTOCOL 157

PARAMETER: GLUCOSE - FASTING TIME POINT: ENDPOINT

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<2.0 MMOL/L)	0	0	0	0	0	0
	LOW (2.0 MMOL/L-<1xLLN)	0	0	0	0	0	0
	NORMAL (1xLLN-1xULN)	106	0	2 (1.9%)	94 (88.7%)	8 (7.5%)	2 (1.9%)
	HIGH (>1xULN-8.0 MMOL/L)	8	0	0	2 (25.0%)	3 (37.5%)	3 (37.5%)
	HIGH CONCERN (>8.0 MMOL/L)	18	0	0	5 (27.8%)	1 (5.6%)	12 (66.7%)
	MISSING	67	0	0	55 (82.1%)	5 (7.5%)	7 (10.4%)
	TOTAL	199	0	2 (1.0%)	156 (78.4%)	17 (8.5%)	24 (12.1%)
SB 207499	LOW CONCERN (<2.0 MMOL/L)	0	0	0	0	0	0
	LOW (2.0 MMOL/L-<1xLLN)	2	0	0	2 (100.0%)	0	0
	NORMAL (1xLLN-1xULN)	118	0	1 (0.8%)	111 (94.1%)	5 (4.2%)	1 (0.8%)
	HIGH (>1xULN-8.0 MMOL/L)	9	0	0	7 (77.8%)	1 (11.1%)	1 (11.1%)
	HIGH CONCERN (>8.0 MMOL/L)	4	0	0	2 (50.0%)	0	2 (50.0%)
	MISSING	61	0	3 (4.9%)	49 (80.3%)	4 (6.6%)	5 (8.2%)
	TOTAL	194	0	4 (2.1%)	171 (88.1%)	10 (5.2%)	9 (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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: ENDPOINT
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE

PROTOCOL 157

PARAMETER: GLUCOSE - RANDOM TIME POINT: TOTAL ON-THERAPY

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<2.0 MMOL/L)	0	0	0	0	0	0
	LOW (2.0 MMOL/L-<1xLLN)	7	0	0	2 (28.6%)	1 (14.3%)	4 (57.1%)
	NORMAL (1xLLN-1xULN)	267	1 (0.4%)	24 (9.0%)	153 (57.3%)	52 (19.5%)	44 (16.5%)
	HIGH (>1xULN-8.0 MMOL/L)	26	0	1 (3.8%)	5 (19.2%)	8 (30.8%)	13 (50.0%)
	HIGH CONCERN (>8.0 MMOL/L)	28	0	1 (3.6%)	3 (10.7%)	2 (7.1%)	23 (82.1%)
	MISSING	39	0	3 (7.7%)	26 (66.7%)	2 (5.1%)	8 (20.5%)
	TOTAL	367	1 (0.3%)	29 (7.9%)	189 (51.5%)	65 (17.7%)	92 (25.1%)
SB 207499	LOW CONCERN (<2.0 MMOL/L)	0	0	0	0	0	0
	LOW (2.0 MMOL/L-<1xLLN)	10	0	5 (50.0%)	4 (40.0%)	2 (20.0%)	1 (10.0%)
	NORMAL (1xLLN-1xULN)	250	1 (0.4%)	20 (8.0%)	151 (60.4%)	47 (18.8%)	37 (14.8%)
	HIGH (>1xULN-8.0 MMOL/L)	27	0	0	8 (29.6%)	7 (25.9%)	12 (44.4%)
	HIGH CONCERN (>8.0 MMOL/L)	25	0	1 (4.0%)	5 (20.0%)	4 (16.0%)	16 (64.0%)
	MISSING	32	0	2 (6.3%)	24 (75.0%)	3 (9.4%)	3 (9.4%)
	TOTAL	344	1 (0.3%)	28 (8.1%)	192 (55.8%)	63 (18.3%)	69 (20.1%)

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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: ENDPOINT
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE

PROTOCOL 157

PARAMETER: GLUCOSE - RANDOM TIME POINT: ENDPOINT

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<2.0 MMOL/L)	0	0	0	0	0	0
	LOW (2.0 MMOL/L-<1xLLN)	7	0	0	5 (71.4%)	1 (14.3%)	1 (14.3%)
	NORMAL (1xLLN-1xULN)	267	0	4 (1.5%)	236 (88.4%)	13 (4.9%)	14 (5.2%)
	HIGH (>1xULN-8.0 MMOL/L)	26	0	0	16 (61.5%)	5 (19.2%)	5 (19.2%)
	HIGH CONCERN (>8.0 MMOL/L)	28	0	1 (3.6%)	6 (21.4%)	6 (21.4%)	15 (53.6%)
	MISSING	39	0	2 (5.1%)	28 (71.8%)	1 (2.6%)	8 (20.5%)
	TOTAL	367	0	7 (1.9%)	291 (79.3%)	26 (7.1%)	43 (11.7%)
SB 207499	LOW CONCERN (<2.0 MMOL/L)	0	0	0	0	0	0
	LOW (2.0 MMOL/L-<1xLLN)	10	0	0	9 (90.0%)	0	1 (10.0%)
	NORMAL (1xLLN-1xULN)	250	0	4 (1.6%)	214 (85.6%)	20 (8.0%)	12 (4.8%)
	HIGH (>1xULN-8.0 MMOL/L)	27	0	0	19 (70.4%)	4 (14.8%)	4 (14.8%)
	HIGH CONCERN (>8.0 MMOL/L)	25	0	0	9 (36.0%)	3 (12.0%)	13 (52.0%)
	MISSING	32	0	1 (3.1%)	29 (90.6%)	0	2 (6.3%)
	TOTAL	344	0	5 (1.5%)	280 (81.4%)	27 (7.8%)	32 (9.3%)

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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: ENDPOINT
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE

PROTOCOL 157

PARAMETER: GAMMA GLUTAMYL TRANSFERASE TIME POINT: TOTAL ON-THERAPY

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL (<=1xULN)	375	329	(87.7%)	38	(10.1%)	8	(2.1%)
	HIGH (>1xULN-2.5xULN)	50	5	(10.0%)	34	(68.0%)	11	(22.0%)
	CONCERN (>2.5xULN)	10	0		2	(20.0%)	8	(80.0%)
	MISSING	0	0		0		0	
	TOTAL	435	334	(76.8%)	74	(17.0%)	27	(6.2%)
SB 207499	NORMAL (<=1xULN)	368	327	(88.9%)	37	(10.1%)	4	(1.1%)
	HIGH (>1xULN-2.5xULN)	40	4	(10.0%)	28	(70.0%)	8	(20.0%)
	CONCERN (>2.5xULN)	10	1	(10.0%)	2	(20.0%)	7	(70.0%)
	MISSING	1	0		1	(100.0%)	0	
	TOTAL	419	332	(79.2%)	68	(16.2%)	19	(4.5%)

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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: ENDPOINT
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE

PROTOCOL 157

PARAMETER: GAMMA GLUTAMYL TRANSFERASE TIME POINT: ENDPOINT

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL (<=1xULN)	375	350	(93.3%)	22	(5.9%)	3	(0.8%)
	HIGH (>1xULN-2.5xULN)	50	18	(36.0%)	30	(60.0%)	2	(4.0%)
	CONCERN (>2.5xULN)	10	1	(10.0%)	4	(40.0%)	5	(50.0%)
	MISSING	0	0		0		0	
	TOTAL	435	369	(84.8%)	56	(12.9%)	10	(2.3%)
SB 207499	NORMAL (<=1xULN)	368	354	(96.2%)	13	(3.5%)	1	(0.3%)
	HIGH (>1xULN-2.5xULN)	40	13	(32.5%)	21	(52.5%)	6	(15.0%)
	CONCERN (>2.5xULN)	10	2	(20.0%)	4	(40.0%)	4	(40.0%)
	MISSING	1	0		1	(100.0%)	0	
	TOTAL	419	369	(88.1%)	39	(9.3%)	11	(2.6%)

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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: ENDPOINT
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.16

DESCRIPTIVE STATISTICS FOR STANDARD VITAL SIGNS BY VISIT/WEEK AND TREATMENT GROUP

PROTOCOL 157

PARAMETER	VISIT/WEEK	TREATMENT GROUP	RESULT N	RESULT MEAN	RESULT STD	RESULT MIN	RESULT MAX	CHANGE FROM BASELINE N	CHANGE FROM BASELINE MEAN	CHANGE FROM BASELINE STD	CHANGE FROM BASELINE MIN	CHANGE FROM BASELINE MAX
SYSTOLIC BP (MM HG)	BASELINE	PLACEBO	446	135.0	15.6	90	200	0	.	.	.	.
		SB 207499	451	134.0	16.1	97	210	0	.	.	.	.
	VISIT 4	PLACEBO	436	134.0	16.0	90	200	436	-0.9	13.0	-50	44
		SB 207499	431	131.7	15.6	90	210	431	-2.3	13.2	-48	50
	VISIT 5	PLACEBO	430	133.2	15.3	80	200	430	-1.9	12.0	-50	42
		SB 207499	406	132.1	15.4	90	191	406	-1.6	13.9	-44	50
	VISIT 6	PLACEBO	415	133.0	15.8	83	210	415	-2.0	13.8	-60	50
		SB 207499	395	131.9	15.6	85	193	395	-1.4	14.5	-75	53
	VISIT 7	PLACEBO	403	133.9	16.4	90	196	403	-1.1	12.9	-50	42
		SB 207499	370	131.7	15.5	90	187	370	-1.3	14.2	-40	60
	VISIT 8	PLACEBO	391	133.1	16.6	85	210	391	-1.5	14.0	-50	50
		SB 207499	345	132.0	13.6	89	188	345	-1.3	15.3	-60	48
	VISIT 9	PLACEBO	380	133.4	16.4	90	192	380	-1.1	14.6	-56	50
		SB 207499	331	132.8	15.4	90	194	331	-0.7	15.0	-45	50
	VISIT 10	PLACEBO	359	132.6	16.2	80	200	359	-2.1	14.7	-56	56
		SB 207499	314	131.6	15.8	90	190	314	-1.9	15.5	-50	50
	VISIT 11	PLACEBO	345	132.6	15.2	85	195	345	-2.0	14.7	-55	57
		SB 207499	297	131.0	14.3	90	180	297	-2.7	14.1	-50	34
	VISIT 12	PLACEBO	327	133.8	16.4	95	220	327	-0.8	14.1	-60	40
		SB 207499	284	132.4	15.3	90	175	284	-1.0	15.1	-40	60
DIASTOLIC BP (MM HG)	BASELINE	PLACEBO	446	80.2	8.8	55	112	0	.	.	.	.
		SB 207499	451	79.5	8.6	55	110	0	.	.	.	.
	VISIT 4	PLACEBO	435	79.4	8.4	55	108	435	-0.8	7.9	-34	27
		SB 207499	431	78.4	8.6	46	120	431	-1.1	8.3	-30	33
	VISIT 5	PLACEBO	430	79.1	8.7	50	106	430	-1.2	8.2	-30	27
		SB 207499	406	78.7	8.5	58	107	406	-0.9	8.6	-30	26
	VISIT 6	PLACEBO	415	78.6	8.9	45	105	415	-1.7	8.8	-35	35
		SB 207499	395	78.2	9.0	50	110	395	-1.2	8.7	-30	33
	VISIT 7	PLACEBO	403	79.8	8.7	55	107	403	-0.6	8.0	-21	25
		SB 207499	370	78.6	8.7	50	100	370	-0.9	8.7	-30	31
	VISIT 8	PLACEBO	391	78.7	9.0	54	115	391	-1.5	9.1	-49	25
		SB 207499	345	78.3	8.3	50	100	345	-1.3	8.9	-37	25

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.16

DESCRIPTIVE STATISTICS FOR STANDARD VITAL SIGNS BY VISIT/WEEK AND TREATMENT GROUP

PROTOCOL 157

PARAMETER	VISIT/WEEK	TREATMENT GROUP	RESULT N	RESULT MEAN	RESULT STD	RESULT MIN	RESULT MAX	CHANGE FROM BASELINE N	CHANGE FROM BASELINE MEAN	CHANGE FROM BASELINE STD	CHANGE FROM BASELINE MIN	CHANGE FROM BASELINE MAX
DIASTOLIC BP (MM HG)	VISIT 9	PLACEBO	380	79.1	8.8	50	106	380	-0.8	8.9	-26	36
		SB 207499	331	78.3	8.6	50	108	331	-1.4	8.7	-30	28
	VISIT 10	PLACEBO	359	79.0	8.9	50	111	359	-1.1	9.2	-25	30
		SB 207499	314	77.1	9.3	50	101	314	-2.5	9.5	-35	23
	VISIT 11	PLACEBO	345	78.1	9.1	8	108	345	-1.9	9.0	-62	22
		SB 207499	297	77.1	8.5	40	100	297	-2.6	8.9	-28	20
	VISIT 12	PLACEBO	327	78.9	8.4	55	106	327	-1.1	9.1	-35	30
		SB 207499	284	78.6	9.2	50	106	284	-1.1	9.6	-35	25
HEART RATE (BPM)	BASELINE	PLACEBO	445	76.3	10.7	52	115	0	.	.	.	.
		SB 207499	451	75.8	10.2	52	120	0	.	.	.	.
	VISIT 4	PLACEBO	436	76.6	10.2	52	112	436	0.3	9.2	-32	35
		SB 207499	431	76.1	9.5	50	112	431	0.2	9.2	-40	56
	VISIT 5	PLACEBO	430	76.3	10.0	52	116	430	0.1	9.9	-55	31
		SB 207499	406	76.7	9.4	48	112	406	0.9	9.3	-34	26
	VISIT 6	PLACEBO	415	76.4	9.6	45	108	415	0.2	9.9	-31	35
		SB 207499	395	76.8	10.3	48	134	395	0.9	9.6	-38	32
	VISIT 7	PLACEBO	403	77.1	11.0	53	124	403	0.9	10.6	-46	38
		SB 207499	370	77.4	10.6	52	124	370	1.5	10.0	-36	48
	VISIT 8	PLACEBO	391	76.7	10.2	51	124	391	0.5	10.9	-51	38
		SB 207499	345	76.6	9.4	48	107	345	0.7	9.7	-38	29
	VISIT 9	PLACEBO	380	76.9	11.5	52	122	380	0.8	10.2	-30	32
		SB 207499	331	77.0	10.9	47	116	331	1.0	9.8	-26	40
	VISIT 10	PLACEBO	359	76.7	9.9	50	104	359	0.5	10.3	-32	28
		SB 207499	314	77.0	10.1	50	111	314	1.1	10.3	-30	35
	VISIT 11	PLACEBO	344	77.0	10.4	56	120	344	0.8	10.0	-33	28
		SB 207499	297	77.0	10.7	44	120	297	1.0	10.6	-36	31
	VISIT 12	PLACEBO	327	76.8	11.9	48	115	327	0.5	10.7	-26	38
		SB 207499	284	77.4	12.4	46	152	284	1.4	11.6	-32	58

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.17

TRANSITIONS FROM BASELINE IN SITTING VITAL SIGNS

PROTOCOL 157

PARAMETER: SYSTOLIC BP TIME POINT: TOTAL ON-THERAPY

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<75 MM HG)	0	0	0	0	0	0
	LOW (75-89 MM HG)	0	0	0	0	0	0
	NORMAL (90-139 MM HG)	245	0	4 (1.6%)	101 (41.2%)	140 (57.1%)	0
	HIGH (140-180 MM HG)	197	0	0	7 (3.6%)	180 (91.4%)	10 (5.1%)
	HIGH CONCERN (>180 MM HG)	1	0	0	0	0	1 (100.0%)
	TOTAL	443	0	4 (0.9%)	108 (24.4%)	320 (72.2%)	11 (2.5%)
SB 207499	LOW CONCERN (<75 MM HG)	0	0	0	0	0	0
	LOW (75-89 MM HG)	0	0	0	0	0	0
	NORMAL (90-139 MM HG)	266	0	2 (0.8%)	115 (43.2%)	149 (56.0%)	0
	HIGH (140-180 MM HG)	167	0	0	11 (6.6%)	152 (91.0%)	4 (2.4%)
	HIGH CONCERN (>180 MM HG)	3	0	0	0	1 (33.3%)	2 (66.7%)
	TOTAL	436	0	2 (0.5%)	126 (28.9%)	302 (69.3%)	6 (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; OTHER PARAMETERS TO BE APPLIED: DIASTOLIC BP, HEART RATE; OTHER INTERVALS TO BE APPLIED: ENDPOINT
5. ON-THERAPY IS DEFINED AS VITAL SIGN ASSESSMENT PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.17

TRANSITIONS FROM BASELINE IN SITTING VITAL SIGNS

PROTOCOL 157

PARAMETER: SYSTOLIC BP TIME POINT: ENDPOINT

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<75 MM HG)	0	0	0	0	0	0
	LOW (75-89 MM HG)	0	0	0	0	0	0
	NORMAL (90-139 MM HG)	245	0	0	181 (73.9%)	64 (26.1%)	0
	HIGH (140-180 MM HG)	197	0	0	72 (36.5%)	122 (61.9%)	3 (1.5%)
	HIGH CONCERN (>180 MM HG)	1	0	0	0	0	1 (100.0%)
	TOTAL	443	0	0	253 (57.1%)	186 (42.0%)	4 (0.9%)
SB 207499	LOW CONCERN (<75 MM HG)	0	0	0	0	0	0
	LOW (75-89 MM HG)	0	0	0	0	0	0
	NORMAL (90-139 MM HG)	266	0	0	204 (76.7%)	62 (23.3%)	0
	HIGH (140-180 MM HG)	167	0	0	69 (41.3%)	98 (58.7%)	0
	HIGH CONCERN (>180 MM HG)	3	0	0	0	2 (66.7%)	1 (33.3%)
	TOTAL	436	0	0	273 (62.6%)	162 (37.2%)	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; OTHER PARAMETERS TO BE APPLIED: DIASTOLIC BP, HEART RATE; OTHER INTERVALS TO BE APPLIED: ENDPOINT
5. ON-THERAPY IS DEFINED AS VITAL SIGN ASSESSMENT PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.17

TRANSITIONS FROM BASELINE IN SITTING VITAL SIGNS

PROTOCOL 157

PARAMETER: DIASTOLIC BP TIME POINT: TOTAL ON-THERAPY

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<50 MM HG)	0	0	0	0	0	0
	LOW (50-59 MM HG)	2	0	2 (100.0%)	0	0	0
	NORMAL (60-89 MM HG)	351	2 (0.6%)	16 (4.6%)	224 (63.8%)	112 (31.9%)	0
	HIGH (90-110 MM HG)	89	0	0	11 (12.4%)	76 (85.4%)	2 (2.2%)
	HIGH CONCERN (>110 MM HG)	1	0	0	0	1 (100.0%)	0
	TOTAL	443	2 (0.5%)	18 (4.1%)	235 (53.0%)	189 (42.7%)	2 (0.5%)
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)	370	2 (0.5%)	20 (5.4%)	250 (67.6%)	100 (27.0%)	0
	HIGH (90-110 MM HG)	64	0	1 (1.6%)	16 (25.0%)	46 (71.9%)	1 (1.6%)
	HIGH CONCERN (>110 MM HG)	0	0	0	0	0	0
	TOTAL	436	2 (0.5%)	21 (4.8%)	268 (61.5%)	146 (33.5%)	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; OTHER PARAMETERS TO BE APPLIED: DIASTOLIC BP, HEART RATE; OTHER INTERVALS TO BE APPLIED: ENDPOINT
5. ON-THERAPY IS DEFINED AS VITAL SIGN ASSESSMENT PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.17

TRANSITIONS FROM BASELINE IN SITTING VITAL SIGNS

PROTOCOL 157

PARAMETER: DIASTOLIC BP TIME POINT: ENDPOINT

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN
PLACEBO	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)	351	0	3 (0.9%)	315 (89.7%)	33 (9.4%)	0
	HIGH (90-110 MM HG)	89	0	0	56 (62.9%)	33 (37.1%)	0
	HIGH CONCERN (>110 MM HG)	1	0	0	1 (100.0%)	0	0
	TOTAL	443	0	3 (0.7%)	374 (84.4%)	66 (14.9%)	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)	370	0	6 (1.6%)	331 (89.5%)	33 (8.9%)	0
	HIGH (90-110 MM HG)	64	0	0	39 (60.9%)	25 (39.1%)	0
	HIGH CONCERN (>110 MM HG)	0	0	0	0	0	0
	TOTAL	436	0	6 (1.4%)	372 (85.3%)	58 (13.3%)	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; OTHER PARAMETERS TO BE APPLIED: DIASTOLIC BP, HEART RATE; OTHER INTERVALS TO BE APPLIED: ENDPOINT
5. ON-THERAPY IS DEFINED AS VITAL SIGN ASSESSMENT PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.17

TRANSITIONS FROM BASELINE IN SITTING VITAL SIGNS

PROTOCOL 157

PARAMETER: HEART RATE TIME POINT: TOTAL ON-THERAPY

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<50 BPM)	0	0	0	0	0	0
	LOW (50-59 BPM)	11	1 (9.1%)	4 (36.4%)	6 (54.5%)	0	0
	NORMAL (60-99 BPM)	418	1 (0.2%)	37 (8.9%)	337 (80.6%)	42 (10.0%)	1 (0.2%)
	HIGH (100-120 BPM)	14	0	0	2 (14.3%)	10 (71.4%)	2 (14.3%)
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0
	TOTAL	443	2 (0.5%)	41 (9.3%)	345 (77.9%)	52 (11.7%)	3 (0.7%)
SB 207499	LOW CONCERN (<50 BPM)	0	0	0	0	0	0
	LOW (50-59 BPM)	9	1 (11.1%)	5 (55.6%)	2 (22.2%)	1 (11.1%)	0
	NORMAL (60-99 BPM)	416	3 (0.7%)	31 (7.5%)	347 (83.4%)	36 (8.7%)	2 (0.5%)
	HIGH (100-120 BPM)	11	0	0	5 (45.5%)	5 (45.5%)	1 (9.1%)
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0
	TOTAL	436	4 (0.9%)	36 (8.3%)	354 (81.2%)	42 (9.6%)	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; OTHER PARAMETERS TO BE APPLIED: DIASTOLIC BP, HEART RATE; OTHER INTERVALS TO BE APPLIED: ENDPOINT
5. ON-THERAPY IS DEFINED AS VITAL SIGN ASSESSMENT PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.17

TRANSITIONS FROM BASELINE IN SITTING VITAL SIGNS

PROTOCOL 157

PARAMETER: HEART RATE TIME POINT: ENDPOINT

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<50 BPM)	0	0	0	0	0	0
	LOW (50-59 BPM)	11	1 (9.1%)	2 (18.2%)	8 (72.7%)	0	0
	NORMAL (60-99 BPM)	418	0	8 (1.9%)	396 (94.7%)	14 (3.3%)	0
	HIGH (100-120 BPM)	14	0	0	8 (57.1%)	6 (42.9%)	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0
	TOTAL	443	1 (0.2%)	10 (2.3%)	412 (93.0%)	20 (4.5%)	0
SB 207499	LOW CONCERN (<50 BPM)	0	0	0	0	0	0
	LOW (50-59 BPM)	9	1 (11.1%)	3 (33.3%)	5 (55.6%)	0	0
	NORMAL (60-99 BPM)	416	2 (0.5%)	9 (2.2%)	392 (94.2%)	12 (2.9%)	1 (0.2%)
	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	436	3 (0.7%)	12 (2.8%)	404 (92.7%)	16 (3.7%)	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; OTHER PARAMETERS TO BE APPLIED: DIASTOLIC BP, HEART RATE; OTHER INTERVALS TO BE APPLIED: ENDPOINT
5. ON-THERAPY IS DEFINED AS VITAL SIGN ASSESSMENT PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.18

DESCRIPTIVE STATISTICS FOR ECGS BY VISIT/WEEK AND TREATMENT GROUP

PROTOCOL 157

PARAMETER	VISIT/WEEK	TREATMENT GROUP	RESULT N	RESULT MEAN	RESULT STD	RESULT MIN	RESULT MAX	CHANGE FROM BASELINE N	CHANGE FROM BASELINE MEAN	CHANGE FROM BASELINE STD	CHANGE FROM BASELINE MIN	CHANGE FROM BASELINE MAX
Atrial rate (BPM)	VISIT 3/BASELINE	PLACEBO	448	73.8	12.7	44	120	0	.	.	.	.
		SB 207499	444	74.5	12.5	40	113	0	.	.	.	.
	VISIT 4/WEEK 2	PLACEBO	6	81.5	6.7	70	88	6	3.2	11.5	-10	19
		SB 207499	12	68.8	12.1	51	88	12	0.7	8.2	-12	12
	VISIT 5/WEEK 4	PLACEBO	3	76.3	10.4	68	88	3	3.7	1.5	2	5
		SB 207499	7	72.1	14.5	53	90	7	2.4	4.0	-4	7
	VISIT 6/WEEK 8	PLACEBO	8	80.1	11.2	64	98	8	2.1	14.3	-21	21
		SB 207499	14	73.6	11.2	47	86	14	1.9	8.0	-13	10
	VISIT 7/WEEK 12	PLACEBO	384	74.8	12.9	44	116	384	1.4	10.1	-45	37
		SB 207499	357	75.8	12.8	43	124	355	1.2	10.8	-40	38
	VISIT 8/WEEK 20	PLACEBO	3	83.3	4.0	81	88	3	11.7	8.3	5	21
		SB 207499	8	80.5	14.0	55	99	8	7.9	8.2	-7	16
	VISIT 9/WEEK 28	PLACEBO	360	76.8	14.2	50	160	360	3.1	13.0	-50	100
		SB 207499	313	75.8	13.0	45	112	311	0.7	11.1	-37	34
	VISIT 10/WEEK 36	PLACEBO	5	66.8	10.6	54	80	5	-0.8	9.6	-14	10
		SB 207499	2	86.0	7.1	81	91	2	6.5	4.9	3	10
	VISIT 11/WEEK 44	PLACEBO	2	76.5	0.7	76	77	2	-11.5	3.5	-14	-9
		SB 207499	1	65.0	.	65	65	1	-8.0	.	-8	-8
	VISIT 12/WEEK 52	PLACEBO	319	76.6	18.7	41	300	319	2.8	17.4	-55	231
		SB 207499	280	75.7	12.6	46	113	280	1.2	11.9	-42	48
Ventricular Rate (BPM)	VISIT 3/BASELINE	PLACEBO	450	73.8	12.9	44	120	0	.	.	.	.
		SB 207499	449	75.1	13.3	40	160	0	.	.	.	.
	VISIT 4/WEEK 2	PLACEBO	6	79.5	7.9	70	88	6	0.0	8.5	-10	13
		SB 207499	13	69.0	11.6	51	88	13	-0.8	9.4	-18	12
	VISIT 5/WEEK 4	PLACEBO	4	80.5	11.9	68	93	4	4.3	1.7	2	6
		SB 207499	9	74.7	13.6	53	90	9	4.6	5.6	-4	15
	VISIT 6/WEEK 8	PLACEBO	7	79.1	11.7	64	98	7	0.7	14.8	-21	21
		SB 207499	14	73.6	11.2	47	86	14	1.9	8.0	-13	10
	VISIT 7/WEEK 12	PLACEBO	385	74.9	13.3	44	130	385	1.4	10.4	-45	37
		SB 207499	361	76.0	13.1	43	124	360	0.7	11.7	-74	46
	VISIT 8/WEEK 20	PLACEBO	2	84.5	4.9	81	88	2	11.0	8.5	5	17

CONFIDENTIAL

SB 207499

TABLE 15.18

DESCRIPTIVE STATISTICS FOR ECGS BY VISIT/WEEK AND TREATMENT GROUP

PROTOCOL 157

PARAMETER	VISIT/WEEK	TREATMENT GROUP	RESULT N	RESULT MEAN	RESULT STD	RESULT MIN	RESULT MAX	CHANGE FROM BASELINE N	CHANGE FROM BASELINE MEAN	CHANGE FROM BASELINE STD	CHANGE FROM BASELINE MIN	CHANGE FROM BASELINE MAX
Ventricular Rate (BPM)	VISIT 8/WEEK 20	SB 207499	9	82.7	14.6	55	100	9	7.0	8.1	-7	16
	VISIT 9/WEEK 28	PLACEBO	361	76.5	14.2	48	160	361	2.9	13.0	-50	100
		SB 207499	316	76.0	13.1	45	112	314	0.3	12.1	-84	34
	VISIT 10/WEEK 36	PLACEBO	5	66.8	10.6	54	80	5	-0.8	9.6	-14	10
		SB 207499	2	86.0	7.1	81	91	2	6.5	4.9	3	10
	VISIT 11/WEEK 44	PLACEBO	3	73.7	4.9	68	77	3	-10.0	3.6	-14	-7
		SB 207499	1	65.0	.	65	65	1	-8.0	.	-8	-8
	VISIT 12/WEEK 52	PLACEBO	319	76.0	13.9	41	120	319	2.2	11.8	-55	45
		SB 207499	285	76.1	13.6	46	150	285	1.0	13.8	-90	65
PR Interval (MSEC)	VISIT 3/BASELINE	PLACEBO	441	161.6	33.9	0	380	0	.	.	.	.
		SB 207499	437	163.0	47.2	21	957	0	.	.	.	.
	VISIT 4/WEEK 2	PLACEBO	5	167.6	29.5	140	218	5	-8.8	23.4	-40	20
		SB 207499	12	165.3	34.3	120	241	12	0.8	20.4	-40	30
	VISIT 5/WEEK 4	PLACEBO	3	382.3	427.9	104	875	3	212.3	399.0	-20	673
		SB 207499	7	148.3	24.5	120	180	7	22.4	60.2	-4	159
	VISIT 6/WEEK 8	PLACEBO	6	171.7	20.5	140	200	6	5.2	30.1	-20	60
		SB 207499	13	153.8	21.6	120	196	13	-0.6	19.2	-40	40
	VISIT 7/WEEK 12	PLACEBO	375	162.6	41.5	0	743	375	0.1	34.9	-162	363
		SB 207499	349	161.5	29.6	80	321	347	-2.3	48.3	-801	113
	VISIT 8/WEEK 20	PLACEBO	2	133.0	18.4	120	146	2	-22.0	25.5	-40	-4
		SB 207499	8	162.5	31.0	120	200	8	-12.0	46.6	-120	40
	VISIT 9/WEEK 28	PLACEBO	357	162.4	44.6	0	740	355	-0.7	42.5	-182	585
		SB 207499	309	159.7	30.6	0	316	305	-3.8	51.6	-771	136
	VISIT 10/WEEK 36	PLACEBO	5	175.8	8.8	160	180	5	8.4	30.2	-30	52
		SB 207499	2	151.0	24.0	134	168	2	-2.0	8.5	-8	4
	VISIT 11/WEEK 44	PLACEBO	2	169.0	41.0	140	198	2	-18.0	31.1	-40	4
		SB 207499	1	160.0	.	160	160	1	10.0	.	10	10
	VISIT 12/WEEK 52	PLACEBO	317	160.4	33.6	0	370	315	-1.7	29.6	-196	194
		SB 207499	278	165.5	54.0	0	847	275	1.8	71.8	-779	705
QRS Interval (MSEC)	VISIT 3/BASELINE	PLACEBO	452	89.1	22.6	30	400	0	.	.	.	.

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.18

DESCRIPTIVE STATISTICS FOR ECGS BY VISIT/WEEK AND TREATMENT GROUP

PROTOCOL 157

PARAMETER	VISIT/WEEK	TREATMENT GROUP	RESULT N	RESULT MEAN	RESULT STD	RESULT MIN	RESULT MAX	CHANGE FROM BASELINE N	CHANGE FROM BASELINE MEAN	CHANGE FROM BASELINE STD	CHANGE FROM BASELINE MIN	CHANGE FROM BASELINE MAX
QRS Interval (MSEC)	VISIT 3/BASELINE	SB 207499	452	92.6	24.2	40	380	0	.	.	.	.
	VISIT 4/WEEK 2	PLACEBO	7	103.7	43.9	80	200	7	2.3	19.2	-20	40
		SB 207499	13	102.0	36.2	80	200	13	7.8	23.3	-9	80
	VISIT 5/WEEK 4	PLACEBO	4	82.0	14.5	68	102	4	-3.5	4.1	-8	2
		SB 207499	9	89.6	25.6	74	156	9	-1.6	12.0	-30	14
	VISIT 6/WEEK 8	PLACEBO	8	80.4	19.2	40	104	8	-0.8	9.9	-12	20
		SB 207499	14	78.4	24.1	8	110	14	-3.9	16.3	-52	20
	VISIT 7/WEEK 12	PLACEBO	388	88.7	17.0	40	180	388	-0.5	19.0	-236	76
		SB 207499	362	93.9	28.1	12	438	361	0.3	29.0	-300	267
	VISIT 8/WEEK 20	PLACEBO	3	88.7	8.1	80	96	3	2.0	5.3	-2	8
		SB 207499	9	89.6	14.5	72	116	9	-0.9	8.5	-20	10
	VISIT 9/WEEK 28	PLACEBO	364	89.5	17.7	40	190	364	0.7	18.5	-220	90
		SB 207499	316	95.3	28.6	10	329	315	1.7	30.0	-300	246
	VISIT 10/WEEK 36	PLACEBO	5	77.8	14.1	60	90	5	-0.6	13.7	-20	15
		SB 207499	2	95.0	1.4	94	96	2	2.0	0.0	2	2
	VISIT 11/WEEK 44	PLACEBO	3	98.0	26.9	76	128	3	-16.0	15.9	-34	-4
		SB 207499	1	90.0	.	90	90	1	10.0	.	10	10
	VISIT 12/WEEK 52	PLACEBO	323	90.0	17.7	40	168	323	1.3	20.3	-240	80
		SB 207499	287	95.3	28.0	22	446	287	1.6	29.1	-300	275
Uncorrected QT (MSEC)	VISIT 3/BASELINE	PLACEBO	452	367.3	47.5	42	480	0	.	.	.	.
		SB 207499	451	367.8	47.2	150	540	0	.	.	.	.
	VISIT 4/WEEK 2	PLACEBO	7	380.1	23.3	346	400	7	1.0	34.5	-54	40
		SB 207499	13	364.3	40.3	320	448	13	-20.6	47.9	-88	80
	VISIT 5/WEEK 4	PLACEBO	4	356.7	25.2	328	388	4	-1.6	13.6	-19	14
		SB 207499	9	358.0	40.8	280	440	9	-22.8	26.7	-89	0
	VISIT 6/WEEK 8	PLACEBO	8	359.5	43.3	302	428	8	-5.4	40.5	-58	62
		SB 207499	14	366.1	32.4	320	452	14	8.9	19.9	-20	44
	VISIT 7/WEEK 12	PLACEBO	386	366.9	43.2	120	514	386	-0.6	40.8	-164	338
		SB 207499	363	367.2	44.7	200	633	361	-1.1	40.0	-130	220
	VISIT 8/WEEK 20	PLACEBO	3	340.2	32.7	320	378	3	-34.4	54.1	-94	11
		SB 207499	9	369.6	30.8	336	439	9	-0.5	25.4	-40	40

CONFIDENTIAL

SB 207499

TABLE 15.18

DESCRIPTIVE STATISTICS FOR ECGS BY VISIT/WEEK AND TREATMENT GROUP

PROTOCOL 157

PARAMETER	VISIT/WEEK	TREATMENT GROUP	RESULT N	RESULT MEAN	RESULT STD	RESULT MIN	RESULT MAX	CHANGE FROM BASELINE N	CHANGE FROM BASELINE MEAN	CHANGE FROM BASELINE STD	CHANGE FROM BASELINE MIN	CHANGE FROM BASELINE MAX
Uncorrected QT (MSEC)	VISIT 9/WEEK 28	PLACEBO	363	364.9	44.5	120	460	363	-2.3	44.9	-190	298
		SB 207499	315	365.8	47.8	200	546	313	-0.3	44.4	-160	234
	VISIT 10/WEEK 36	PLACEBO	5	383.5	41.6	329	425	5	-1.0	28.8	-40	33
		SB 207499	2	356.2	11.1	348	364	2	-11.8	5.6	-16	-8
	VISIT 11/WEEK 44	PLACEBO	3	400.3	69.0	360	480	3	69.0	74.3	14	153
		SB 207499	1	400.0	.	400	400	1	50.0	.	50	50
	VISIT 12/WEEK 52	PLACEBO	321	364.6	44.1	79	544	321	-1.8	46.6	-155	344
		SB 207499	284	366.1	50.8	200	629	283	0.4	45.8	-138	226
Corrected QT (Bazett method) (MSEC)	VISIT 3/BASELINE	PLACEBO	450	403.6	47.4	48	566	0	.	.	.	.
		SB 207499	448	407.3	46.4	173	621	0	.	.	.	.
	VISIT 4/WEEK 2	PLACEBO	6	433.6	28.7	397	484	6	5.2	34.1	-28	50
		SB 207499	13	388.4	46.3	309	470	13	-20.7	41.4	-71	75
	VISIT 5/WEEK 4	PLACEBO	4	411.0	16.8	397	434	4	9.4	17.3	-9	30
		SB 207499	9	398.3	59.3	268	458	9	-11.7	33.4	-92	34
	VISIT 6/WEEK 8	PLACEBO	7	407.3	45.3	340	475	7	-11.8	29.0	-55	20
		SB 207499	14	403.4	36.1	319	463	14	14.9	23.1	-32	67
	VISIT 7/WEEK 12	PLACEBO	382	406.1	43.5	131	547	382	3.4	44.7	-208	382
		SB 207499	360	408.7	40.5	216	601	358	0.3	39.5	-237	145
	VISIT 8/WEEK 20	PLACEBO	2	381.3	8.9	375	388	2	-34.0	30.6	-56	-12
		SB 207499	9	429.6	18.7	405	465	9	16.2	33.0	-33	86
	VISIT 9/WEEK 28	PLACEBO	360	408.5	49.2	120	653	360	5.8	50.3	-190	337
		SB 207499	314	407.5	46.8	200	590	311	0.2	48.8	-188	287
	VISIT 10/WEEK 36	PLACEBO	5	401.4	26.6	355	417	5	-2.8	14.2	-26	10
		SB 207499	2	426.0	4.2	423	429	2	2.5	4.9	-1	6
	VISIT 11/WEEK 44	PLACEBO	3	444.2	84.2	383	540	3	52.9	77.3	-7	140
		SB 207499	1	416.3	.	416	416	1	30.3	.	30	30
	VISIT 12/WEEK 52	PLACEBO	317	407.0	48.7	90	623	317	4.5	50.2	-188	362
		SB 207499	282	407.7	47.2	193	613	281	3.1	48.4	-210	277
Axis (Degrees)	VISIT 3/BASELINE	PLACEBO	402	36.4	43.7	-150	135	0	.	.	.	.
		SB 207499	403	34.7	47.8	-120	270	0	.	.	.	.

CONFIDENTIAL

SB 207499

TABLE 15.18

DESCRIPTIVE STATISTICS FOR ECGS BY VISIT/WEEK AND TREATMENT GROUP

PROTOCOL 157

PARAMETER	VISIT/WEEK	TREATMENT GROUP	RESULT N	RESULT MEAN	RESULT STD	RESULT MIN	RESULT MAX	CHANGE FROM BASELINE N	CHANGE FROM BASELINE MEAN	CHANGE FROM BASELINE STD	CHANGE FROM BASELINE MIN	CHANGE FROM BASELINE MAX
Axis (Degrees)	VISIT 4/WEEK 2	PLACEBO	4	-7.4	59.1	-70	70	4	2.3	41.3	-38	60
		SB 207499	11	28.8	56.9	-120	98	11	-8.4	68.4	-206	60
	VISIT 5/WEEK 4	PLACEBO	4	50.0	42.5	-11	88	4	16.5	40.1	-32	62
		SB 207499	6	55.2	107.1	-26	261	6	-3.0	15.7	-30	17
	VISIT 6/WEEK 8	PLACEBO	4	20.5	35.8	-30	50	4	-14.8	20.6	-45	0
		SB 207499	14	33.9	43.1	-30	109	14	-5.5	31.1	-75	60
	VISIT 7/WEEK 12	PLACEBO	344	35.2	46.2	-150	168	344	-0.0	32.4	-156	198
		SB 207499	328	37.9	46.3	-112	233	326	2.7	31.7	-125	200
	VISIT 8/WEEK 20	SB 207499	9	58.8	31.8	0	101	8	37.5	78.8	-30	196
	VISIT 9/WEEK 28	PLACEBO	328	36.1	44.5	-180	140	327	0.9	34.2	-139	170
		SB 207499	284	37.2	47.2	-120	234	283	3.1	35.4	-174	191
	VISIT 10/WEEK 36	PLACEBO	3	58.3	32.5	25	90	3	3.3	5.8	0	10
		SB 207499	2	48.0	17.0	36	60	2	-2.5	2.1	-4	-1
	VISIT 11/WEEK 44	PLACEBO	3	68.0	13.0	60	83	3	8.0	19.5	-7	30
		SB 207499	1	60.0	.	60	60	1	0.0	.	0	0
	VISIT 12/WEEK 52	PLACEBO	287	37.0	45.9	-180	200	286	1.3	34.7	-165	230
		SB 207499	257	37.3	46.4	-90	259	257	4.3	37.5	-122	200
(MSEC)	VISIT 12/WEEK 52	SB 207499	1	360.0	.	360	360	0	.	.	.	.

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: ATRIAL RATE TIME POINT: VISIT 4/WEEK 2

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<45 BPM) or (<50 BPM and >=2 BPM DECREASE FROM BASELINE)	0	0	0	0	0	0
	LOW (45-49 BPM and NOT >=2 BPM DECREASE FROM BASELINE) or (50-55 BPM)	0	0	0	0	0	0
	NORMAL (56-99 BPM)	2	0	0	2 (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	2	0	0	2 (100.0%)	0	0
SB 207499	LOW CONCERN (<45 BPM) or (<50 BPM and >=2 BPM DECREASE FROM BASELINE)	0	0	0	0	0	0
	LOW (45-49 BPM and NOT >=2 BPM DECREASE FROM BASELINE) or (50-55 BPM)	0	0	0	0	0	0
	NORMAL (56-99 BPM)	4	0	1 (25.0%)	3 (75.0%)	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	5	0	1 (20.0%)	4 (80.0%)	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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: ATRIAL RATE TIME POINT: VISIT 5/WEEK 4

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: LOW CONCERN	LOW		NORMAL		HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<45 BPM) or (<50 BPM and >=2 BPM DECREASE FROM BASELINE)	0	0	0		0		0	0
	LOW (45-49 BPM and NOT >=2 BPM DECREASE FROM BASELINE) or (50-55 BPM)	0	0	0		0		0	0
	NORMAL (56-99 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 (<45 BPM) or (<50 BPM and >=2 BPM DECREASE FROM BASELINE)	0	0	0		0		0	0
	LOW (45-49 BPM and NOT >=2 BPM DECREASE FROM BASELINE) or (50-55 BPM)	0	0	0		0		0	0
	NORMAL (56-99 BPM)	1	0	1	(100.0%)	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	1	(100.0%)	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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: ATRIAL RATE TIME POINT: VISIT 6/WEEK 8

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<45 BPM) or (<50 BPM and >=2 BPM DECREASE FROM BASELINE)	0	0	0	0	0	0
	LOW (45-49 BPM and NOT >=2 BPM DECREASE FROM BASELINE) or (50-55 BPM)	0	0	0	0	0	0
	NORMAL (56-99 BPM)	2	0	0	2 (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	2	0	0	2 (100.0%)	0	0
SB 207499	LOW CONCERN (<45 BPM) or (<50 BPM and >=2 BPM DECREASE FROM BASELINE)	0	0	0	0	0	0
	LOW (45-49 BPM and NOT >=2 BPM DECREASE FROM BASELINE) or (50-55 BPM)	1	0	0	1 (100.0%)	0	0
	NORMAL (56-99 BPM)	8	1 (12.5%)	0	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	1 (11.1%)	0	8 (88.9%)	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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: ATRIAL RATE TIME POINT: VISIT 7/WEEK 12

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<45 BPM) or (<50 BPM and >=2 BPM DECREASE FROM BASELINE)	0	0	0	0	0	0
	LOW (45-49 BPM and NOT >=2 BPM DECREASE FROM BASELINE) or (50-55 BPM)	16	2 (12.5%)	6 (37.5%)	8 (50.0%)	0	0
	NORMAL (56-99 BPM)	355	1 (0.3%)	11 (3.1%)	332 (93.5%)	11 (3.1%)	0
	HIGH (100-120 BPM)	13	0	0	6 (46.2%)	7 (53.8%)	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0
	MISSING	0	0	0	0	0	0
	TOTAL	384	3 (0.8%)	17 (4.4%)	346 (90.1%)	18 (4.7%)	0
SB 207499	LOW CONCERN (<45 BPM) or (<50 BPM and >=2 BPM DECREASE FROM BASELINE)	0	0	0	0	0	0
	LOW (45-49 BPM and NOT >=2 BPM DECREASE FROM BASELINE) or (50-55 BPM)	14	2 (14.3%)	2 (14.3%)	10 (71.4%)	0	0
	NORMAL (56-99 BPM)	319	1 (0.3%)	7 (2.2%)	299 (93.7%)	12 (3.8%)	0
	HIGH (100-120 BPM)	16	0	0	11 (68.8%)	4 (25.0%)	1 (6.3%)
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0
	MISSING	1	0	0	1 (100.0%)	0	0
	TOTAL	350	3 (0.9%)	9 (2.6%)	321 (91.7%)	16 (4.6%)	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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: ATRIAL RATE TIME POINT: VISIT 8/WEEK 20

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<45 BPM) or (<50 BPM and >=2 BPM DECREASE FROM BASELINE)	0	0	0	0	0	0
	LOW (45-49 BPM and NOT >=2 BPM DECREASE FROM BASELINE) or (50-55 BPM)	0	0	0	0	0	0
	NORMAL (56-99 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 (<45 BPM) or (<50 BPM and >=2 BPM DECREASE FROM BASELINE)	0	0	0	0	0	0
	LOW (45-49 BPM and NOT >=2 BPM DECREASE FROM BASELINE) or (50-55 BPM)	0	0	0	0	0	0
	NORMAL (56-99 BPM)	4	0	1 (25.0%)	3 (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	4	0	1 (25.0%)	3 (75.0%)	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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: ATRIAL RATE TIME POINT: VISIT 9/WEEK 28

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<45 BPM) or (<50 BPM and >=2 BPM DECREASE FROM BASELINE)	1	0	1 (100.0%)	0	0	0
	LOW (45-49 BPM and NOT >=2 BPM DECREASE FROM BASELINE) or (50-55 BPM)	15	0	3 (20.0%)	11 (73.3%)	1 (6.7%)	0
	NORMAL (56-99 BPM)	331	0	4 (1.2%)	313 (94.6%)	12 (3.6%)	2 (0.6%)
	HIGH (100-120 BPM)	11	0	0	3 (27.3%)	8 (72.7%)	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0
	MISSING	0	0	0	0	0	0
	TOTAL	358	0	8 (2.2%)	327 (91.3%)	21 (5.9%)	2 (0.6%)
SB 207499	LOW CONCERN (<45 BPM) or (<50 BPM and >=2 BPM DECREASE FROM BASELINE)	0	0	0	0	0	0
	LOW (45-49 BPM and NOT >=2 BPM DECREASE FROM BASELINE) or (50-55 BPM)	11	1 (9.1%)	3 (27.3%)	7 (63.6%)	0	0
	NORMAL (56-99 BPM)	284	2 (0.7%)	10 (3.5%)	260 (91.5%)	12 (4.2%)	0
	HIGH (100-120 BPM)	15	0	0	10 (66.7%)	5 (33.3%)	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0
	MISSING	2	0	0	2 (100.0%)	0	0
	TOTAL	312	3 (1.0%)	13 (4.2%)	279 (89.4%)	17 (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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: ATRIAL RATE TIME POINT: VISIT 10/WEEK 36

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<45 BPM) or (<50 BPM and >=2 BPM DECREASE FROM BASELINE)	0	0	0	0	0	0
	LOW (45-49 BPM and NOT >=2 BPM DECREASE FROM BASELINE) or (50-55 BPM)	0	0	0	0	0	0
	NORMAL (56-99 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 (<45 BPM) or (<50 BPM and >=2 BPM DECREASE FROM BASELINE)	0	0	0	0	0	0
	LOW (45-49 BPM and NOT >=2 BPM DECREASE FROM BASELINE) or (50-55 BPM)	0	0	0	0	0	0
	NORMAL (56-99 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

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: ATRIAL RATE TIME POINT: VISIT 11/WEEK 44

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE					
			LOW CONCERN	LOW	NORMAL		HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<45 BPM) or (<50 BPM and >=2 BPM DECREASE FROM BASELINE)	0	0	0	0		0	0
	LOW (45-49 BPM and NOT >=2 BPM DECREASE FROM BASELINE) or (50-55 BPM)	0	0	0	0		0	0
	NORMAL (56-99 BPM)	2	0	0	2	(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	2	0	0	2	(100.0%)	0	0
SB 207499	LOW CONCERN (<45 BPM) or (<50 BPM and >=2 BPM DECREASE FROM BASELINE)	0	0	0	0		0	0
	LOW (45-49 BPM and NOT >=2 BPM DECREASE FROM BASELINE) or (50-55 BPM)	0	0	0	0		0	0
	NORMAL (56-99 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

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: ATRIAL RATE TIME POINT: VISIT 12/WEEK 52

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<45 BPM) or (<50 BPM and >=2 BPM DECREASE FROM BASELINE)	0	0	0	0	0	0
	LOW (45-49 BPM and NOT >=2 BPM DECREASE FROM BASELINE) or (50-55 BPM)	13	1 (7.7%)	1 (7.7%)	11 (84.6%)	0	0
	NORMAL (56-99 BPM)	292	0	10 (3.4%)	268 (91.8%)	13 (4.5%)	1 (0.3%)
	HIGH (100-120 BPM)	11	0	0	6 (54.5%)	5 (45.5%)	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0
	MISSING	0	0	0	0	0	0
	TOTAL	316	1 (0.3%)	11 (3.5%)	285 (90.2%)	18 (5.7%)	1 (0.3%)
SB 207499	LOW CONCERN (<45 BPM) or (<50 BPM and >=2 BPM DECREASE FROM BASELINE)	0	0	0	0	0	0
	LOW (45-49 BPM and NOT >=2 BPM DECREASE FROM BASELINE) or (50-55 BPM)	12	0	3 (25.0%)	9 (75.0%)	0	0
	NORMAL (56-99 BPM)	248	2 (0.8%)	5 (2.0%)	229 (92.3%)	12 (4.8%)	0
	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	0	0	0	0	0	0
	TOTAL	272	2 (0.7%)	8 (2.9%)	245 (90.1%)	17 (6.3%)	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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: ATRIAL RATE TIME POINT: TOTAL ON-THERAPY

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<45 BPM) or (<50 BPM and >=2 BPM DECREASE FROM BASELINE)	1	0	1 (100.0%)	0	0	0
	LOW (45-49 BPM and NOT >=2 BPM DECREASE FROM BASELINE) or (50-55 BPM)	17	2 (11.8%)	6 (35.3%)	9 (52.9%)	1 (5.9%)	0
	NORMAL (56-99 BPM)	376	1 (0.3%)	19 (5.1%)	326 (86.7%)	27 (7.2%)	3 (0.8%)
	HIGH (100-120 BPM)	13	0	0	4 (30.8%)	9 (69.2%)	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0
	MISSING	0	0	0	0	0	0
	TOTAL	407	3 (0.7%)	26 (6.4%)	339 (83.3%)	37 (9.1%)	3 (0.7%)
SB 207499	LOW CONCERN (<45 BPM) or (<50 BPM and >=2 BPM DECREASE FROM BASELINE)	0	0	0	0	0	0
	LOW (45-49 BPM and NOT >=2 BPM DECREASE FROM BASELINE) or (50-55 BPM)	16	2 (12.5%)	4 (25.0%)	10 (62.5%)	0	0
	NORMAL (56-99 BPM)	348	4 (1.1%)	17 (4.9%)	297 (85.3%)	30 (8.6%)	0
	HIGH (100-120 BPM)	18	0	0	8 (44.4%)	9 (50.0%)	1 (5.6%)
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0
	MISSING	2	0	0	2 (100.0%)	0	0
	TOTAL	384	6 (1.6%)	21 (5.5%)	317 (82.6%)	39 (10.2%)	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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: ATRIAL RATE TIME POINT: ENDPOINT

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<45 BPM) or (<50 BPM and >=2 BPM DECREASE FROM BASELINE)	1	0	1 (100.0%)	0	0	0
	LOW (45-49 BPM and NOT >=2 BPM DECREASE FROM BASELINE) or (50-55 BPM)	17	1 (5.9%)	1 (5.9%)	15 (88.2%)	0	0
	NORMAL (56-99 BPM)	376	1 (0.3%)	13 (3.5%)	347 (92.3%)	14 (3.7%)	1 (0.3%)
	HIGH (100-120 BPM)	13	0	0	7 (53.8%)	6 (46.2%)	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0
	MISSING	0	0	0	0	0	0
	TOTAL	407	2 (0.5%)	15 (3.7%)	369 (90.7%)	20 (4.9%)	1 (0.2%)
SB 207499	LOW CONCERN (<45 BPM) or (<50 BPM and >=2 BPM DECREASE FROM BASELINE)	0	0	0	0	0	0
	LOW (45-49 BPM and NOT >=2 BPM DECREASE FROM BASELINE) or (50-55 BPM)	16	1 (6.3%)	3 (18.8%)	12 (75.0%)	0	0
	NORMAL (56-99 BPM)	348	2 (0.6%)	11 (3.2%)	319 (91.7%)	16 (4.6%)	0
	HIGH (100-120 BPM)	18	0	0	12 (66.7%)	6 (33.3%)	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%)	14 (3.6%)	345 (89.8%)	22 (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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: VENTRICULAR RATE TIME POINT: VISIT 4/WEEK 2

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<45 BPM) or (<50 BPM and >=2 BPM DECREASE FROM BASELINE)	0	0	0	0	0	0
	LOW (45-49 BPM and NOT>=2 BPM DECREASE FROM BASELINE) or (50-55 BPM)	0	0	0	0	0	0
	NORMAL (56-99 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 (<45 BPM) or (<50 BPM and >=2 BPM DECREASE FROM BASELINE)	0	0	0	0	0	0
	LOW (45-49 BPM and NOT>=2 BPM DECREASE FROM BASELINE) or (50-55 BPM)	0	0	0	0	0	0
	NORMAL (56-99 BPM)	4	0	1 (25.0%)	3 (75.0%)	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	5	0	1 (20.0%)	4 (80.0%)	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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: VENTRICULAR RATE TIME POINT: VISIT 5/WEEK 4

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<45 BPM) or (<50 BPM and >=2 BPM DECREASE FROM BASELINE)	0	0	0	0	0	0
	LOW (45-49 BPM and NOT>=2 BPM DECREASE FROM BASELINE) or (50-55 BPM)	0	0	0	0	0	0
	NORMAL (56-99 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 (<45 BPM) or (<50 BPM and >=2 BPM DECREASE FROM BASELINE)	0	0	0	0	0	0
	LOW (45-49 BPM and NOT>=2 BPM DECREASE FROM BASELINE) or (50-55 BPM)	0	0	0	0	0	0
	NORMAL (56-99 BPM)	1	0	1 (100.0%)	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	1 (100.0%)	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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: VENTRICULAR RATE TIME POINT: VISIT 6/WEEK 8

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<45 BPM) or (<50 BPM and >=2 BPM DECREASE FROM BASELINE)	0	0	0	0	0	0
	LOW (45-49 BPM and NOT>=2 BPM DECREASE FROM BASELINE) or (50-55 BPM)	0	0	0	0	0	0
	NORMAL (56-99 BPM)	2	0	0	2 (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	2	0	0	2 (100.0%)	0	0
SB 207499	LOW CONCERN (<45 BPM) or (<50 BPM and >=2 BPM DECREASE FROM BASELINE)	0	0	0	0	0	0
	LOW (45-49 BPM and NOT>=2 BPM DECREASE FROM BASELINE) or (50-55 BPM)	1	0	0	1 (100.0%)	0	0
	NORMAL (56-99 BPM)	8	1 (12.5%)	0	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	1 (11.1%)	0	8 (88.9%)	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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: VENTRICULAR RATE TIME POINT: VISIT 7/WEEK 12

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<45 BPM) or (<50 BPM and >=2 BPM DECREASE FROM BASELINE)	0	0	0	0	0	0
	LOW (45-49 BPM and NOT>=2 BPM DECREASE FROM BASELINE) or (50-55 BPM)	17	2 (11.8%)	6 (35.3%)	9 (52.9%)	0	0
	NORMAL (56-99 BPM)	353	1 (0.3%)	11 (3.1%)	329 (93.2%)	12 (3.4%)	0
	HIGH (100-120 BPM)	14	0	0	7 (50.0%)	7 (50.0%)	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0
	MISSING	0	0	0	0	0	0
	TOTAL	384	3 (0.8%)	17 (4.4%)	345 (89.8%)	19 (4.9%)	0
SB 207499	LOW CONCERN (<45 BPM) or (<50 BPM and >=2 BPM DECREASE FROM BASELINE)	0	0	0	0	0	0
	LOW (45-49 BPM and NOT>=2 BPM DECREASE FROM BASELINE) or (50-55 BPM)	13	2 (15.4%)	2 (15.4%)	9 (69.2%)	0	0
	NORMAL (56-99 BPM)	320	1 (0.3%)	8 (2.5%)	297 (92.8%)	14 (4.4%)	0
	HIGH (100-120 BPM)	19	0	0	14 (73.7%)	4 (21.1%)	1 (5.3%)
	HIGH CONCERN (>120 BPM)	1	0	0	1 (100.0%)	0	0
	MISSING	1	0	0	1 (100.0%)	0	0
	TOTAL	354	3 (0.8%)	10 (2.8%)	322 (91.0%)	18 (5.1%)	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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: VENTRICULAR RATE TIME POINT: VISIT 8/WEEK 20

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<45 BPM) or (<50 BPM and >=2 BPM DECREASE FROM BASELINE)	0	0	0	0	0	0
	LOW (45-49 BPM and NOT>=2 BPM DECREASE FROM BASELINE) or (50-55 BPM)	0	0	0	0	0	0
	NORMAL (56-99 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 (<45 BPM) or (<50 BPM and >=2 BPM DECREASE FROM BASELINE)	0	0	0	0	0	0
	LOW (45-49 BPM and NOT>=2 BPM DECREASE FROM BASELINE) or (50-55 BPM)	0	0	0	0	0	0
	NORMAL (56-99 BPM)	4	0	1 (25.0%)	3 (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	4	0	1 (25.0%)	3 (75.0%)	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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: VENTRICULAR RATE TIME POINT: VISIT 9/WEEK 28

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<45 BPM) or (<50 BPM and >=2 BPM DECREASE FROM BASELINE)	1	0	1 (100.0%)	0	0	0
	LOW (45-49 BPM and NOT>=2 BPM DECREASE FROM BASELINE) or (50-55 BPM)	16	0	3 (18.8%)	12 (75.0%)	1 (6.3%)	0
	NORMAL (56-99 BPM)	330	1 (0.3%)	4 (1.2%)	311 (94.2%)	12 (3.6%)	2 (0.6%)
	HIGH (100-120 BPM)	12	0	0	4 (33.3%)	8 (66.7%)	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0
	MISSING	0	0	0	0	0	0
	TOTAL	359	1 (0.3%)	8 (2.2%)	327 (91.1%)	21 (5.8%)	2 (0.6%)
SB 207499	LOW CONCERN (<45 BPM) or (<50 BPM and >=2 BPM DECREASE FROM BASELINE)	0	0	0	0	0	0
	LOW (45-49 BPM and NOT>=2 BPM DECREASE FROM BASELINE) or (50-55 BPM)	10	1 (10.0%)	3 (30.0%)	6 (60.0%)	0	0
	NORMAL (56-99 BPM)	285	2 (0.7%)	10 (3.5%)	263 (92.3%)	10 (3.5%)	0
	HIGH (100-120 BPM)	17	0	0	10 (58.8%)	7 (41.2%)	0
	HIGH CONCERN (>120 BPM)	1	0	0	1 (100.0%)	0	0
	MISSING	2	0	0	2 (100.0%)	0	0
	TOTAL	315	3 (1.0%)	13 (4.1%)	282 (89.5%)	17 (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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: VENTRICULAR RATE TIME POINT: VISIT 10/WEEK 36

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<45 BPM) or (<50 BPM and >=2 BPM DECREASE FROM BASELINE)	0	0	0	0	0	0
	LOW (45-49 BPM and NOT>=2 BPM DECREASE FROM BASELINE) or (50-55 BPM)	0	0	0	0	0	0
	NORMAL (56-99 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 (<45 BPM) or (<50 BPM and >=2 BPM DECREASE FROM BASELINE)	0	0	0	0	0	0
	LOW (45-49 BPM and NOT>=2 BPM DECREASE FROM BASELINE) or (50-55 BPM)	0	0	0	0	0	0
	NORMAL (56-99 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

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: VENTRICULAR RATE TIME POINT: VISIT 11/WEEK 44

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE					
			LOW CONCERN	LOW	NORMAL		HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<45 BPM) or (<50 BPM and >=2 BPM DECREASE FROM BASELINE)	0	0	0	0		0	0
	LOW (45-49 BPM and NOT>=2 BPM DECREASE FROM BASELINE) or (50-55 BPM)	0	0	0	0		0	0
	NORMAL (56-99 BPM)	2	0	0	2	(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	2	0	0	2	(100.0%)	0	0
SB 207499	LOW CONCERN (<45 BPM) or (<50 BPM and >=2 BPM DECREASE FROM BASELINE)	0	0	0	0		0	0
	LOW (45-49 BPM and NOT>=2 BPM DECREASE FROM BASELINE) or (50-55 BPM)	0	0	0	0		0	0
	NORMAL (56-99 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

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: VENTRICULAR RATE TIME POINT: VISIT 12/WEEK 52

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<45 BPM) or (<50 BPM and >=2 BPM DECREASE FROM BASELINE)	0	0	0	0	0	0
	LOW (45-49 BPM and NOT>=2 BPM DECREASE FROM BASELINE) or (50-55 BPM)	14	1 (7.1%)	1 (7.1%)	12 (85.7%)	0	0
	NORMAL (56-99 BPM)	290	0	10 (3.4%)	266 (91.7%)	14 (4.8%)	0
	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	0	0	0	0	0	0
	TOTAL	316	1 (0.3%)	11 (3.5%)	285 (90.2%)	19 (6.0%)	0
SB 207499	LOW CONCERN (<45 BPM) or (<50 BPM and >=2 BPM DECREASE FROM BASELINE)	0	0	0	0	0	0
	LOW (45-49 BPM and NOT>=2 BPM DECREASE FROM BASELINE) or (50-55 BPM)	12	0	4 (33.3%)	8 (66.7%)	0	0
	NORMAL (56-99 BPM)	251	2 (0.8%)	6 (2.4%)	229 (91.2%)	13 (5.2%)	1 (0.4%)
	HIGH (100-120 BPM)	13	0	0	8 (61.5%)	5 (38.5%)	0
	HIGH CONCERN (>120 BPM)	1	0	0	1 (100.0%)	0	0
	MISSING	0	0	0	0	0	0
	TOTAL	277	2 (0.7%)	10 (3.6%)	246 (88.8%)	18 (6.5%)	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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: VENTRICULAR RATE TIME POINT: TOTAL ON-THERAPY

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<45 BPM) or (<50 BPM and >=2 BPM DECREASE FROM BASELINE)	1	0	1 (100.0%)	0	0	0
	LOW (45-49 BPM and NOT>=2 BPM DECREASE FROM BASELINE) or (50-55 BPM)	18	2 (11.1%)	6 (33.3%)	10 (55.6%)	1 (5.6%)	0
	NORMAL (56-99 BPM)	373	2 (0.5%)	19 (5.1%)	321 (86.1%)	29 (7.8%)	2 (0.5%)
	HIGH (100-120 BPM)	14	0	0	5 (35.7%)	9 (64.3%)	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0
	MISSING	0	0	0	0	0	0
	TOTAL	406	4 (1.0%)	26 (6.4%)	336 (82.8%)	39 (9.6%)	2 (0.5%)
SB 207499	LOW CONCERN (<45 BPM) or (<50 BPM and >=2 BPM DECREASE FROM BASELINE)	0	0	0	0	0	0
	LOW (45-49 BPM and NOT>=2 BPM DECREASE FROM BASELINE) or (50-55 BPM)	15	2 (13.3%)	4 (26.7%)	9 (60.0%)	0	0
	NORMAL (56-99 BPM)	347	4 (1.2%)	19 (5.5%)	293 (84.4%)	30 (8.6%)	1 (0.3%)
	HIGH (100-120 BPM)	21	0	0	9 (42.9%)	11 (52.4%)	1 (4.8%)
	HIGH CONCERN (>120 BPM)	1	0	0	1 (100.0%)	0	0
	MISSING	2	0	0	2 (100.0%)	0	0
	TOTAL	386	6 (1.6%)	23 (6.0%)	314 (81.3%)	41 (10.6%)	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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: VENTRICULAR RATE TIME POINT: ENDPOINT

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<45 BPM) or (<50 BPM and >=2 BPM DECREASE FROM BASELINE)	1	0	1 (100.0%)	0	0	0
	LOW (45-49 BPM and NOT>=2 BPM DECREASE FROM BASELINE) or (50-55 BPM)	18	1 (5.6%)	1 (5.6%)	16 (88.9%)	0	0
	NORMAL (56-99 BPM)	373	1 (0.3%)	13 (3.5%)	344 (92.2%)	15 (4.0%)	0
	HIGH (100-120 BPM)	14	0	0	8 (57.1%)	6 (42.9%)	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0
	MISSING	0	0	0	0	0	0
	TOTAL	406	2 (0.5%)	15 (3.7%)	368 (90.6%)	21 (5.2%)	0
SB 207499	LOW CONCERN (<45 BPM) or (<50 BPM and >=2 BPM DECREASE FROM BASELINE)	0	0	0	0	0	0
	LOW (45-49 BPM and NOT>=2 BPM DECREASE FROM BASELINE) or (50-55 BPM)	15	0	4 (26.7%)	11 (73.3%)	0	0
	NORMAL (56-99 BPM)	347	2 (0.6%)	12 (3.5%)	316 (91.1%)	16 (4.6%)	1 (0.3%)
	HIGH (100-120 BPM)	21	0	0	13 (61.9%)	8 (38.1%)	0
	HIGH CONCERN (>120 BPM)	1	0	0	1 (100.0%)	0	0
	MISSING	2	0	0	2 (100.0%)	0	0
	TOTAL	386	2 (0.5%)	16 (4.1%)	343 (88.9%)	24 (6.2%)	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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: PR INTERVAL TIME POINT: VISIT 4/WEEK 2

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: NORMAL		HIGH		CONCERN
PLACEBO	NORMAL (<200 MSEC)	1	1	(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	1	1	(100.0%)	0		0
SB 207499	NORMAL (<200 MSEC)	4	4	(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	5	4	(80.0%)	1	(20.0%)	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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: PR INTERVAL TIME POINT: VISIT 5/WEEK 4

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE NORMAL		HIGH	CONCERN
PLACEBO	NORMAL (<200 MSEC)	1	1	(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	1	1	(100.0%)	0	0
SB 207499	NORMAL (<200 MSEC)	1	1	(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	1	1	(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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: PR INTERVAL TIME POINT: VISIT 6/WEEK 8

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE NORMAL		HIGH	CONCERN
PLACEBO	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
SB 207499	NORMAL (<200 MSEC)	8	8	(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	8	8	(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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: PR INTERVAL TIME POINT: VISIT 7/WEEK 12

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL (<200 MSEC)	326	305	(93.6%)	21	(6.4%)	0	
	HIGH (200-249 MSEC)	45	22	(48.9%)	23	(51.1%)	0	
	CONCERN (>=250 MSEC)	4	1	(25.0%)	1	(25.0%)	2	(50.0%)
	MISSING	0	0		0		0	
	TOTAL	375	328	(87.5%)	45	(12.0%)	2	(0.5%)
SB 207499	NORMAL (<200 MSEC)	307	293	(95.4%)	14	(4.6%)	0	
	HIGH (200-249 MSEC)	30	9	(30.0%)	20	(66.7%)	1	(3.3%)
	CONCERN (>=250 MSEC)	4	1	(25.0%)	0		3	(75.0%)
	MISSING	2	2	(100.0%)	0		0	
	TOTAL	343	305	(88.9%)	34	(9.9%)	4	(1.2%)

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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: PR INTERVAL TIME POINT: VISIT 8/WEEK 20

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE NORMAL		HIGH	CONCERN
PLACEBO	NORMAL (<200 MSEC)	1	1	(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	1	1	(100.0%)	0	0
SB 207499	NORMAL (<200 MSEC)	3	3	(100.0%)	0	0
	HIGH (200-249 MSEC)	1	1	(100.0%)	0	0
	CONCERN (>=250 MSEC)	0	0		0	0
	MISSING	0	0		0	0
	TOTAL	4	4	(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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: PR INTERVAL TIME POINT: VISIT 9/WEEK 28

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL (<200 MSEC)	306	284	(92.8%)	20	(6.5%)	2	(0.7%)
	HIGH (200-249 MSEC)	44	23	(52.3%)	21	(47.7%)	0	
	CONCERN (>=250 MSEC)	3	0		1	(33.3%)	2	(66.7%)
	MISSING	2	1	(50.0%)	0		1	(50.0%)
	TOTAL	355	308	(86.8%)	42	(11.8%)	5	(1.4%)
SB 207499	NORMAL (<200 MSEC)	275	267	(97.1%)	7	(2.5%)	1	(0.4%)
	HIGH (200-249 MSEC)	26	8	(30.8%)	17	(65.4%)	1	(3.8%)
	CONCERN (>=250 MSEC)	3	2	(66.7%)	0		1	(33.3%)
	MISSING	4	2	(50.0%)	2	(50.0%)	0	
	TOTAL	308	279	(90.6%)	26	(8.4%)	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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: PR INTERVAL TIME POINT: VISIT 10/WEEK 36

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: 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)	1	1	(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	1	1	(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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: PR INTERVAL TIME POINT: VISIT 11/WEEK 44

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: NORMAL		HIGH	CONCERN
PLACEBO	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
SB 207499	NORMAL (<200 MSEC)	1	1	(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	1	1	(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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: PR INTERVAL TIME POINT: VISIT 12/WEEK 52

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL (<200 MSEC)	273	258	(94.5%)	14	(5.1%)	1	(0.4%)
	HIGH (200-249 MSEC)	37	17	(45.9%)	20	(54.1%)	0	
	CONCERN (>=250 MSEC)	3	0		2	(66.7%)	1	(33.3%)
	MISSING	1	1	(100.0%)	0		0	
	TOTAL	314	276	(87.9%)	36	(11.5%)	2	(0.6%)
SB 207499	NORMAL (<200 MSEC)	239	224	(93.7%)	11	(4.6%)	4	(1.7%)
	HIGH (200-249 MSEC)	25	11	(44.0%)	13	(52.0%)	1	(4.0%)
	CONCERN (>=250 MSEC)	3	2	(66.7%)	0		1	(33.3%)
	MISSING	3	1	(33.3%)	1	(33.3%)	1	(33.3%)
	TOTAL	270	238	(88.1%)	25	(9.3%)	7	(2.6%)

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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: PR INTERVAL TIME POINT: TOTAL ON-THERAPY

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL (<200 MSEC)	347	306	(88.2%)	38	(11.0%)	3	(0.9%)
	HIGH (200-249 MSEC)	50	13	(26.0%)	37	(74.0%)	0	
	CONCERN (>=250 MSEC)	4	0		1	(25.0%)	3	(75.0%)
	MISSING	2	1	(50.0%)	0		1	(50.0%)
	TOTAL	403	320	(79.4%)	76	(18.9%)	7	(1.7%)
SB 207499	NORMAL (<200 MSEC)	335	303	(90.4%)	28	(8.4%)	4	(1.2%)
	HIGH (200-249 MSEC)	36	6	(16.7%)	28	(77.8%)	2	(5.6%)
	CONCERN (>=250 MSEC)	4	1	(25.0%)	0		3	(75.0%)
	MISSING	4	2	(50.0%)	1	(25.0%)	1	(25.0%)
	TOTAL	379	312	(82.3%)	57	(15.0%)	10	(2.6%)

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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: PR INTERVAL TIME POINT: ENDPOINT

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL (<200 MSEC)	347	327	(94.2%)	18	(5.2%)	2	(0.6%)
	HIGH (200-249 MSEC)	50	23	(46.0%)	27	(54.0%)	0	
	CONCERN (>=250 MSEC)	4	1	(25.0%)	2	(50.0%)	1	(25.0%)
	MISSING	2	1	(50.0%)	0		1	(50.0%)
	TOTAL	403	352	(87.3%)	47	(11.7%)	4	(1.0%)
SB 207499	NORMAL (<200 MSEC)	335	315	(94.0%)	16	(4.8%)	4	(1.2%)
	HIGH (200-249 MSEC)	36	16	(44.4%)	19	(52.8%)	1	(2.8%)
	CONCERN (>=250 MSEC)	4	2	(50.0%)	0		2	(50.0%)
	MISSING	4	2	(50.0%)	1	(25.0%)	1	(25.0%)
	TOTAL	379	335	(88.4%)	36	(9.5%)	8	(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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: QRS INTERVAL TIME POINT: VISIT 4/WEEK 2

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: NORMAL		HIGH		CONCERN
PLACEBO	NORMAL (<120 MSEC)	2	2	(100.0%)	0		0
	HIGH (120-199 MSEC)	0	0		0		0
	CONCERN (>=200 MSEC)	0	0		0		0
	MISSING	0	0		0		0
	TOTAL	2	2	(100.0%)	0		0
SB 207499	NORMAL (<120 MSEC)	4	4	(100.0%)	0		0
	HIGH (120-199 MSEC)	1	0		1	(100.0%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	MISSING	0	0		0		0
	TOTAL	5	4	(80.0%)	1	(20.0%)	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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: QRS INTERVAL TIME POINT: VISIT 5/WEEK 4

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: 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
	MISSING	0	0		0	0
	TOTAL	1	1	(100.0%)	0	0
SB 207499	NORMAL (<120 MSEC)	1	1	(100.0%)	0	0
	HIGH (120-199 MSEC)	0	0		0	0
	CONCERN (>=200 MSEC)	0	0		0	0
	MISSING	0	0		0	0
	TOTAL	1	1	(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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: QRS INTERVAL TIME POINT: VISIT 6/WEEK 8

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE NORMAL		HIGH	CONCERN
PLACEBO	NORMAL (<120 MSEC)	2	2	(100.0%)	0	0
	HIGH (120-199 MSEC)	0	0		0	0
	CONCERN (>=200 MSEC)	0	0		0	0
	MISSING	0	0		0	0
	TOTAL	2	2	(100.0%)	0	0
SB 207499	NORMAL (<120 MSEC)	9	9	(100.0%)	0	0
	HIGH (120-199 MSEC)	0	0		0	0
	CONCERN (>=200 MSEC)	0	0		0	0
	MISSING	0	0		0	0
	TOTAL	9	9	(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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: QRS INTERVAL TIME POINT: VISIT 7/WEEK 12

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL (<120 MSEC)	365	353	(96.7%)	12	(3.3%)	0	
	HIGH (120-199 MSEC)	21	11	(52.4%)	10	(47.6%)	0	
	CONCERN (>=200 MSEC)	1	0		1	(100.0%)	0	
	MISSING	0	0		0		0	
	TOTAL	387	364	(94.1%)	23	(5.9%)	0	
SB 207499	NORMAL (<120 MSEC)	314	303	(96.5%)	10	(3.2%)	1	(0.3%)
	HIGH (120-199 MSEC)	39	12	(30.8%)	26	(66.7%)	1	(2.6%)
	CONCERN (>=200 MSEC)	1	1	(100.0%)	0		0	
	MISSING	1	1	(100.0%)	0		0	
	TOTAL	355	317	(89.3%)	36	(10.1%)	2	(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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: QRS INTERVAL TIME POINT: VISIT 8/WEEK 20

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE 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
	MISSING	0	0		0	0
	TOTAL	1	1	(100.0%)	0	0
SB 207499	NORMAL (<120 MSEC)	3	3	(100.0%)	0	0
	HIGH (120-199 MSEC)	1	1	(100.0%)	0	0
	CONCERN (>=200 MSEC)	0	0		0	0
	MISSING	0	0		0	0
	TOTAL	4	4	(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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: QRS INTERVAL TIME POINT: VISIT 9/WEEK 28

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL (<120 MSEC)	344	329	(95.6%)	15	(4.4%)	0	
	HIGH (120-199 MSEC)	17	7	(41.2%)	10	(58.8%)	0	
	CONCERN (>=200 MSEC)	1	0		1	(100.0%)	0	
	MISSING	0	0		0		0	
	TOTAL	362	336	(92.8%)	26	(7.2%)	0	
SB 207499	NORMAL (<120 MSEC)	279	269	(96.4%)	8	(2.9%)	2	(0.7%)
	HIGH (120-199 MSEC)	34	8	(23.5%)	24	(70.6%)	2	(5.9%)
	CONCERN (>=200 MSEC)	1	1	(100.0%)	0		0	
	MISSING	1	1	(100.0%)	0		0	
	TOTAL	315	279	(88.6%)	32	(10.2%)	4	(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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: QRS INTERVAL TIME POINT: VISIT 10/WEEK 36

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: 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
	MISSING	0	0		0	0
	TOTAL	3	3	(100.0%)	0	0
SB 207499	NORMAL (<120 MSEC)	1	1	(100.0%)	0	0
	HIGH (120-199 MSEC)	0	0		0	0
	CONCERN (>=200 MSEC)	0	0		0	0
	MISSING	0	0		0	0
	TOTAL	1	1	(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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: QRS INTERVAL TIME POINT: VISIT 11/WEEK 44

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: NORMAL		HIGH		CONCERN
PLACEBO	NORMAL (<120 MSEC)	1	1	(100.0%)	0		0
	HIGH (120-199 MSEC)	1	0		1	(100.0%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	MISSING	0	0		0		0
	TOTAL	2	1	(50.0%)	1	(50.0%)	0
SB 207499	NORMAL (<120 MSEC)	1	1	(100.0%)	0		0
	HIGH (120-199 MSEC)	0	0		0		0
	CONCERN (>=200 MSEC)	0	0		0		0
	MISSING	0	0		0		0
	TOTAL	1	1	(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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: QRS INTERVAL TIME POINT: VISIT 12/WEEK 52

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL (<120 MSEC)	302	292	(96.7%)	10	(3.3%)	0	
	HIGH (120-199 MSEC)	17	9	(52.9%)	8	(47.1%)	0	
	CONCERN (>=200 MSEC)	1	0		1	(100.0%)	0	
	MISSING	0	0		0		0	
	TOTAL	320	301	(94.1%)	19	(5.9%)	0	
SB 207499	NORMAL (<120 MSEC)	249	239	(96.0%)	10	(4.0%)	0	
	HIGH (120-199 MSEC)	29	9	(31.0%)	19	(65.5%)	1	(3.4%)
	CONCERN (>=200 MSEC)	1	1	(100.0%)	0		0	
	MISSING	0	0		0		0	
	TOTAL	279	249	(89.2%)	29	(10.4%)	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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: QRS INTERVAL TIME POINT: TOTAL ON-THERAPY

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL (<120 MSEC)	388	360	(92.8%)	28	(7.2%)	0	
	HIGH (120-199 MSEC)	22	9	(40.9%)	13	(59.1%)	0	
	CONCERN (>=200 MSEC)	1	0		1	(100.0%)	0	
	MISSING	0	0		0		0	
	TOTAL	411	369	(89.8%)	42	(10.2%)	0	
SB 207499	NORMAL (<120 MSEC)	343	320	(93.3%)	21	(6.1%)	2	(0.6%)
	HIGH (120-199 MSEC)	43	8	(18.6%)	33	(76.7%)	2	(4.7%)
	CONCERN (>=200 MSEC)	1	1	(100.0%)	0		0	
	MISSING	1	1	(100.0%)	0		0	
	TOTAL	388	330	(85.1%)	54	(13.9%)	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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: QRS INTERVAL TIME POINT: ENDPOINT

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL (<120 MSEC)	388	376	(96.9%)	12	(3.1%)	0	
	HIGH (120-199 MSEC)	22	12	(54.5%)	10	(45.5%)	0	
	CONCERN (>=200 MSEC)	1	0		1	(100.0%)	0	
	MISSING	0	0		0		0	
	TOTAL	411	388	(94.4%)	23	(5.6%)	0	
SB 207499	NORMAL (<120 MSEC)	343	328	(95.6%)	14	(4.1%)	1	(0.3%)
	HIGH (120-199 MSEC)	43	13	(30.2%)	29	(67.4%)	1	(2.3%)
	CONCERN (>=200 MSEC)	1	1	(100.0%)	0		0	
	MISSING	1	1	(100.0%)	0		0	
	TOTAL	388	343	(88.4%)	43	(11.1%)	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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: UNCORRECTED QT TIME POINT: VISIT 4/WEEK 2

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE NORMAL		DOUBLE BLIND PHASE CONCERN
PLACEBO	NORMAL(<500 MSEC)	2	2	(100.0%)	0
	CONCERN(>=500 MSEC)	0	0		0
	MISSING	0	0		0
	TOTAL	2	2	(100.0%)	0
SB 207499	NORMAL(<500 MSEC)	5	5	(100.0%)	0
	CONCERN(>=500 MSEC)	0	0		0
	MISSING	0	0		0
	TOTAL	5	5	(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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: UNCORRECTED QT TIME POINT: VISIT 5/WEEK 4

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: NORMAL		DOUBLE BLIND PHASE: CONCERN
PLACEBO	NORMAL(<500 MSEC)	1	1	(100.0%)	0
	CONCERN(>=500 MSEC)	0	0		0
	MISSING	0	0		0
	TOTAL	1	1	(100.0%)	0
SB 207499	NORMAL(<500 MSEC)	1	1	(100.0%)	0
	CONCERN(>=500 MSEC)	0	0		0
	MISSING	0	0		0
	TOTAL	1	1	(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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: UNCORRECTED QT TIME POINT: VISIT 6/WEEK 8

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE NORMAL		DOUBLE BLIND PHASE CONCERN
PLACEBO	NORMAL(<500 MSEC)	2	2	(100.0%)	0
	CONCERN(>=500 MSEC)	0	0		0
	MISSING	0	0		0
	TOTAL	2	2	(100.0%)	0
SB 207499	NORMAL(<500 MSEC)	9	9	(100.0%)	0
	CONCERN(>=500 MSEC)	0	0		0
	MISSING	0	0		0
	TOTAL	9	9	(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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: UNCORRECTED QT TIME POINT: VISIT 7/WEEK 12

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE NORMAL		CONCERN	
PLACEBO	NORMAL(<500 MSEC)	385	384	(99.7%)	1	(0.3%)
	CONCERN(>=500 MSEC)	0	0		0	
	MISSING	0	0		0	
	TOTAL	385	384	(99.7%)	1	(0.3%)
SB 207499	NORMAL(<500 MSEC)	351	349	(99.4%)	2	(0.6%)
	CONCERN(>=500 MSEC)	3	3	(100.0%)	0	
	MISSING	2	2	(100.0%)	0	
	TOTAL	356	354	(99.4%)	2	(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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: UNCORRECTED QT TIME POINT: VISIT 8/WEEK 20

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE NORMAL		DOUBLE BLIND PHASE CONCERN
PLACEBO	NORMAL(<500 MSEC)	1	1	(100.0%)	0
	CONCERN(>=500 MSEC)	0	0		0
	MISSING	0	0		0
	TOTAL	1	1	(100.0%)	0
SB 207499	NORMAL(<500 MSEC)	4	4	(100.0%)	0
	CONCERN(>=500 MSEC)	0	0		0
	MISSING	0	0		0
	TOTAL	4	4	(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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: UNCORRECTED QT TIME POINT: VISIT 9/WEEK 28

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE NORMAL		CONCERN	
PLACEBO	NORMAL(<500 MSEC)	361	361	(100.0%)	0	
	CONCERN(>=500 MSEC)	0	0		0	
	MISSING	0	0		0	
	TOTAL	361	361	(100.0%)	0	
SB 207499	NORMAL(<500 MSEC)	309	307	(99.4%)	2	(0.6%)
	CONCERN(>=500 MSEC)	3	3	(100.0%)	0	
	MISSING	2	2	(100.0%)	0	
	TOTAL	314	312	(99.4%)	2	(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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: UNCORRECTED QT TIME POINT: VISIT 10/WEEK 36

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: NORMAL		DOUBLE BLIND PHASE: CONCERN
PLACEBO	NORMAL(<500 MSEC)	3	3	(100.0%)	0
	CONCERN(>=500 MSEC)	0	0		0
	MISSING	0	0		0
	TOTAL	3	3	(100.0%)	0
SB 207499	NORMAL(<500 MSEC)	1	1	(100.0%)	0
	CONCERN(>=500 MSEC)	0	0		0
	MISSING	0	0		0
	TOTAL	1	1	(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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: UNCORRECTED QT TIME POINT: VISIT 11/WEEK 44

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE NORMAL		DOUBLE BLIND PHASE CONCERN
PLACEBO	NORMAL(<500 MSEC)	2	2	(100.0%)	0
	CONCERN(>=500 MSEC)	0	0		0
	MISSING	0	0		0
	TOTAL	2	2	(100.0%)	0
SB 207499	NORMAL(<500 MSEC)	1	1	(100.0%)	0
	CONCERN(>=500 MSEC)	0	0		0
	MISSING	0	0		0
	TOTAL	1	1	(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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: UNCORRECTED QT TIME POINT: VISIT 12/WEEK 52

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE NORMAL		CONCERN	
PLACEBO	NORMAL(<500 MSEC)	318	317	(99.7%)	1	(0.3%)
	CONCERN(>=500 MSEC)	0	0		0	
	MISSING	0	0		0	
	TOTAL	318	317	(99.7%)	1	(0.3%)
SB 207499	NORMAL(<500 MSEC)	273	272	(99.6%)	1	(0.4%)
	CONCERN(>=500 MSEC)	2	1	(50.0%)	1	(50.0%)
	MISSING	1	1	(100.0%)	0	
	TOTAL	276	274	(99.3%)	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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: UNCORRECTED QT TIME POINT: TOTAL ON-THERAPY

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE NORMAL		CONCERN	
PLACEBO	NORMAL(<500 MSEC)	411	410	(99.8%)	1	(0.2%)
	CONCERN(>=500 MSEC)	0	0		0	
	MISSING	0	0		0	
	TOTAL	411	410	(99.8%)	1	(0.2%)
SB 207499	NORMAL(<500 MSEC)	383	380	(99.2%)	3	(0.8%)
	CONCERN(>=500 MSEC)	3	2	(66.7%)	1	(33.3%)
	MISSING	2	2	(100.0%)	0	
	TOTAL	388	384	(99.0%)	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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: UNCORRECTED QT TIME POINT: ENDPOINT

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE NORMAL		CONCERN	
PLACEBO	NORMAL(<500 MSEC)	411	410	(99.8%)	1	(0.2%)
	CONCERN(>=500 MSEC)	0	0		0	
	MISSING	0	0		0	
	TOTAL	411	410	(99.8%)	1	(0.2%)
SB 207499	NORMAL(<500 MSEC)	383	382	(99.7%)	1	(0.3%)
	CONCERN(>=500 MSEC)	3	2	(66.7%)	1	(33.3%)
	MISSING	2	2	(100.0%)	0	
	TOTAL	388	386	(99.5%)	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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: CORRECTED QT (BAZETT METHOD) TIME POINT: VISIT 4/WEEK 2

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: NORMAL		HIGH		CONCERN
PLACEBO	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	0	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])	1	0		1	(100.0%)	0
	MISSING	0	0		0		0
	TOTAL	1	0		1	(100.0%)	0
SB 207499	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	4	4	(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
	MISSING	0	0		0		0
	TOTAL	5	4	(80.0%)	1	(20.0%)	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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: CORRECTED QT (BAZETT METHOD) TIME POINT: VISIT 5/WEEK 4

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: 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
	MISSING	0	0		0	0
	TOTAL	1	1	(100.0%)	0	0
SB 207499	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
	MISSING	0	0		0	0
	TOTAL	1	1	(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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: CORRECTED QT (BAZETT METHOD) TIME POINT: VISIT 6/WEEK 8

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: 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])	1	1	(100.0%)	0		0	
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	0	0		0		0	
	MISSING	0	0		0		0	
	TOTAL	2	2	(100.0%)	0		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])	0	0		0		0	
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	1	0		0		1	(100.0%)
	MISSING	0	0		0		0	
	TOTAL	9	8	(88.9%)	0		1	(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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: CORRECTED QT (BAZETT METHOD) TIME POINT: VISIT 7/WEEK 12

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	315	277	(87.9%)	24	(7.6%)	14	(4.4%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	32	14	(43.8%)	12	(37.5%)	6	(18.8%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	34	12	(35.3%)	8	(23.5%)	14	(41.2%)
	MISSING	0	0		0		0	
	TOTAL	381	303	(79.5%)	44	(11.5%)	34	(8.9%)
SB 207499	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	262	230	(87.8%)	19	(7.3%)	13	(5.0%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	47	28	(59.6%)	14	(29.8%)	5	(10.6%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	42	15	(35.7%)	13	(31.0%)	14	(33.3%)
	MISSING	2	2	(100.0%)	0		0	
	TOTAL	353	275	(77.9%)	46	(13.0%)	32	(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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: CORRECTED QT (BAZETT METHOD) TIME POINT: VISIT 8/WEEK 20

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: 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
	MISSING	0	0		0		0
	TOTAL	1	1	(100.0%)	0		0
SB 207499	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	4	3	(75.0%)	1	(25.0%)	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
	MISSING	0	0		0		0
	TOTAL	4	3	(75.0%)	1	(25.0%)	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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: CORRECTED QT (BAZETT METHOD) TIME POINT: VISIT 9/WEEK 28

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	297	247	(83.2%)	24	(8.1%)	26	(8.8%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	30	14	(46.7%)	8	(26.7%)	8	(26.7%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	31	15	(48.4%)	8	(25.8%)	8	(25.8%)
	MISSING	0	0		0		0	
	TOTAL	358	276	(77.1%)	40	(11.2%)	42	(11.7%)
SB 207499	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	231	203	(87.9%)	16	(6.9%)	12	(5.2%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	43	23	(53.5%)	13	(30.2%)	7	(16.3%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	36	12	(33.3%)	8	(22.2%)	16	(44.4%)
	MISSING	3	2	(66.7%)	1	(33.3%)	0	
	TOTAL	313	240	(76.7%)	38	(12.1%)	35	(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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: CORRECTED QT (BAZETT METHOD) TIME POINT: VISIT 10/WEEK 36

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: NORMAL		HIGH	CONCERN
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
	MISSING	0	0		0	0
	TOTAL	3	3	(100.0%)	0	0
SB 207499	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
	MISSING	0	0		0	0
	TOTAL	1	1	(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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: CORRECTED QT (BAZETT METHOD) TIME POINT: VISIT 11/WEEK 44

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: NORMAL		HIGH	CONCERN	
PLACEBO	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	2	1	(50.0%)	0	1	(50.0%)
	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	
	MISSING	0	0		0	0	
	TOTAL	2	1	(50.0%)	0	1	(50.0%)
SB 207499	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	
	MISSING	0	0		0	0	
	TOTAL	1	1	(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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: CORRECTED QT (BAZETT METHOD) TIME POINT: VISIT 12/WEEK 52

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	259	219	(84.6%)	25	(9.7%)	15	(5.8%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	28	14	(50.0%)	7	(25.0%)	7	(25.0%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	27	11	(40.7%)	7	(25.9%)	9	(33.3%)
	MISSING	0	0		0		0	
	TOTAL	314	244	(77.7%)	39	(12.4%)	31	(9.9%)
SB 207499	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	209	173	(82.8%)	22	(10.5%)	14	(6.7%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	35	22	(62.9%)	6	(17.1%)	7	(20.0%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	29	9	(31.0%)	5	(17.2%)	15	(51.7%)
	MISSING	1	1	(100.0%)	0		0	
	TOTAL	274	205	(74.8%)	33	(12.0%)	36	(13.1%)

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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: CORRECTED QT (BAZETT METHOD) TIME POINT: TOTAL ON-THERAPY

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	336	242	(72.0%)	44	(13.1%)	50	(14.9%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	33	10	(30.3%)	12	(36.4%)	11	(33.3%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	37	6	(16.2%)	7	(18.9%)	24	(64.9%)
	MISSING	0	0		0		0	
	TOTAL	406	258	(63.5%)	63	(15.5%)	85	(20.9%)
SB 207499	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	287	212	(73.9%)	42	(14.6%)	33	(11.5%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	52	18	(34.6%)	20	(38.5%)	14	(26.9%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	44	7	(15.9%)	7	(15.9%)	30	(68.2%)
	MISSING	3	2	(66.7%)	1	(33.3%)	0	
	TOTAL	386	239	(61.9%)	70	(18.1%)	77	(19.9%)

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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS

PROTOCOL 157

PARAMETER: CORRECTED QT (BAZETT METHOD) TIME POINT: ENDPOINT

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	336	282	(83.9%)	30	(8.9%)	24	(7.1%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	33	19	(57.6%)	7	(21.2%)	7	(21.2%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	37	14	(37.8%)	9	(24.3%)	14	(37.8%)
	MISSING	0	0		0		0	
	TOTAL	406	315	(77.6%)	46	(11.3%)	45	(11.1%)
SB 207499	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	287	242	(84.3%)	26	(9.1%)	19	(6.6%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	52	29	(55.8%)	14	(26.9%)	9	(17.3%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	44	14	(31.8%)	5	(11.4%)	25	(56.8%)
	MISSING	3	3	(100.0%)	0		0	
	TOTAL	386	288	(74.6%)	45	(11.7%)	53	(13.7%)

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; OTHER PARAMETERS TO BE APPLIED: SEE PROTOCOL; OTHER INTERVALS TO BE APPLIED: WEEK 2, 4, 8, 12, 20, 28, 36, 44, ENDPOINT
5. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE-BLIND PERIOD

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.19B

CHANGE FROM BASELINE IN QTC

PROTOCOL 157

PARAMETER: CORRECTED QT INTERVAL (BAZETT) - CHANGE FROM BASELINE TIME POINT: VISIT 4/WEEK 2

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: NORMAL (<30 MSEC)		HIGH (30-60 MSEC)	CONCERN (>60 MSEC)	
PLACEBO	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	0	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])	1	1	(100.0%)	0	0	
	MISSING	0	0		0	0	
	TOTAL	1	1	(100.0%)	0	0	
SB 207499	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	4	3	(75.0%)	0	1	(25.0%)
	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	
	MISSING	0	0		0	0	
	TOTAL	5	4	(80.0%)	0	1	(20.0%)

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
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY; OTHER INTERVALS TO BE APPLIED:WEEK2, 4, 8, 12, 20, 28, 36, 44, 52, ENDPOINT
4. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.19B

CHANGE FROM BASELINE IN QTC

PROTOCOL 157

PARAMETER: CORRECTED QT INTERVAL (BAZETT) - CHANGE FROM BASELINE TIME POINT: VISIT 5/WEEK 4

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: 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
	MISSING	0	0		0	0
	TOTAL	1	1	(100.0%)	0	0
SB 207499	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
	MISSING	0	0		0	0
	TOTAL	1	1	(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
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY; OTHER INTERVALS TO BE APPLIED:WEEK2, 4, 8, 12, 20, 28, 36, 44, 52, ENDPOINT
4. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.19B

CHANGE FROM BASELINE IN QTC

PROTOCOL 157

PARAMETER: CORRECTED QT INTERVAL (BAZETT) - CHANGE FROM BASELINE TIME POINT: VISIT 6/WEEK 8

			DOUBLE BLIND PHASE					
TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	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])	1	1	(100.0%)	0		0	
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	0	0		0		0	
	MISSING	0	0		0		0	
	TOTAL	2	2	(100.0%)	0		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])	0	0		0		0	
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	1	1	(100.0%)	0		0	
	MISSING	0	0		0		0	
	TOTAL	9	9	(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
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY; OTHER INTERVALS TO BE APPLIED:WEEK2, 4, 8, 12, 20, 28, 36, 44, 52, ENDPOINT
4. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.19B

CHANGE FROM BASELINE IN QTC

PROTOCOL 157

PARAMETER: CORRECTED QT INTERVAL (BAZETT) - CHANGE FROM BASELINE TIME POINT: VISIT 7/WEEK 12

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE NORMAL (<30 MSEC)		HIGH (30-60 MSEC)		CONCERN (>60 MSEC)	
PLACEBO	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	315	262	(83.2%)	33	(10.5%)	20	(6.3%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	32	31	(96.9%)	1	(3.1%)	0	
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	34	34	(100.0%)	0		0	
	MISSING	0	0		0		0	
	TOTAL	381	327	(85.8%)	34	(8.9%)	20	(5.2%)
SB 207499	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	262	209	(79.8%)	28	(10.7%)	25	(9.5%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	47	47	(100.0%)	0		0	
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	42	39	(92.9%)	2	(4.8%)	1	(2.4%)
	MISSING	2	2	(100.0%)	0		0	
	TOTAL	353	297	(84.1%)	30	(8.5%)	26	(7.4%)

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
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY; OTHER INTERVALS TO BE APPLIED:WEEK2, 4, 8, 12, 20, 28, 36, 44, 52, ENDPOINT
4. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.19B

CHANGE FROM BASELINE IN QTC

PROTOCOL 157

PARAMETER: CORRECTED QT INTERVAL (BAZETT) - CHANGE FROM BASELINE TIME POINT: VISIT 8/WEEK 20

			DOUBLE BLIND PHASE					
			NORMAL		HIGH		CONCERN	
TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	(<30 MSEC)		(30-60 MSEC)		(>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	
	MISSING	0	0		0		0	
	TOTAL	1	1	(100.0%)	0		0	
SB 207499	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	4	3	(75.0%)	0		1	(25.0%)
	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	
	MISSING	0	0		0		0	
	TOTAL	4	3	(75.0%)	0		1	(25.0%)

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
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY; OTHER INTERVALS TO BE APPLIED:WEEK2, 4, 8, 12, 20, 28, 36, 44, 52, ENDPOINT
4. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.19B

CHANGE FROM BASELINE IN QTC

PROTOCOL 157

PARAMETER: CORRECTED QT INTERVAL (BAZETT) - CHANGE FROM BASELINE TIME POINT: VISIT 9/WEEK 28

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: NORMAL (<30 MSEC)		HIGH (30-60 MSEC)		CONCERN (>60 MSEC)	
PLACEBO	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	297	225	(75.8%)	40	(13.5%)	32	(10.8%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	30	28	(93.3%)	1	(3.3%)	1	(3.3%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	31	30	(96.8%)	0		1	(3.2%)
	MISSING	0	0		0		0	
	TOTAL	358	283	(79.1%)	41	(11.5%)	34	(9.5%)
SB 207499	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	231	176	(76.2%)	38	(16.5%)	17	(7.4%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	43	41	(95.3%)	1	(2.3%)	1	(2.3%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	36	31	(86.1%)	2	(5.6%)	3	(8.3%)
	MISSING	3	3	(100.0%)	0		0	
	TOTAL	313	251	(80.2%)	41	(13.1%)	21	(6.7%)

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
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY; OTHER INTERVALS TO BE APPLIED:WEEK2, 4, 8, 12, 20, 28, 36, 44, 52, ENDPOINT
4. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.19B

CHANGE FROM BASELINE IN QTC

PROTOCOL 157

PARAMETER: CORRECTED QT INTERVAL (BAZETT) - CHANGE FROM BASELINE TIME POINT: VISIT 10/WEEK 36

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: 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
	MISSING	0	0		0	0
	TOTAL	3	3	(100.0%)	0	0
SB 207499	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
	MISSING	0	0		0	0
	TOTAL	1	1	(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
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY; OTHER INTERVALS TO BE APPLIED:WEEK2, 4, 8, 12, 20, 28, 36, 44, 52, ENDPOINT
4. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.19B

CHANGE FROM BASELINE IN QTC

PROTOCOL 157

PARAMETER: CORRECTED QT INTERVAL (BAZETT) - CHANGE FROM BASELINE TIME POINT: VISIT 11/WEEK 44

			DOUBLE BLIND PHASE					
TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	NORMAL (<30 MSEC)		HIGH (30-60 MSEC)		CONCERN (>60 MSEC)	
PLACEBO	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	2	1	(50.0%)	0		1	(50.0%)
	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	
	MISSING	0	0		0		0	
	TOTAL	2	1	(50.0%)	0		1	(50.0%)
SB 207499	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	1	0		1	(100.0%)	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	
	MISSING	0	0		0		0	
	TOTAL	1	0		1	(100.0%)	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
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY; OTHER INTERVALS TO BE APPLIED:WEEK2, 4, 8, 12, 20, 28, 36, 44, 52, ENDPOINT
4. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.19B

CHANGE FROM BASELINE IN QTC

PROTOCOL 157

PARAMETER: CORRECTED QT INTERVAL (BAZETT) - CHANGE FROM BASELINE TIME POINT: VISIT 12/WEEK 52

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: NORMAL (<30 MSEC)		HIGH (30-60 MSEC)		CONCERN (>60 MSEC)	
PLACEBO	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	259	197	(76.1%)	37	(14.3%)	25	(9.7%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	28	26	(92.9%)	1	(3.6%)	1	(3.6%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	27	27	(100.0%)	0		0	
	MISSING	0	0		0		0	
	TOTAL	314	250	(79.6%)	38	(12.1%)	26	(8.3%)
SB 207499	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	209	159	(76.1%)	31	(14.8%)	19	(9.1%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	35	31	(88.6%)	1	(2.9%)	3	(8.6%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	29	27	(93.1%)	1	(3.4%)	1	(3.4%)
	MISSING	1	1	(100.0%)	0		0	
	TOTAL	274	218	(79.6%)	33	(12.0%)	23	(8.4%)

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
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY; OTHER INTERVALS TO BE APPLIED:WEEK2, 4, 8, 12, 20, 28, 36, 44, 52, ENDPOINT
4. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.19B

CHANGE FROM BASELINE IN QTC

PROTOCOL 157

PARAMETER: CORRECTED QT INTERVAL (BAZETT) - CHANGE FROM BASELINE TIME POINT: TOTAL ON-THERAPY

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: NORMAL (<30 MSEC)		HIGH (30-60 MSEC)		CONCERN (>60 MSEC)	
PLACEBO	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	336	212	(63.1%)	69	(20.5%)	55	(16.4%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	33	28	(84.8%)	3	(9.1%)	2	(6.1%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	37	36	(97.3%)	0		1	(2.7%)
	MISSING	0	0		0		0	
	TOTAL	406	276	(68.0%)	72	(17.7%)	58	(14.3%)
SB 207499	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	287	178	(62.0%)	66	(23.0%)	43	(15.0%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	52	46	(88.5%)	2	(3.8%)	4	(7.7%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	44	36	(81.8%)	5	(11.4%)	3	(6.8%)
	MISSING	3	3	(100.0%)	0		0	
	TOTAL	386	263	(68.1%)	73	(18.9%)	50	(13.0%)

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
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY; OTHER INTERVALS TO BE APPLIED:WEEK2, 4, 8, 12, 20, 28, 36, 44, 52, ENDPOINT
4. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.19B

CHANGE FROM BASELINE IN QTC

PROTOCOL 157

PARAMETER: CORRECTED QT INTERVAL (BAZETT) - CHANGE FROM BASELINE TIME POINT: ENDPOINT

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: NORMAL (<30 MSEC)		HIGH (30-60 MSEC)		CONCERN (>60 MSEC)	
PLACEBO	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	336	256	(76.2%)	47	(14.0%)	33	(9.8%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	33	31	(93.9%)	1	(3.0%)	1	(3.0%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	37	37	(100.0%)	0		0	
	MISSING	0	0		0		0	
	TOTAL	406	324	(79.8%)	48	(11.8%)	34	(8.4%)
SB 207499	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	287	220	(76.7%)	42	(14.6%)	25	(8.7%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	52	48	(92.3%)	1	(1.9%)	3	(5.8%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	44	40	(90.9%)	2	(4.5%)	2	(4.5%)
	MISSING	3	3	(100.0%)	0		0	
	TOTAL	386	311	(80.6%)	45	(11.7%)	30	(7.8%)

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
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY; OTHER INTERVALS TO BE APPLIED:WEEK2, 4, 8, 12, 20, 28, 36, 44, 52, ENDPOINT
4. ON-THERAPY IS DEFINED AS ECG PERFORMED DURING 52-WEEK DOUBLE BLIND PERIOD

CONFIDENTIAL

SB 207499

TABLE 15.20

INCIDENCE OF NEW-ONSET ON-THERAPY ECG ABNORMALITIES BY TREATMENT GROUP

PROTOCOL 157

ECG ABNORMALITY		TREATMENT GROUP PLACEBO (N=411)	SB 207499 (N=387)
ATRIAL FIBRILLATION	NOT PRESENT PRE-THERAPY	404	379
	NEW ONSET	2 (0.5%)	6 (1.6%)
ATRIAL FLUTTER	NOT PRESENT PRE-THERAPY	410	387
	NEW ONSET	1 (0.2%)	3 (0.8%)
AV JUNCTIONAL TACHYCARDIA NOS	NOT PRESENT PRE-THERAPY	411	387
	NEW ONSET	1 (0.2%)	0 (0.0%)
EKG FINDINGS OF ISCHEMIA	NOT PRESENT PRE-THERAPY	407	383
	NEW ONSET	6 (1.5%)	2 (0.5%)
EKG NORMAL	NOT PRESENT PRE-THERAPY	110	144
	NEW ONSET	36 (32.7%)	59 (41.0%)
FIRST DEGREE AV BLOCK	NOT PRESENT PRE-THERAPY	401	381
	NEW ONSET	6 (1.5%)	6 (1.6%)
GALLOP RHYTHM	NOT PRESENT PRE-THERAPY	411	387
	NEW ONSET	1 (0.2%)	0 (0.0%)
IDIOJUNCTIONAL TACHYCARDIA	NOT PRESENT PRE-THERAPY	411	387
	NEW ONSET	1 (0.2%)	0 (0.0%)
INCOMPLETE BUNDLE BRANCH BLOCK	NOT PRESENT PRE-THERAPY	398	373
	NEW ONSET	3 (0.8%)	8 (2.1%)
INCREASED VENTRICULAR VOLTAGE NOS	NOT PRESENT PRE-THERAPY	411	387
	NEW ONSET	1 (0.2%)	0 (0.0%)
LEFT ANTERIOR HEMIBLOCK	NOT PRESENT PRE-THERAPY	394	372
	NEW ONSET	4 (1.0%)	2 (0.5%)
LEFT ATRIAL HYPERTROPHY (P MITRALE)	NOT PRESENT PRE-THERAPY	405	382
	NEW ONSET	7 (1.7%)	4 (1.0%)
LEFT AXIS DEVIATION EKG	NOT PRESENT PRE-THERAPY	389	363
	NEW ONSET	9 (2.3%)	11 (3.0%)
LEFT BUNDLE BRANCH BLOCK NOS	NOT PRESENT PRE-THERAPY	408	380
	NEW ONSET	4 (1.0%)	2 (0.5%)

1. EACH PATIENT COUNTED ONCE PER ABNORMALITY
2. PERCENTAGES FOR EACH ABNORMALITY ARE BASED ON NUMBER OF PATIENTS WITH SPECIFIC ABNORMALITY ABSENT AT BASELINE AND SCREENING

CONFIDENTIAL

SB 207499

TABLE 15.20

INCIDENCE OF NEW-ONSET ON-THERAPY ECG ABNORMALITIES BY TREATMENT GROUP

PROTOCOL 157

ECG ABNORMALITY		TREATMENT GROUP PLACEBO (N=411)	SB 207499 (N=387)
LEFT POSTERIOR HEMIBLOCK	NOT PRESENT PRE-THERAPY	409	386
	NEW ONSET	1 (0.2%)	0 (0.0%)
LEFT VENTRICULAR HYPERTROPHY	NOT PRESENT PRE-THERAPY	384	367
	NEW ONSET	3 (0.8%)	7 (1.9%)
LOW VENTRICULAR VOLTAGE NOS	NOT PRESENT PRE-THERAPY	408	385
	NEW ONSET	0 (0.0%)	1 (0.3%)
MISCELLANEOUS EKG FINDING NOS	NOT PRESENT PRE-THERAPY	411	387
	NEW ONSET	0 (0.0%)	1 (0.3%)
MULTIFOCAL ATRIAL TACHYCARDIA	NOT PRESENT PRE-THERAPY	411	387
	NEW ONSET	0 (0.0%)	1 (0.3%)
MYOCARDIAL INFARCTION ACUTE	NOT PRESENT PRE-THERAPY	410	387
	NEW ONSET	1 (0.2%)	1 (0.3%)
MYOCARDIAL INFARCTION ANTERIOR ACUTE	NOT PRESENT PRE-THERAPY	410	387
	NEW ONSET	1 (0.2%)	0 (0.0%)
MYOCARDIAL INFARCTION INFERIOR OLD	NOT PRESENT PRE-THERAPY	408	377
	NEW ONSET	4 (1.0%)	3 (0.8%)
MYOCARDIAL INFARCTION OLD	NOT PRESENT PRE-THERAPY	400	371
	NEW ONSET	3 (0.8%)	1 (0.3%)
MYOCARDIAL INFARCTION SEPTAL ACUTE	NOT PRESENT PRE-THERAPY	411	387
	NEW ONSET	1 (0.2%)	0 (0.0%)
MYOCARDIAL INFARCTION SEPTAL OLD	NOT PRESENT PRE-THERAPY	410	383
	NEW ONSET	1 (0.2%)	2 (0.5%)
MYOCARDIAL ISCHEMIA ANTERIOR	NOT PRESENT PRE-THERAPY	411	387
	NEW ONSET	1 (0.2%)	1 (0.3%)
MYOCARDIAL ISCHEMIA INFERIOR	NOT PRESENT PRE-THERAPY	410	384
	NEW ONSET	7 (1.7%)	2 (0.5%)
MYOCARDIAL ISCHEMIA LATERAL	NOT PRESENT PRE-THERAPY	410	384
	NEW ONSET	7 (1.7%)	1 (0.3%)

1. EACH PATIENT COUNTED ONCE PER ABNORMALITY
2. PERCENTAGES FOR EACH ABNORMALITY ARE BASED ON NUMBER OF PATIENTS WITH SPECIFIC ABNORMALITY ABSENT AT BASELINE AND SCREENING

CONFIDENTIAL

GM2004/00073/00
SB-207499/157

SB 207499

TABLE 15.20

INCIDENCE OF NEW-ONSET ON-THERAPY ECG ABNORMALITIES BY TREATMENT GROUP

PROTOCOL 157

ECG ABNORMALITY		TREATMENT GROUP PLACEBO (N=411)	SB 207499 (N=387)
MYOCARDIAL ISCHEMIA POSTERIOR	NOT PRESENT PRE-THERAPY	410	387
	NEW ONSET	0 (0.0%)	1 (0.3%)
MYOCARDIAL ISCHEMIA SEPTAL	NOT PRESENT PRE-THERAPY	411	386
	NEW ONSET	1 (0.2%)	0 (0.0%)
PAROXYSMAL ATRIAL TACHYCARDIA (PAT)	NOT PRESENT PRE-THERAPY	410	387
	NEW ONSET	1 (0.2%)	0 (0.0%)
POOR R-WAVE PROGRESSION	NOT PRESENT PRE-THERAPY	405	383
	NEW ONSET	4 (1.0%)	1 (0.3%)
PREMATURE ATRIAL CONTRACTIONS NOS	NOT PRESENT PRE-THERAPY	405	374
	NEW ONSET	10 (2.5%)	12 (3.2%)
PREMATURE VENTRICULAR CONTRACTIONS NOS	NOT PRESENT PRE-THERAPY	405	376
	NEW ONSET	10 (2.5%)	5 (1.3%)
PVCS MULTIFOCAL	NOT PRESENT PRE-THERAPY	410	387
	NEW ONSET	1 (0.2%)	1 (0.3%)
PVCS UNIFOCAL	NOT PRESENT PRE-THERAPY	410	383
	NEW ONSET	4 (1.0%)	8 (2.1%)
Q-T INTERVAL INCREASED	NOT PRESENT PRE-THERAPY	405	380
	NEW ONSET	1 (0.2%)	1 (0.3%)
Q-T INTERVAL NOS	NOT PRESENT PRE-THERAPY	410	385
	NEW ONSET	1 (0.2%)	0 (0.0%)
Q-WAVE > . SECONDS	NOT PRESENT PRE-THERAPY	410	386
	NEW ONSET	1 (0.2%)	0 (0.0%)
RIGHT ATRIAL HYPERTROPHY (P PULMONALE)	NOT PRESENT PRE-THERAPY	399	376
	NEW ONSET	7 (1.8%)	5 (1.3%)
RIGHT AXIS DEVIATION EKG	NOT PRESENT PRE-THERAPY	401	381
	NEW ONSET	5 (1.2%)	5 (1.3%)
RIGHT BUNDLE BRANCH BLOCK	NOT PRESENT PRE-THERAPY	389	349
	NEW ONSET	5 (1.3%)	7 (2.0%)

1. EACH PATIENT COUNTED ONCE PER ABNORMALITY
2. PERCENTAGES FOR EACH ABNORMALITY ARE BASED ON NUMBER OF PATIENTS WITH SPECIFIC ABNORMALITY ABSENT AT BASELINE AND SCREENING

CONFIDENTIAL

SB 207499

TABLE 15.20

INCIDENCE OF NEW-ONSET ON-THERAPY ECG ABNORMALITIES BY TREATMENT GROUP

PROTOCOL 157

ECG ABNORMALITY		TREATMENT GROUP PLACEBO (N=411)	SB 207499 (N=387)
RIGHT VENTRICULAR HYPERTROPHY	NOT PRESENT PRE-THERAPY	404	381
	NEW ONSET	1 (0.2%)	4 (1.0%)
S-T CHANGES NONSPECIFIC	NOT PRESENT PRE-THERAPY	383	371
	NEW ONSET	15 (3.9%)	13 (3.5%)
S-T CHANGES SEGMENT ELEVATION	NOT PRESENT PRE-THERAPY	410	385
	NEW ONSET	3 (0.7%)	1 (0.3%)
S-T CHANGES STRAIN	NOT PRESENT PRE-THERAPY	411	387
	NEW ONSET	0 (0.0%)	1 (0.3%)
S-T SEGMENT DEPRESSION	NOT PRESENT PRE-THERAPY	405	384
	NEW ONSET	1 (0.2%)	0 (0.0%)
SINUS ARRHYTHMIA	NOT PRESENT PRE-THERAPY	400	377
	NEW ONSET	4 (1.0%)	8 (2.1%)
SINUS BRADYCARDIA	NOT PRESENT PRE-THERAPY	390	368
	NEW ONSET	9 (2.3%)	9 (2.4%)
SINUS TACHYCARDIA	NOT PRESENT PRE-THERAPY	395	368
	NEW ONSET	22 (5.6%)	15 (4.1%)
T-WAVE FLAT	NOT PRESENT PRE-THERAPY	400	378
	NEW ONSET	7 (1.8%)	8 (2.1%)
T-WAVE INVERSION	NOT PRESENT PRE-THERAPY	406	379
	NEW ONSET	5 (1.2%)	0 (0.0%)
T-WAVE PEAKED	NOT PRESENT PRE-THERAPY	411	386
	NEW ONSET	0 (0.0%)	1 (0.3%)
TACHYCARDIA NOS	NOT PRESENT PRE-THERAPY	409	385
	NEW ONSET	0 (0.0%)	2 (0.5%)
TACHYCARDIA SUPRAVENTRICULAR NOS	NOT PRESENT PRE-THERAPY	411	386
	NEW ONSET	1 (0.2%)	1 (0.3%)
U WAVE	NOT PRESENT PRE-THERAPY	411	387
	NEW ONSET	0 (0.0%)	2 (0.5%)

1. EACH PATIENT COUNTED ONCE PER ABNORMALITY
2. PERCENTAGES FOR EACH ABNORMALITY ARE BASED ON NUMBER OF PATIENTS WITH SPECIFIC ABNORMALITY ABSENT AT BASELINE AND SCREENING

CONFIDENTIAL

SB 207499

TABLE 15.20

INCIDENCE OF NEW-ONSET ON-THERAPY ECG ABNORMALITIES BY TREATMENT GROUP

PROTOCOL 157

ECG ABNORMALITY		TREATMENT GROUP PLACEBO (N=411)	SB 207499 (N=387)
VENTRICULAR COUPLETS	NOT PRESENT PRE-THERAPY	410	387
	NEW ONSET	1 (0.2%)	1 (0.3%)
WANDERING ATRIAL PACEMAKER	NOT PRESENT PRE-THERAPY	411	386
	NEW ONSET	2 (0.5%)	1 (0.3%)

1. EACH PATIENT COUNTED ONCE PER ABNORMALITY
2. PERCENTAGES FOR EACH ABNORMALITY ARE BASED ON NUMBER OF PATIENTS WITH SPECIFIC ABNORMALITY ABSENT AT BASELINE AND SCREENING

CONFIDENTIAL

This section contained patient narratives which are textual descriptions of medical history, treatment and outcome for individual patients who experienced a clinically important adverse event including serious adverse events during the trial. They have been excluded to protect patient privacy. This data may be made available subject to an approved research proposal and a determination of the ability to provide information from the specific narratives whilst protecting the patient's privacy. For further information please see the Patient Level Data section of the ***GSK Clinical Study Register****.*

18. Health Outcomes Data Source Tables

Page

TABLE 18.2 SUMMARY OF UTILIZATION-FREE SURVIVAL AND TOTAL NUMBER OF UTILIZATIONS BY TYPE OF UTILIZATION AND TREATMENT GROUP 1400

TABLE 18.3 RATES OF RESOURCE UTILIZATION PER 10,000 TREATMENT EXPOSURE DAYS BY TREATMENT GROUP - ITT 1401

TABLE 18.4 SUMMARY OF POISSON REGRESSION ON PROGNOSTIC FACTORS FOR UTILIZATION RATES BY TYPE - ITT 1402

TABLE 18.5 SUMMARY STATISTICS FOR PERCENT OF TIME RESOUCE UTILIZATION BY TYPE AND TREATMENT GROUP - ITT 1403

TABLE 18.12 NUMBERS AND PERCENT OF PATIENTS BY DAYS IN HOSPITAL AND TREATMENT GROUP - ITT 1404

TABLE 18.13 NUMBERS AND PERCENT OF PATIENTS BY DAYS IN ICU AND TREATMENT GROUP - ITT 1405

SB 207499

TABLE 18.2

SUMMARY OF UTILIZATION-FREE SURVIVAL AND TOTAL NUMBER OF UTILIZATIONS BY TYPE OF UTILIZATION AND TREATMENT GROUP

PROTOCOL 157

				UTILIZATION-FREE SURVIVAL AT 52 WEEKS		
UTILIZATION TYPE	TREATMENT GROUP	PATIENTS AT-RISK	PATIENTS UTILIZATION-FREE	PERCENT OF PATIENTS UTILIZATION-FREE	95% CI	P-VALUE
PHYSICIAN VISITS	PLACEBO	437	328	71.7	(67.1, 76.3)	.
	SB 207499	442	329	67.7	(62.7, 72.7)	0.202
ER/URGENT CARE	PLACEBO	437	426	96.9	(95.1, 98.7)	.
	SB 207499	442	427	95.4	(93.0, 97.7)	0.275
HOSPITALIZATION	PLACEBO	437	419	95.1	(92.9, 97.3)	.
	SB 207499	442	426	95.2	(92.9, 97.5)	0.999
ICU	PLACEBO	437	436	99.7	(99.2, 100.0)	.
	SB 207499	442	441	99.7	(99.1, 100.0)	0.929
ALL UTILIZATIONS	PLACEBO	437	320	69.7	(65.1, 74.4)	.
	SB 207499	442	325	66.6	(61.6, 71.6)	0.309

1. UTILIZATION-FREE SURVIVAL IS ESTIMATED USING KAPLAN-MEIER ESTIMATES OF TIME TO FIRST UTILIZATION
2. P-VALUE IS BASED ON LOG-RANK TEST

CONFIDENTIAL

SB 207499

TABLE 18.3

RATES OF RESOURCE UTILIZATION PER 10,000 TREATMENT EXPOSURE DAYS BY TREATMENT GROUP - ITT
PROTOCOL 157

		PLACEBO	SB 207499
Number of Patients		437	442
Total Treatment Exposure (Days)		135236	121657
Mean Treatment Exposure (Days)		309.46	275.24
Physician Visits	Events	237	219
	Event Rate	17.52	18.00
ER/Urgent Care	Events	12	23
	Event Rate	0.89	1.89
Hospitalizations	Events	19	20
	Event Rate	1.40	1.64
	Days of Utilization	581	116
	Utilization Rate	42.96	9.54
ICU	Events	1	1
	Event Rate	0.07	0.08
	Days of Utilization	3	3
	Utilization Rate	0.22	0.25
All Utilizations	Events	269	263
	Event Rate	19.89	21.62

1. EVENT RATE = 10,000 X (NUMBER OF EVENTS) / (TOTAL TREATMENT EXPOSURE)
2. UTILIZATION RATE = 10,000 X (DAYS OF UTILIZATION) / (TOTAL TREATMENT EXPOSURE)

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

SB 207499

TABLE 18.4

SUMMARY OF POISSON REGRESSION ON PROGNOSTIC FACTORS FOR UTILIZATION RATES BY TYPE - ITT
PROTOCOL 157

UTILIZATION TYPE	FACTOR	INCIDENCE DENSITY RATIO	95% CI	P-VALUE
PHYS. VISIT	% PREDICTED FEV	0.99	(0.98, 1.00)	0.100
	AGE	1.02	(1.00, 1.04)	0.052
	GENDER	1.35	(0.99, 1.85)	0.059
	SMOKING STATUS	1.14	(0.82, 1.59)	0.429
	TREATMENT	1.01	(0.75, 1.37)	0.935
ER/URGENT CARE	% PREDICTED FEV	0.99	(0.95, 1.03)	0.615
	AGE	1.05	(1.00, 1.10)	0.038
	GENDER	1.17	(0.42, 3.25)	0.768
	SMOKING STATUS	1.12	(0.44, 2.84)	0.808
	TREATMENT	1.81	(0.74, 4.42)	0.193
HOSPITALIZATION	% PREDICTED FEV	0.97	(0.94, 1.00)	0.085
	AGE	1.05	(0.99, 1.11)	0.076
	GENDER	1.06	(0.49, 2.29)	0.891
	SMOKING STATUS	0.84	(0.37, 1.87)	0.663
	TREATMENT	0.95	(0.45, 2.00)	0.897
ALL UTILIZATION	% PREDICTED FEV	0.99	(0.97, 1.00)	0.075
	AGE	1.02	(1.00, 1.04)	0.016
	GENDER	1.32	(0.96, 1.82)	0.088
	SMOKING STATUS	1.11	(0.79, 1.56)	0.547
	TREATMENT	1.05	(0.77, 1.43)	0.777

1. RELATIVE RATE IS PER PATIENT MONTH OF FOLLOW UP.

CONFIDENTIAL

SB 207499

TABLE 18.5

SUMMARY STATISTICS FOR PERCENT OF TIME RESOUCE UTILIZATION BY TYPE AND TREATMENT GROUP - ITT
PROTOCOL 157

			CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
Type	Treatment Group	N	MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
Hospitalization	PLACEBO	19	30.58	13.59	3.04	58.12	.	.	.	.
	SB 207499	20	5.80	13.25	-21.0	32.64	-24.8	-63.2	13.67	0.200
ICU Admission	PLACEBO	1	3.00	0.00	.	.	.	.	.	.
	SB 207499	1	3.00	0.00	.	.	0.00	.	.	.

1. ONLY PATIENTS WITH HOSPITALIZATION ARE INCLUDED IN THE ANALYSIS

CONFIDENTIAL

SB 207499

TABLE 18.12

NUMBERS AND PERCENT OF PATIENTS BY DAYS IN HOSPITAL AND TREATMENT GROUP - ITT
PROTOCOL 157

Treatment Group	N	Mean	Days In Hospital 0	1 - 2	3 - 5	6 - 10	11 - 20	> 20
PLACEBO	437	1.3295	419 (95.9)	0 (0.0)	3 (0.7)	9 (2.1)	4 (0.9)	2 (0.5)
SB 207499	442	0.2624	426 (96.4)	2 (0.5)	4 (0.9)	7 (1.6)	3 (0.7)	0 (0.0)

CONFIDENTIAL

SB 207499

TABLE 18.13

NUMBERS AND PERCENT OF PATIENTS BY DAYS IN ICU AND TREATMENT GROUP - ITT
PROTOCOL 157

Treatment Group	N	Mean	Days In ICU 0	1 - 2	3 - 5	6 - 10	11 - 20	> 20
PLACEBO	437	0.0069	436 (99.8)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
SB 207499	442	0.0068	441 (99.8)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)

CONFIDENTIAL
GM2004/00073/00
SB-207499/157

Figure 19.27
Mean (SEM) Change from Baseline in Domicilliary Breathlessness
ITT
Protocol 157

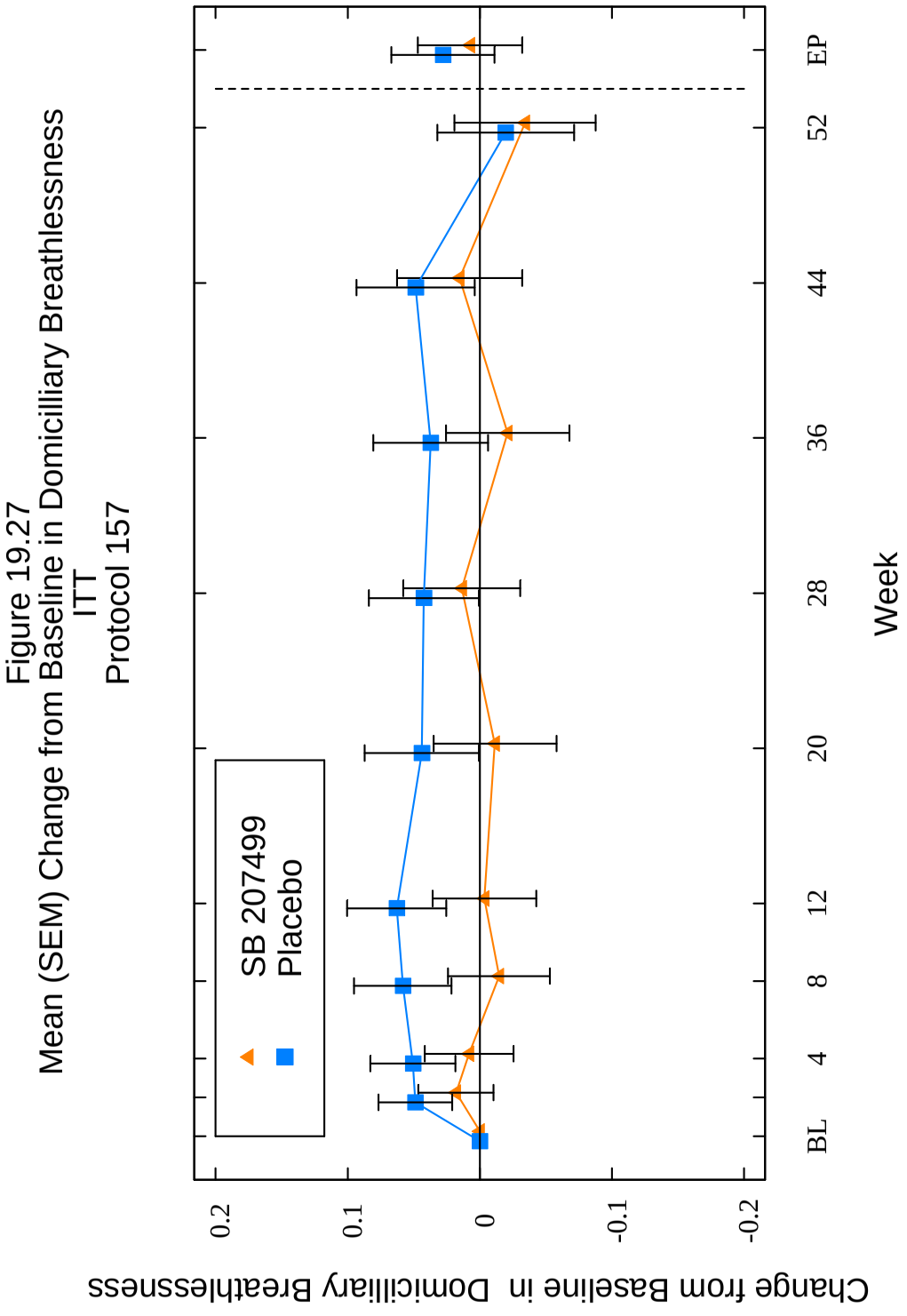


Figure 19.18
Cumulative Incidence of Vomiting - ITT
By Time of Initial Onset and Treatment Group
Protocol 157

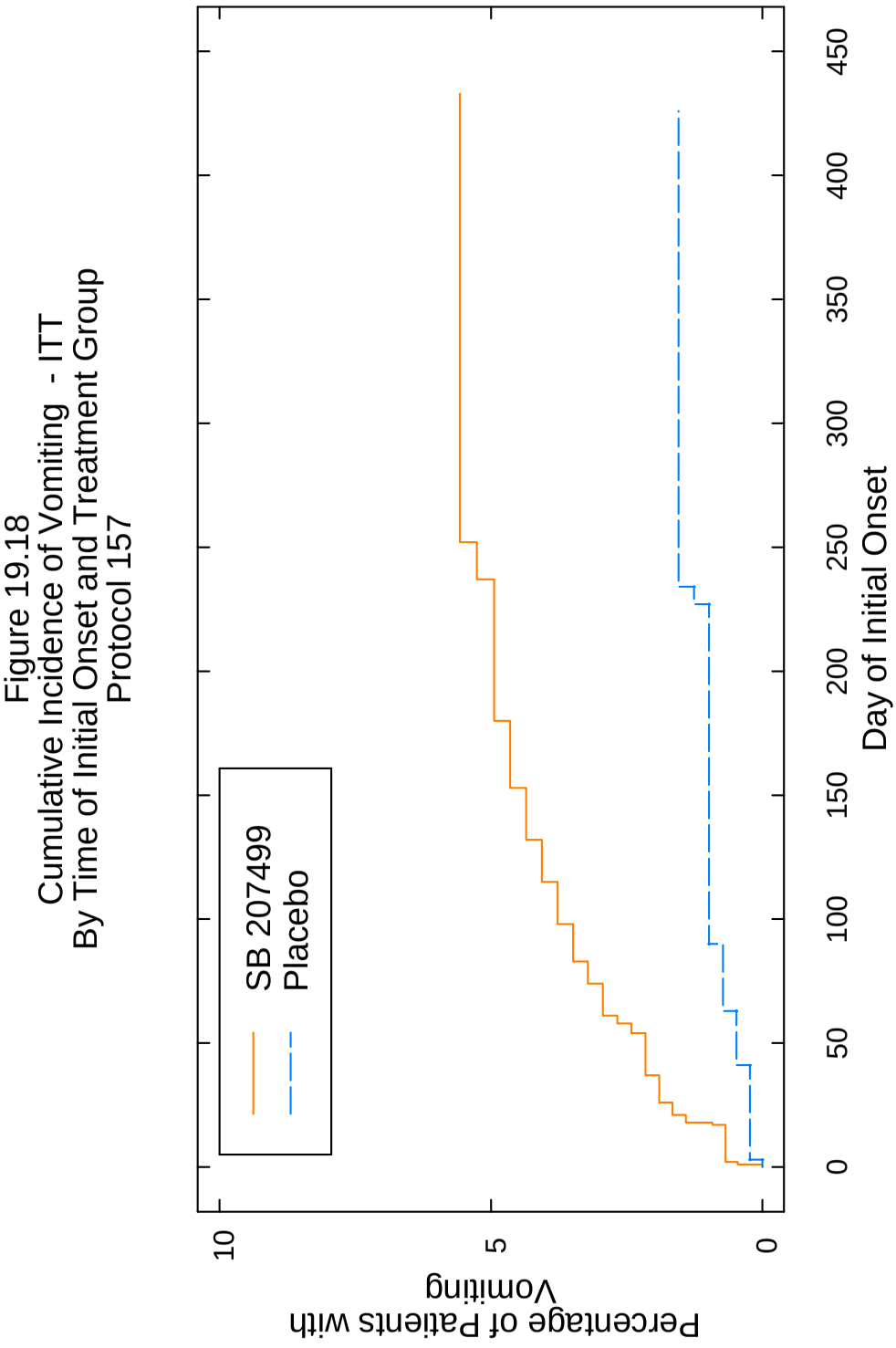


Figure 19.1D
Mean (SEM) Change from Baseline in Pre-BD FEV1(L)
ITT Withdrawals Imputed With Worst Scores
Protocol 157

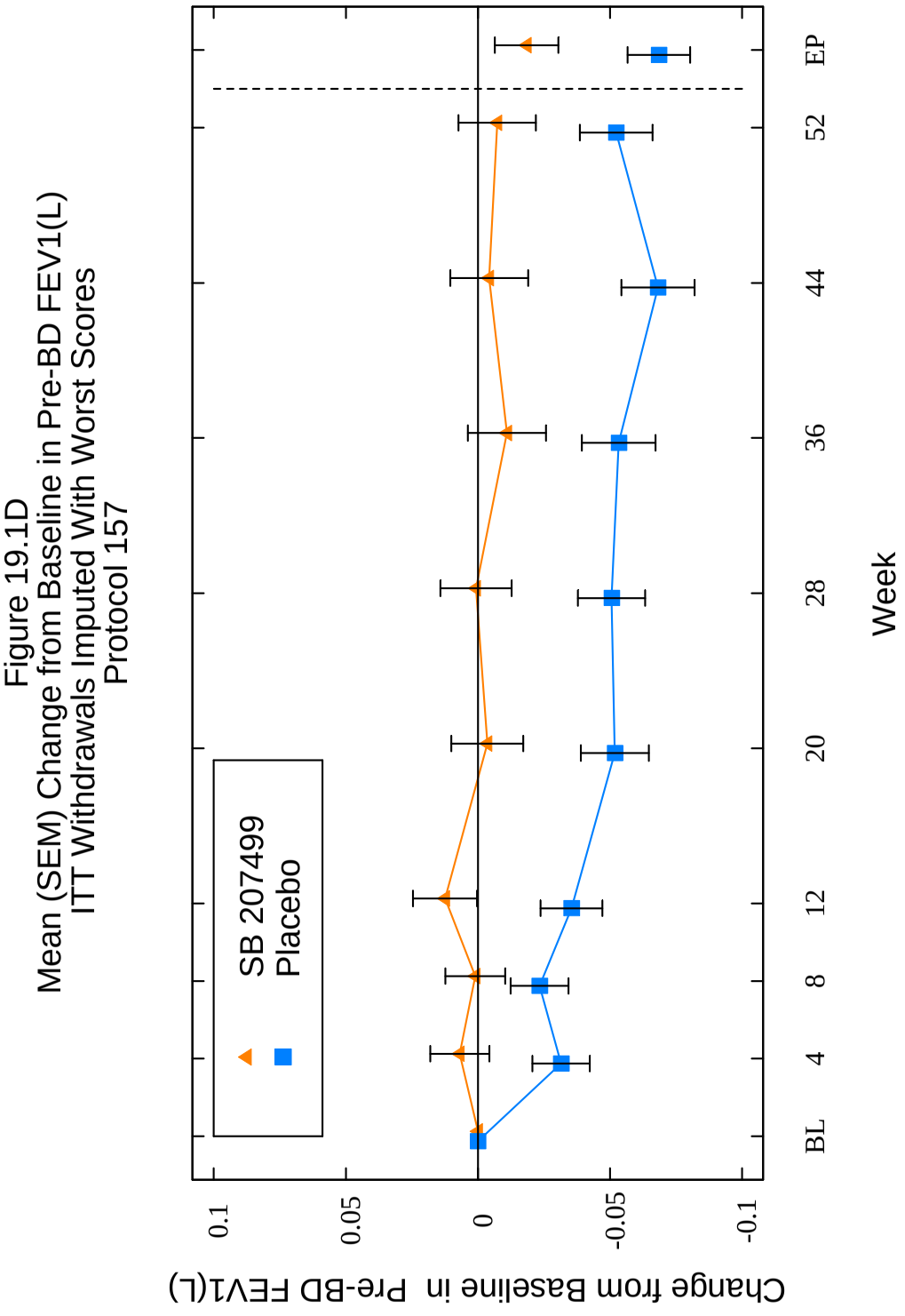


Figure 19.23
Mean (SEM) Change from Baseline in SGRQ Symptoms Score
ITT
Protocol 157

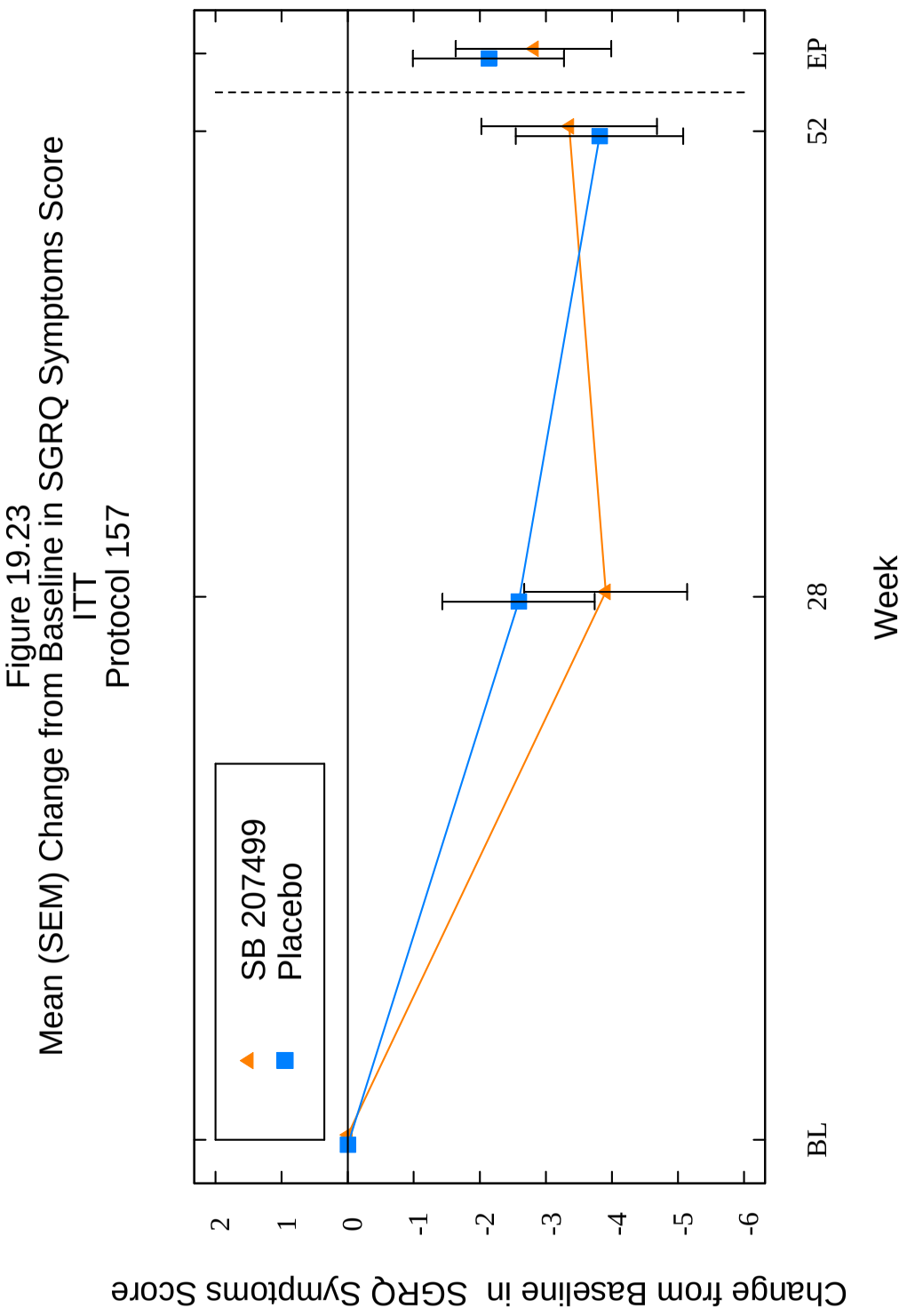


Figure 19.7L

Mean (95% CI) Rate of Exacerbations Per Patient Year - ITT

Protocol 157

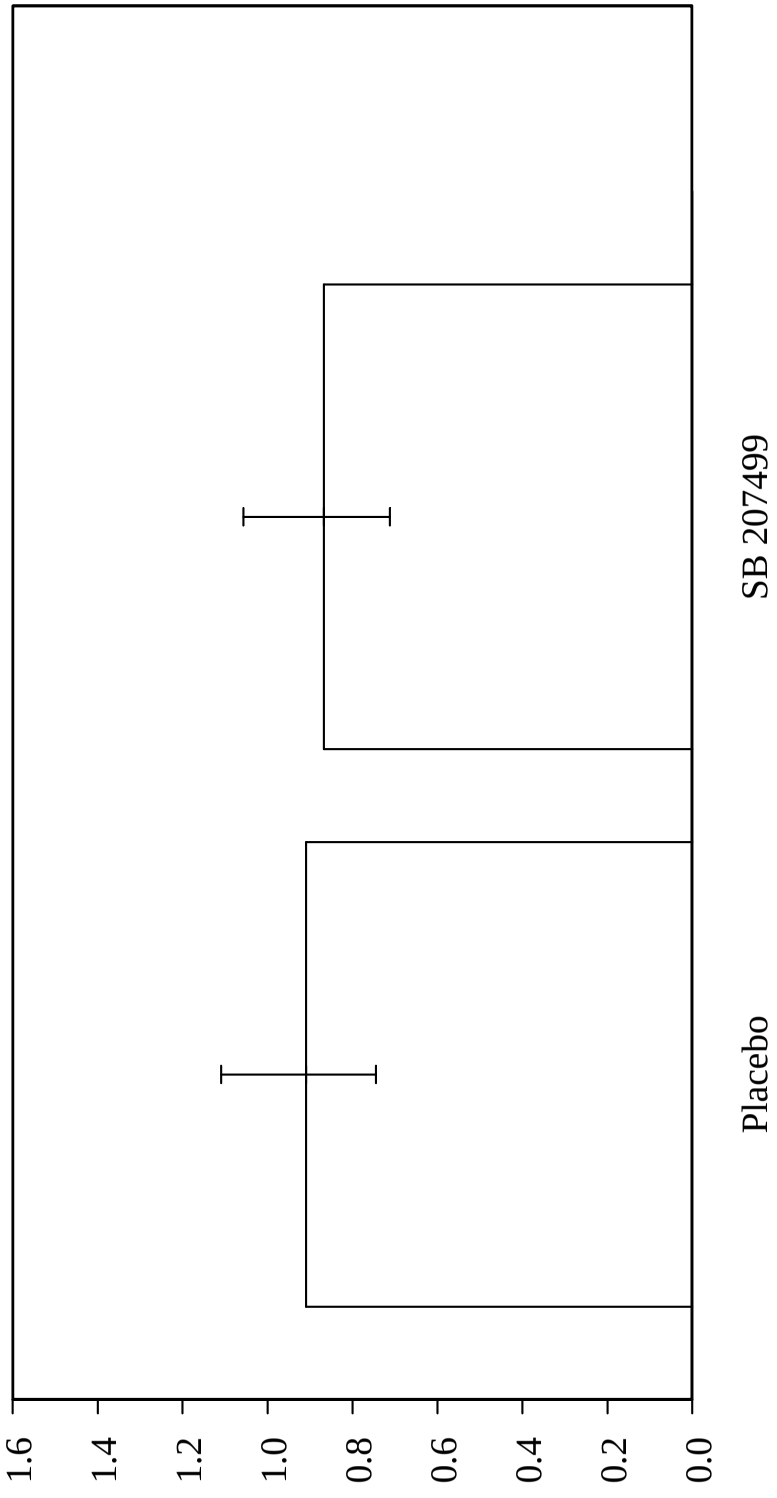


Figure 19.15
Cumulative Incidence of Nausea - ITT
By Time of Initial Onset and Treatment Group
Protocol 157

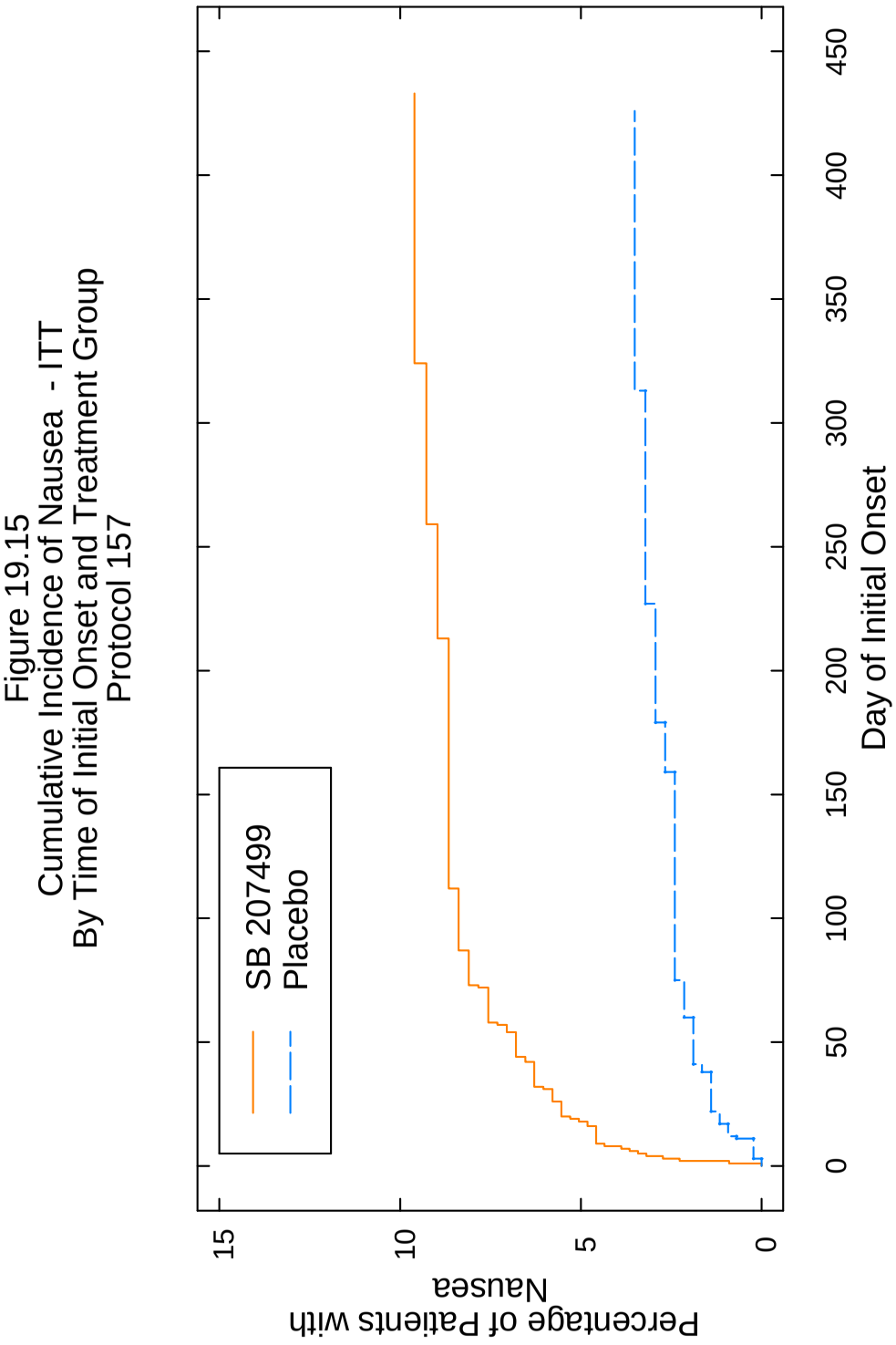


Figure 19.2J
Cumulative Incidence of Change From Baseline Total SGRQ at ITT Endpoint
By Treatment Group - ITT Completers
Protocol 157

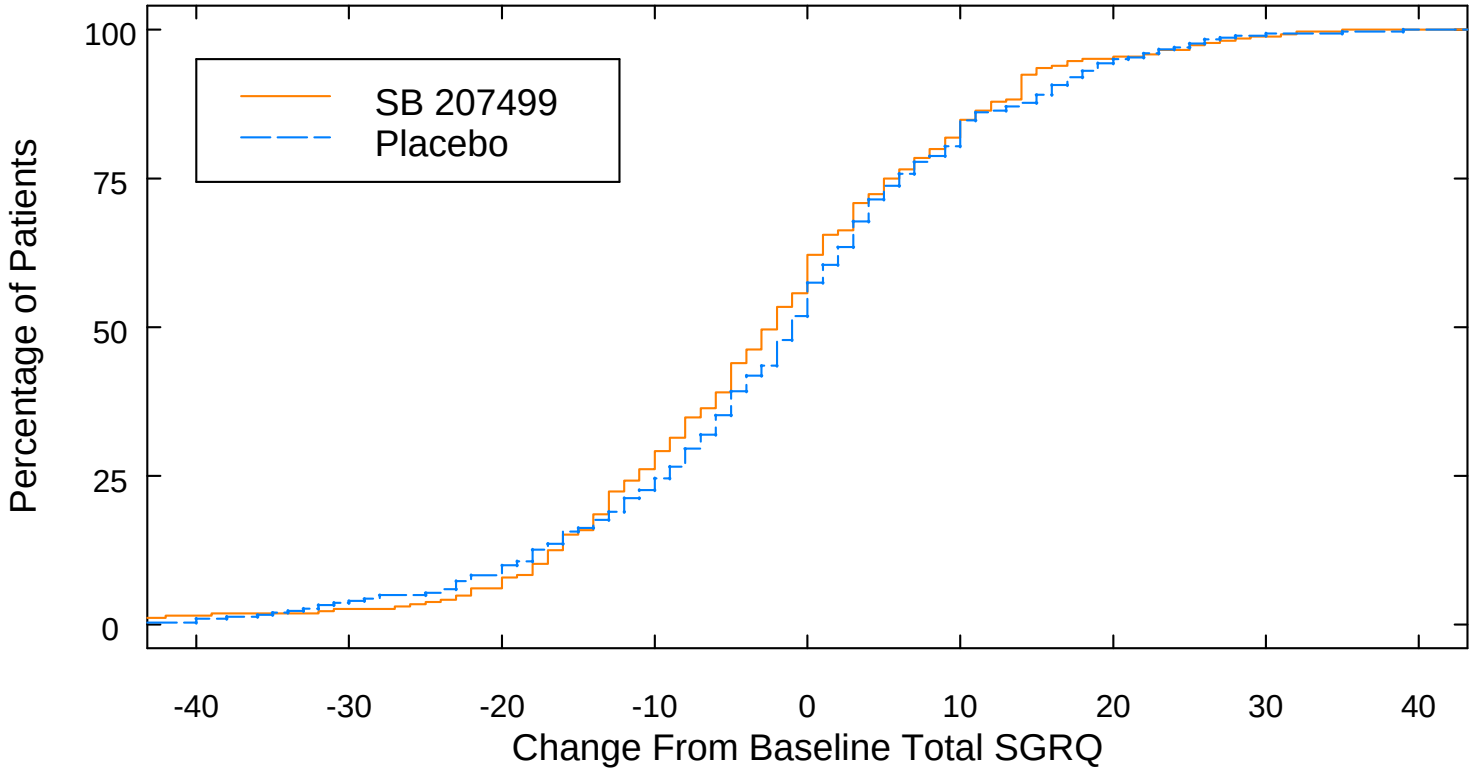


Figure 19.1I
Cumulative Incidence of Change From Baseline FEV1 (L) at ITT Endpoint
By Treatment Group - ITT
Protocol 157

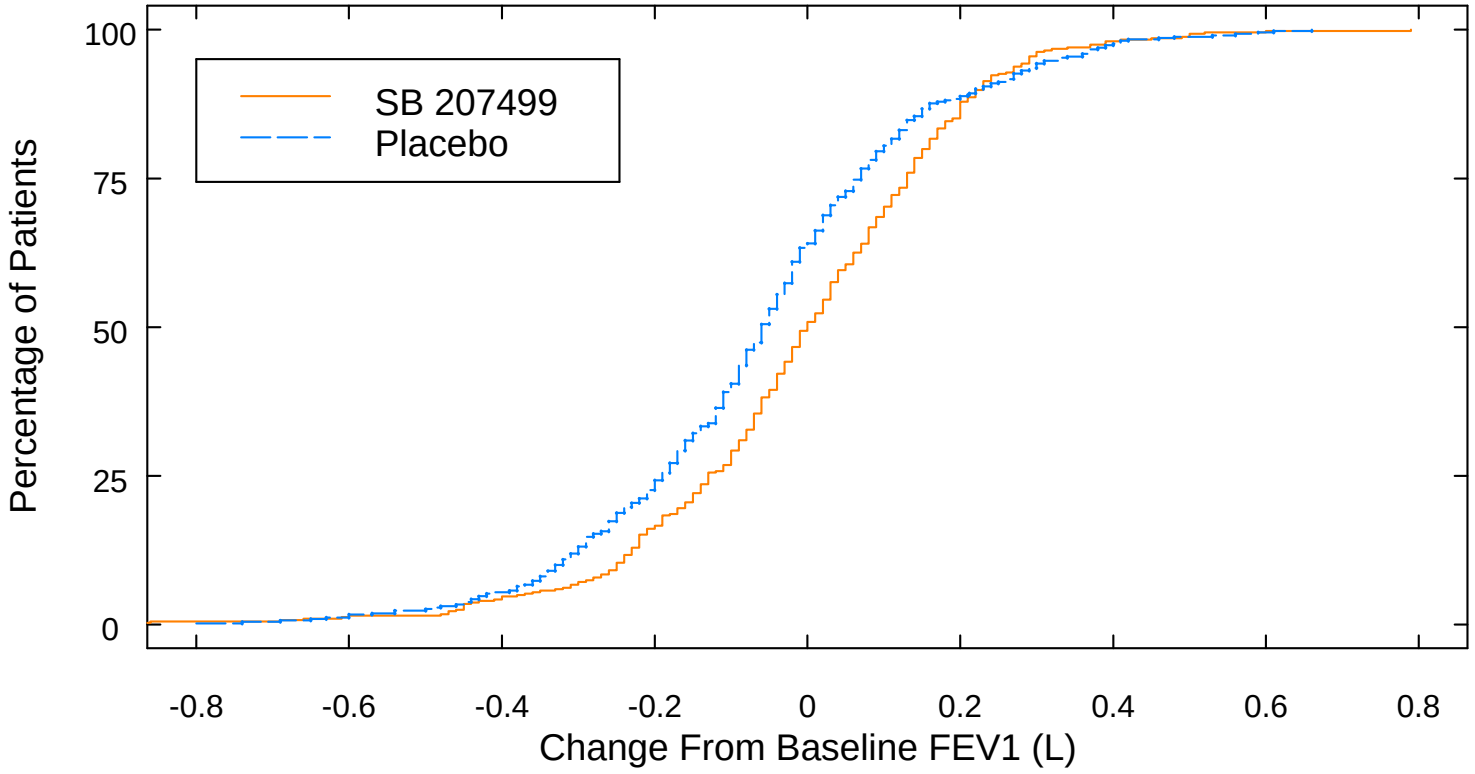


Figure 19.19
Cumulative Incidence of GI AEs of Concern - ITT
By Time of Initial Onset and Treatment Group
Protocol 157

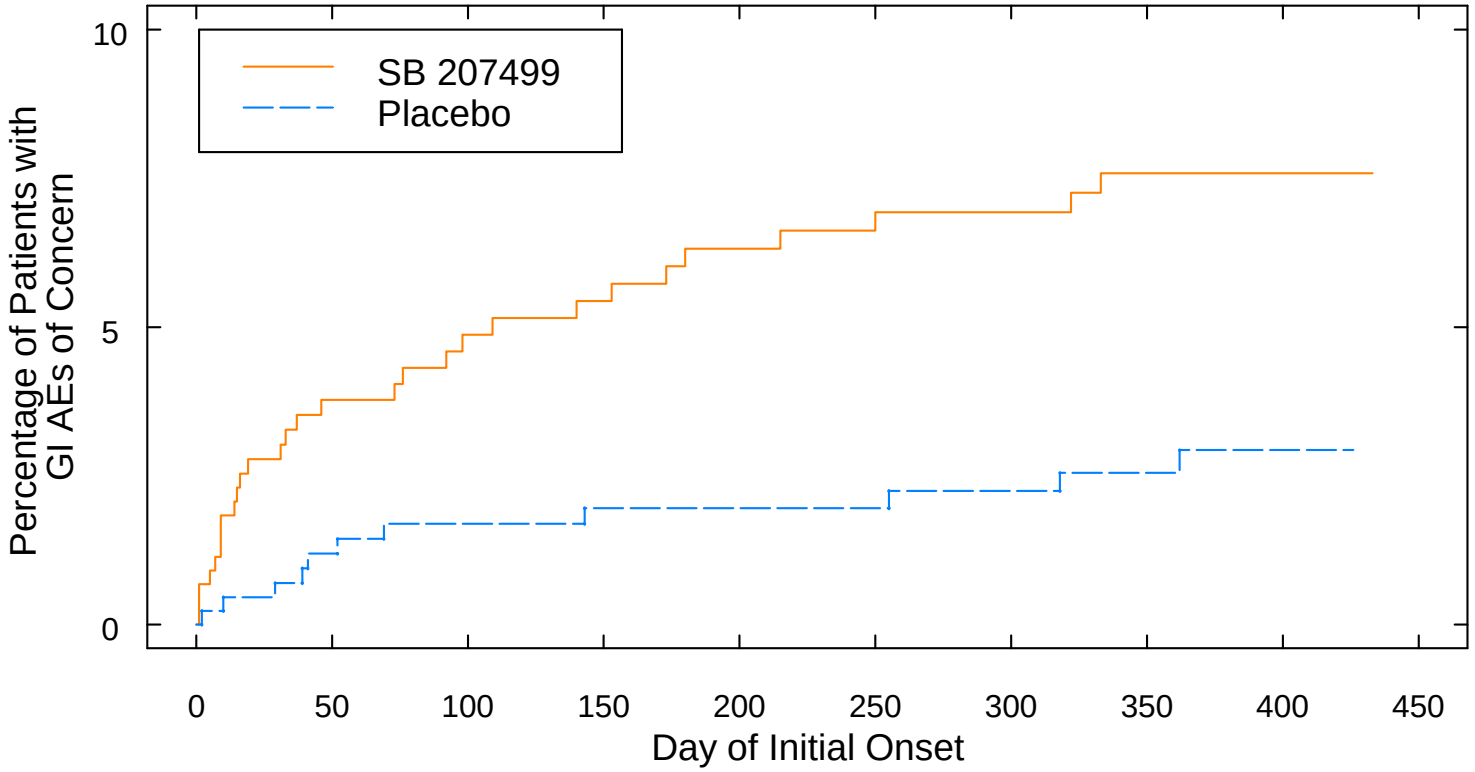


Figure 19.2A
Mean (SEM) Change from Baseline in SGRQ Total Score
ITT
Protocol 157

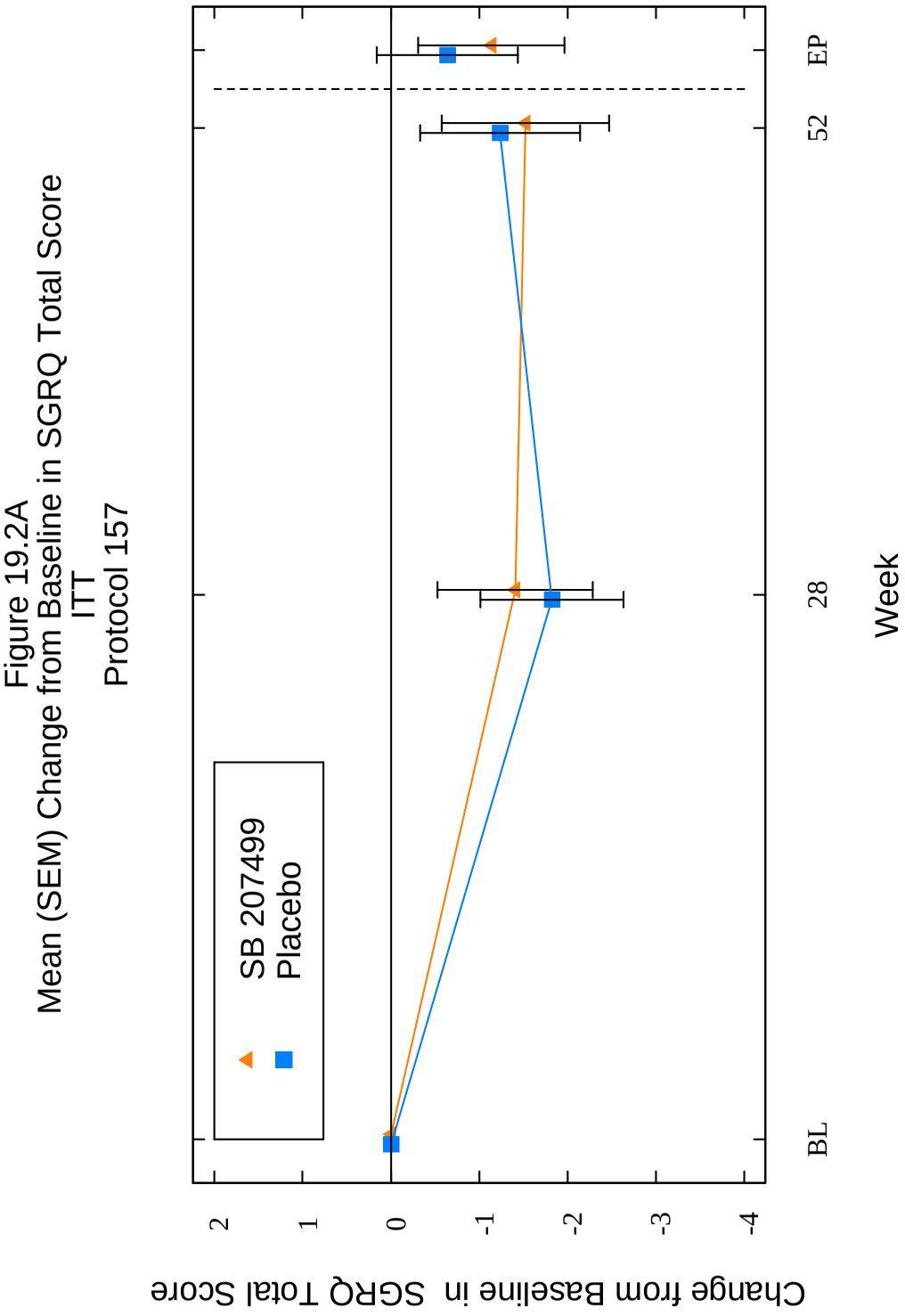


Figure 19A.1F

Mean (SEM) Change from Baseline in Pre-BD FEV1 (L) Averaged Over 52 Weeks-PP

Protocol 157

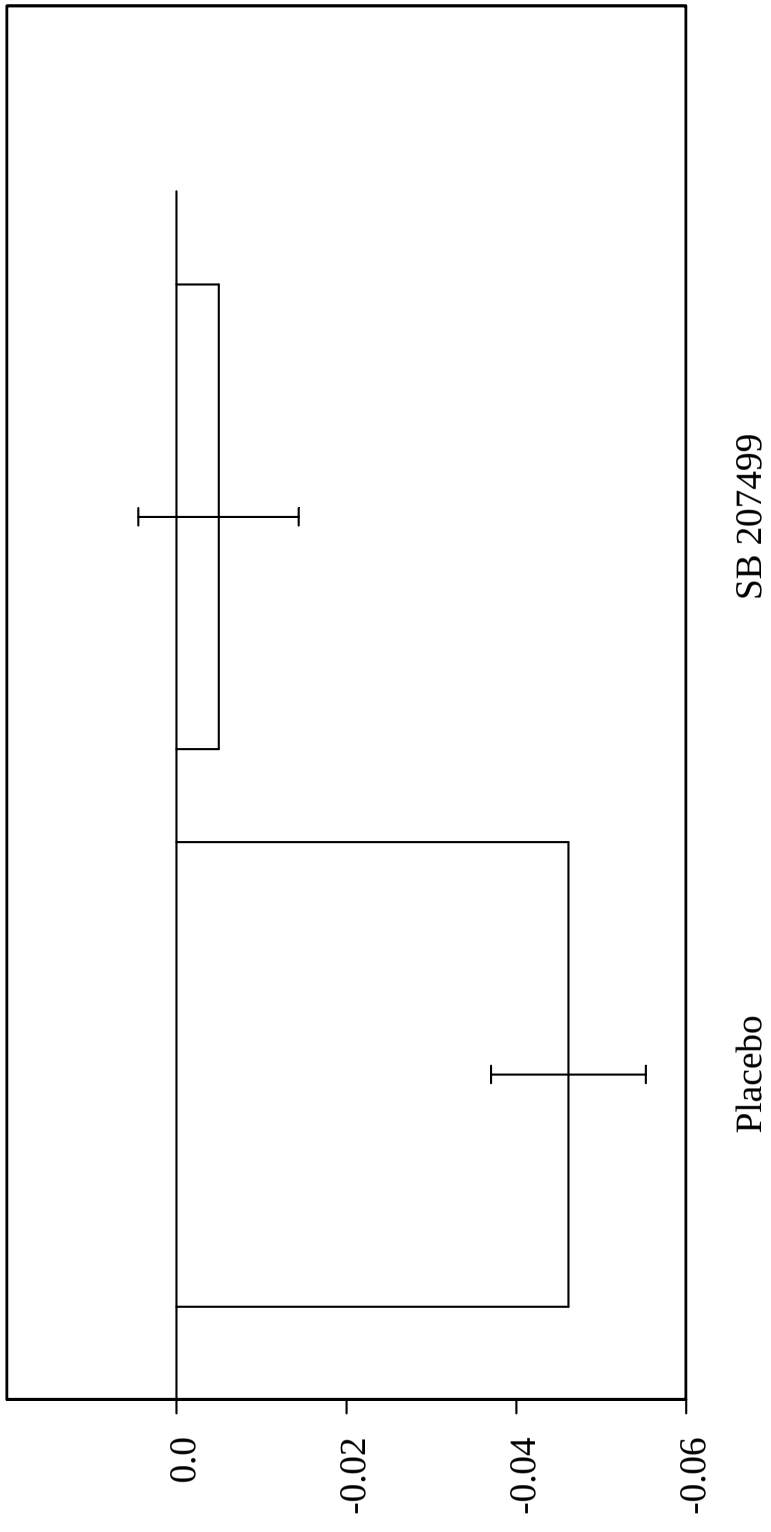


Figure 19.1C
Mean (SEM) Change from Baseline in Pre-BD FEV1(L)
ITT Withdrawals
Protocol 157

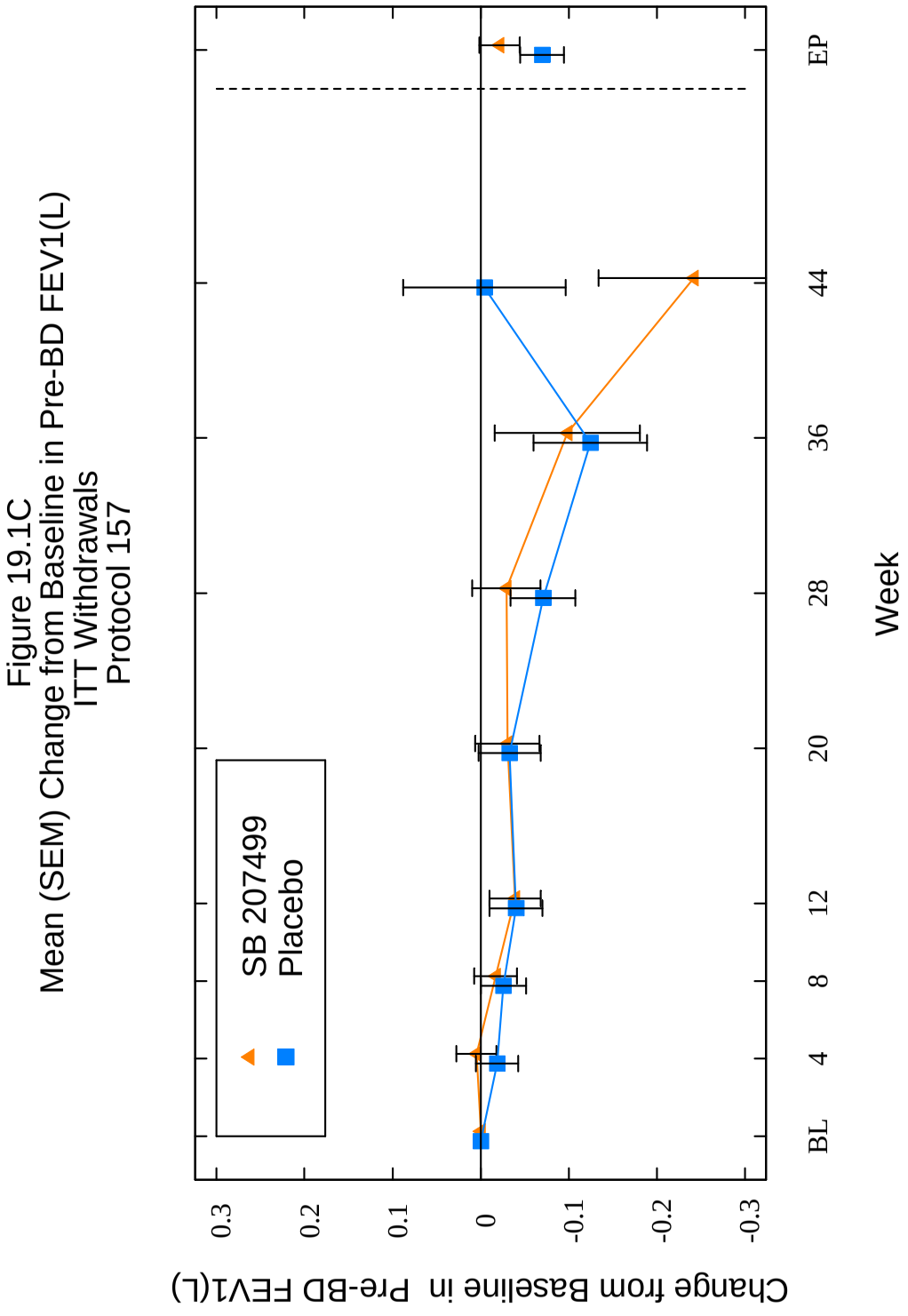


Figure 19.1J
Cumulative Incidence of Change From Baseline FEV1 (L) at ITT Endpoint
By Treatment Group - ITT Completers
Protocol 157

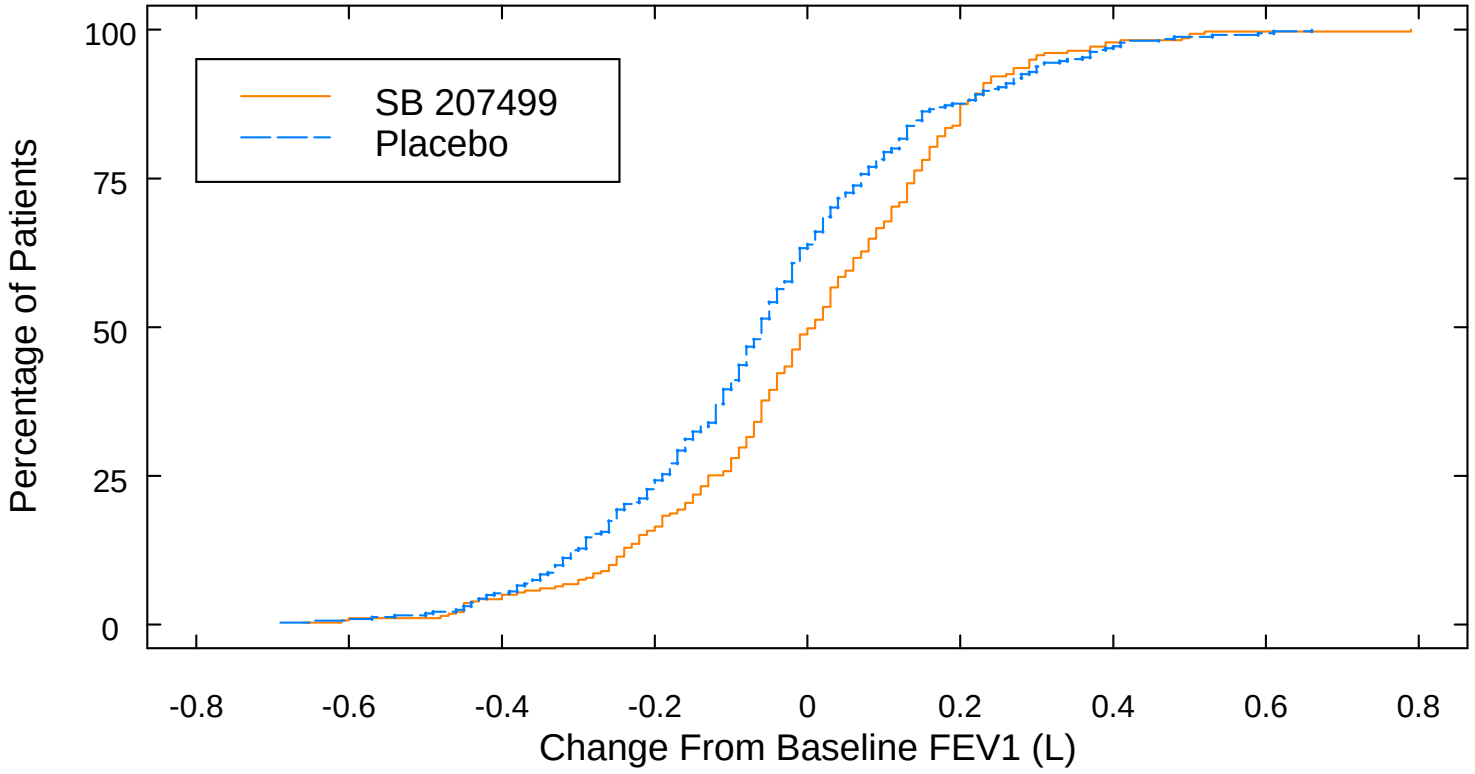


Figure 19.22
Mean (SEM) Change from Baseline in SGRQ Impact Score
ITT
Protocol 157

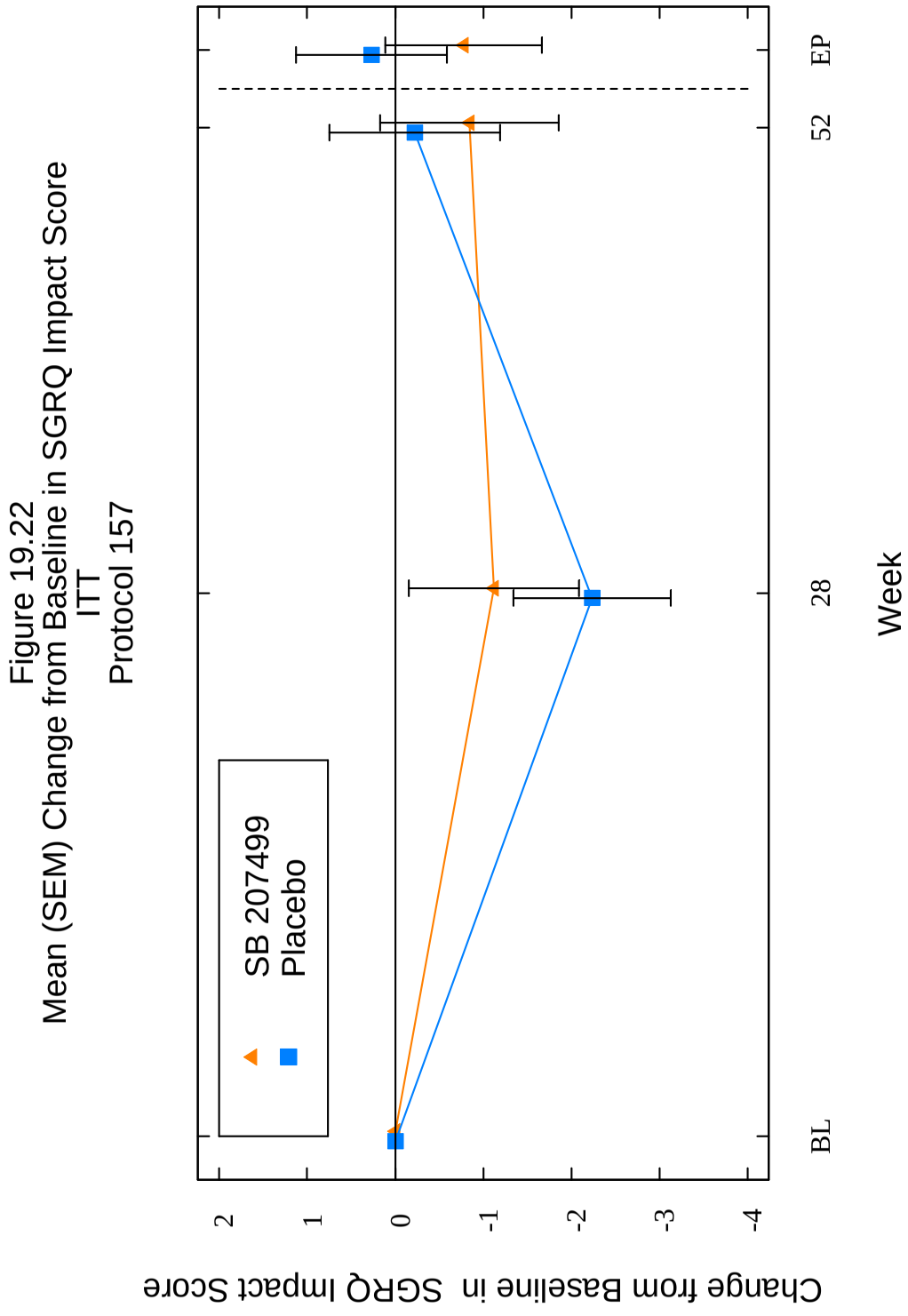


Figure 19.24
Mean (SEM) Change from Baseline in FEF25-75 (L/Sec)
ITT
Protocol 157

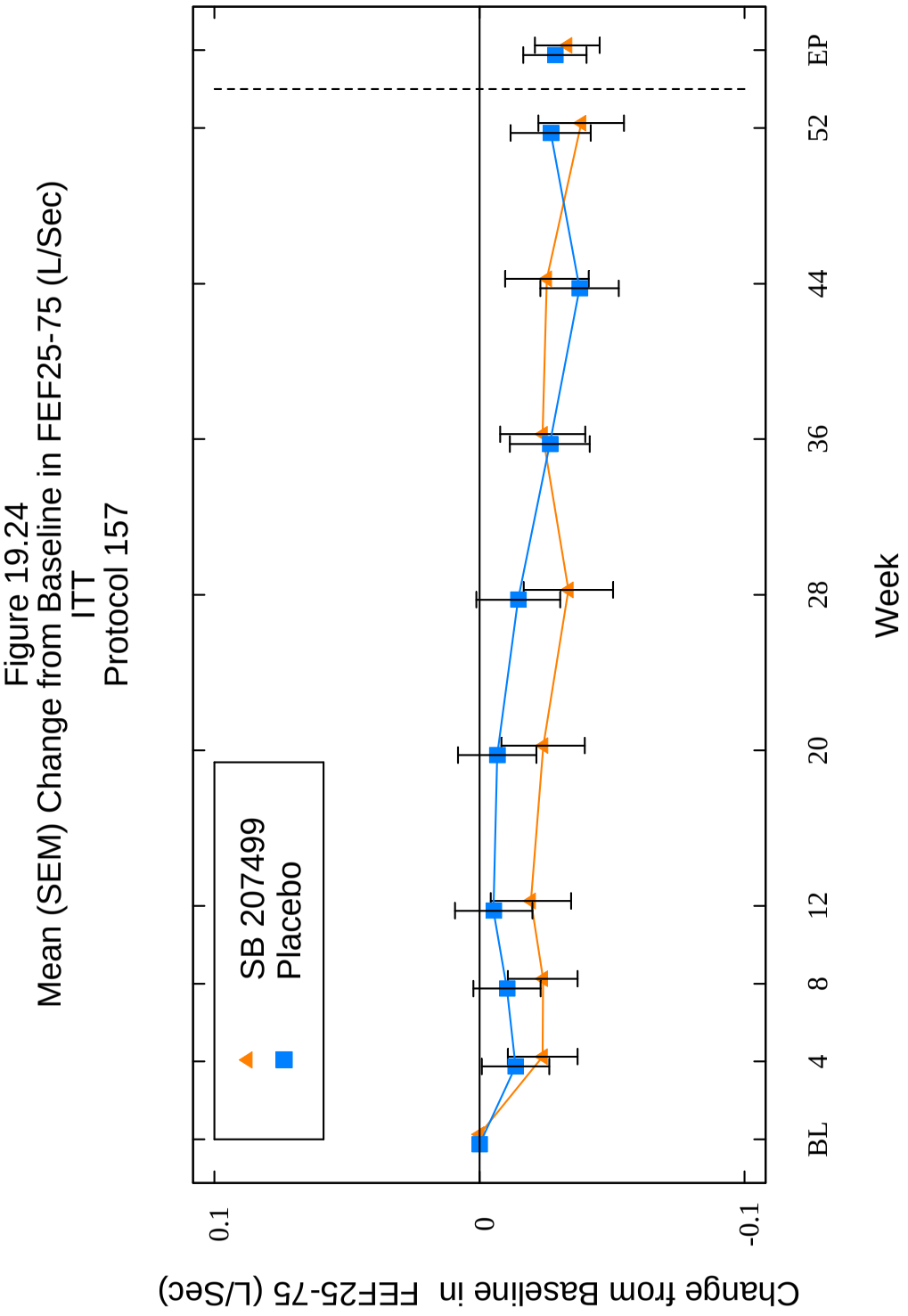


Figure 19.26
Mean (SEM) Change from Baseline in Domicilliary Sputum
ITT
Protocol 157

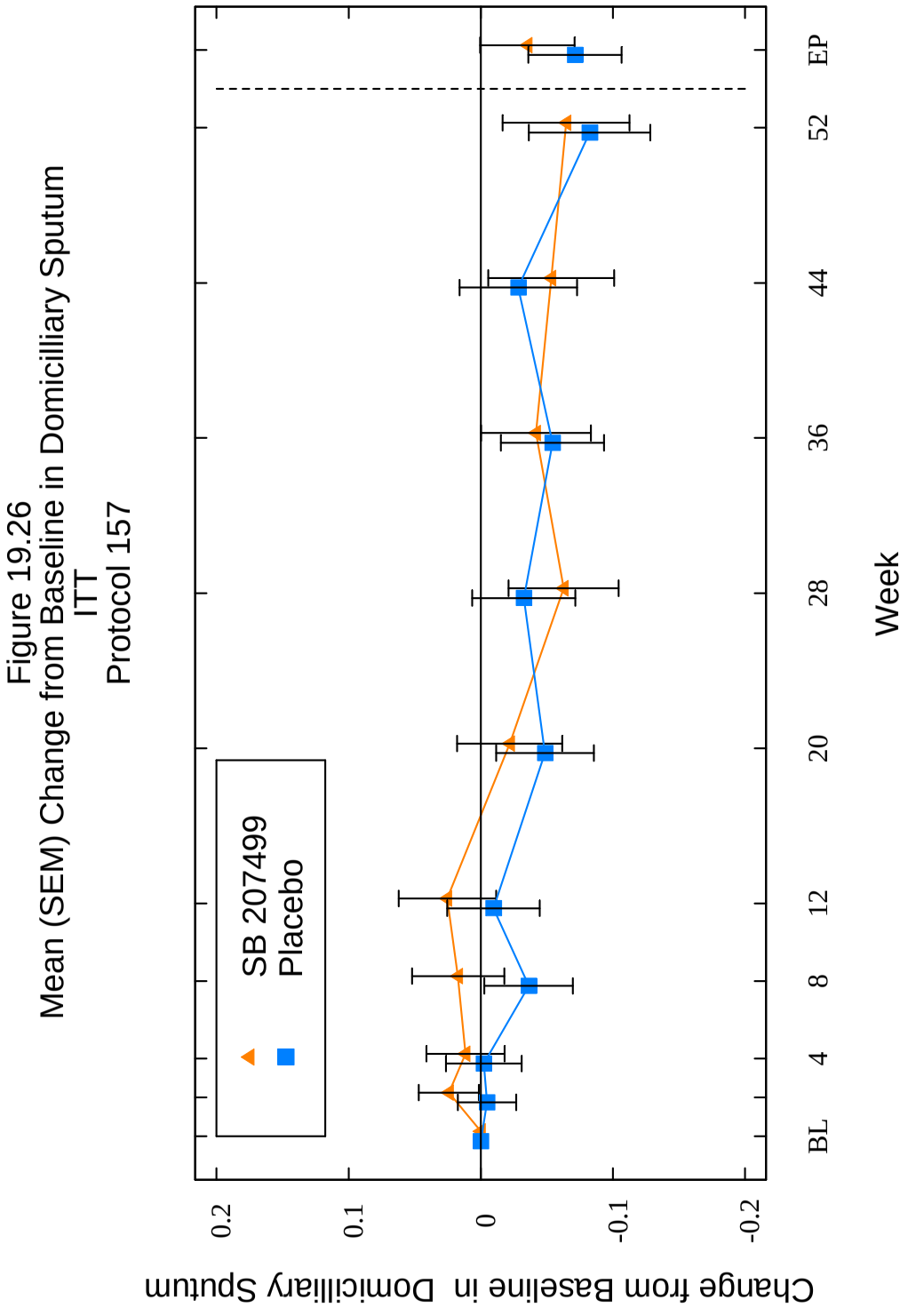


Figure 19.2I
Cumulative Incidence of Change From Baseline Total SGRQ at ITT Endpoint
By Treatment Group - ITT
Protocol 157

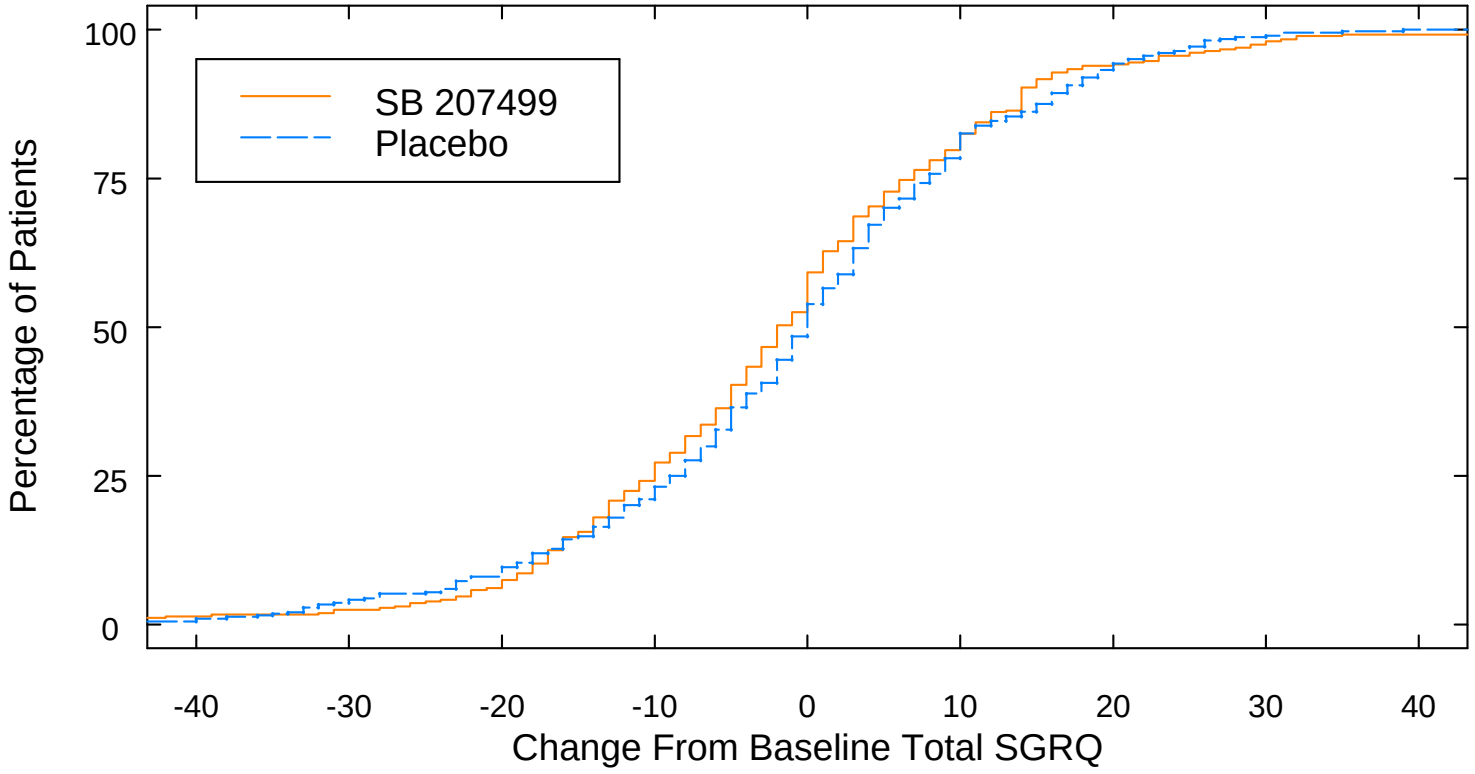


Figure 19.5
Mean (SEM) Change from Baseline in FVC (L)
ITT
Protocol 157

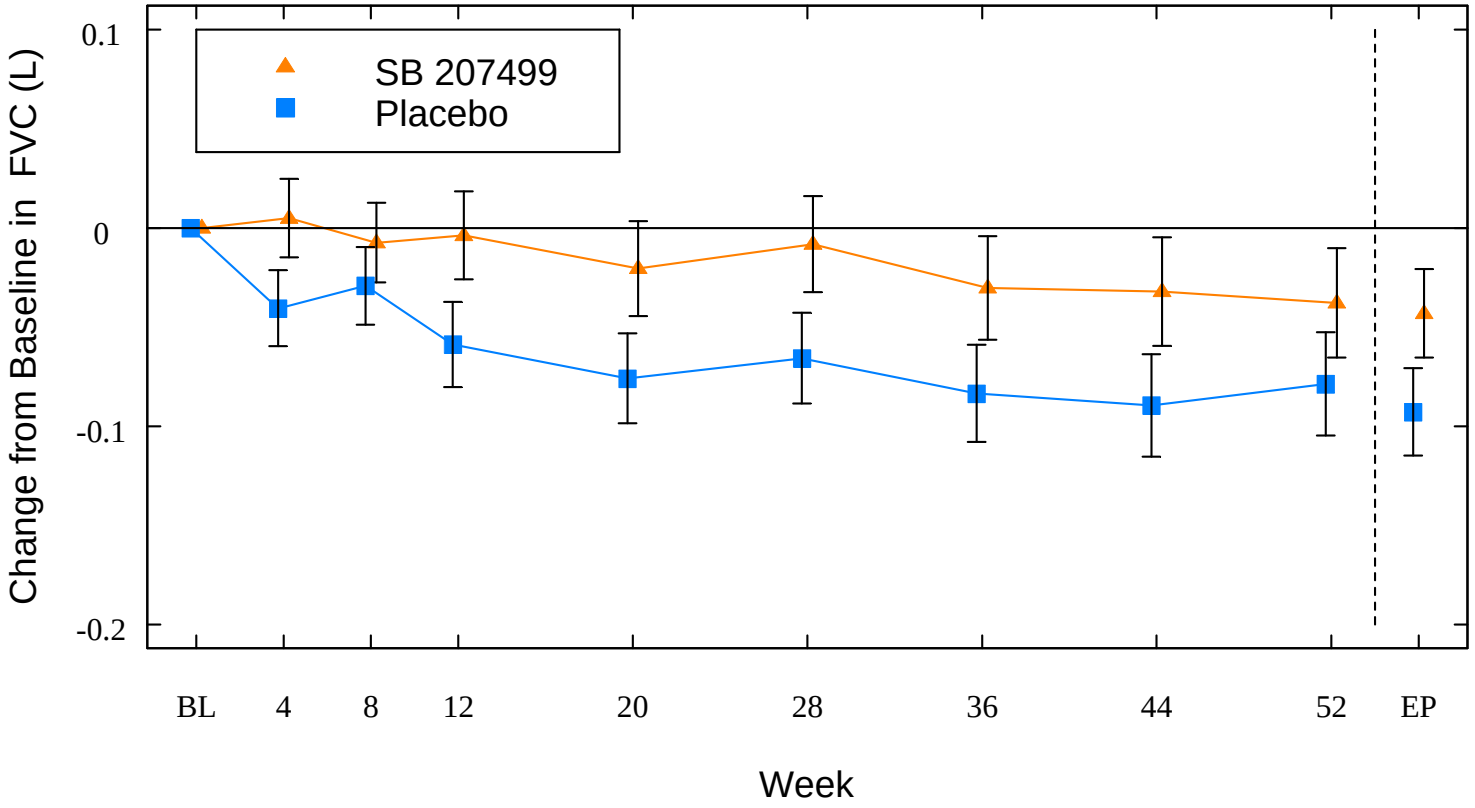


Figure 19.9
Mean (SEM) Change from Baseline in PEF (L/Min)
ITT
Protocol 157

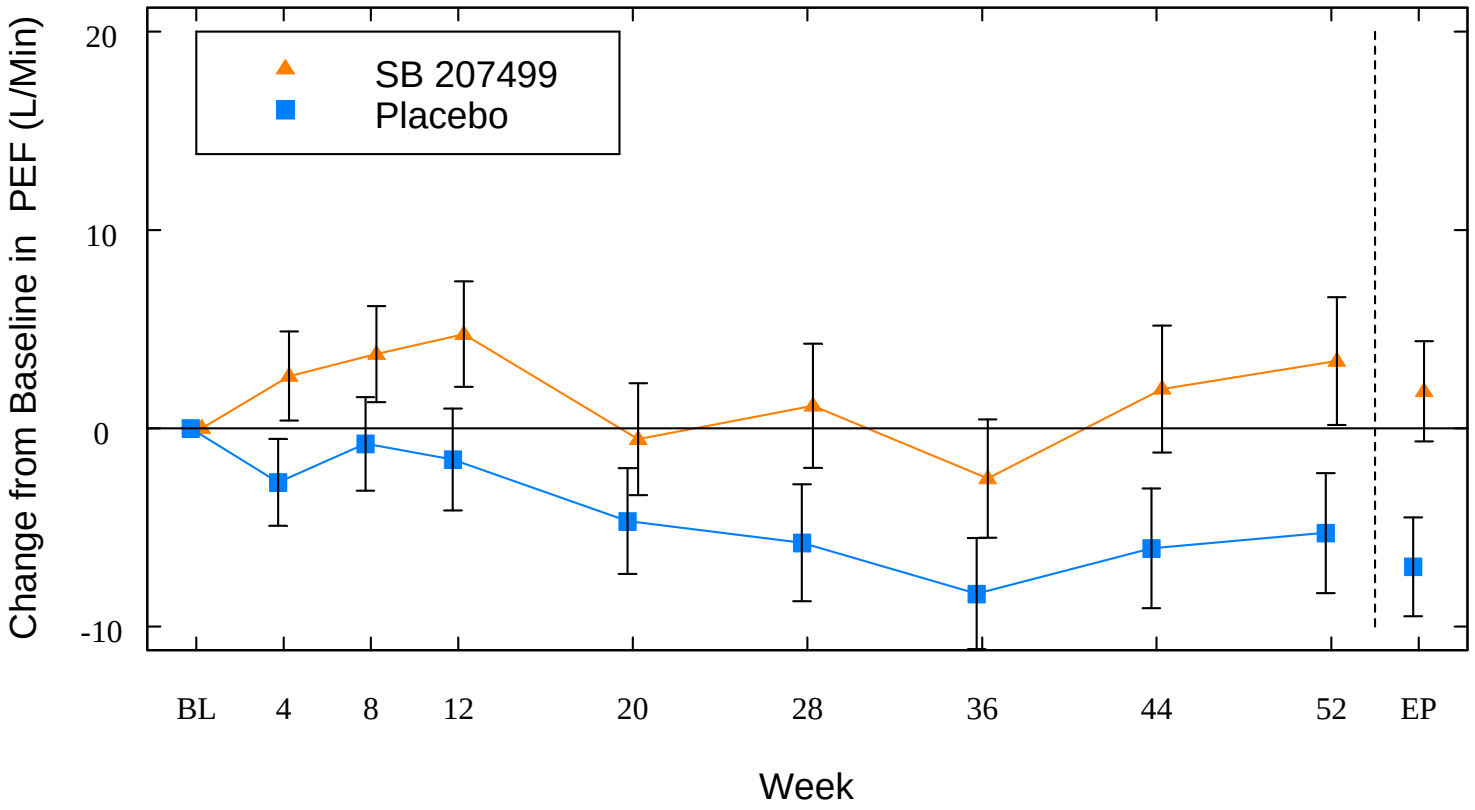


Figure 19.3
Mean (SEM) Change from Baseline in Post-BD FEV1
ITT
Protocol 157

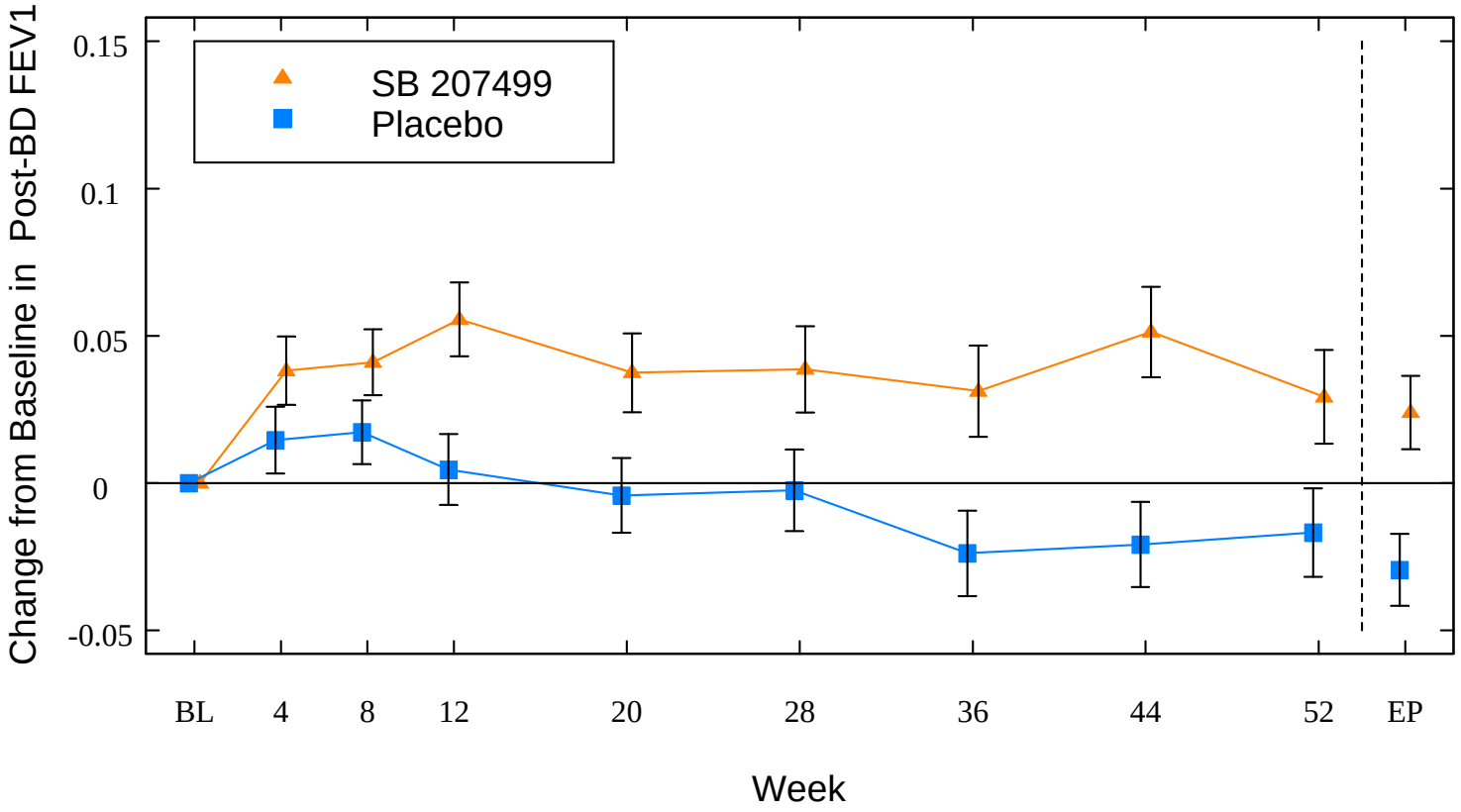


Figure 19.7K

Mean (95% CI) Rate of Level II/III Exacerbations Per Patient Year - ITT

Protocol 157

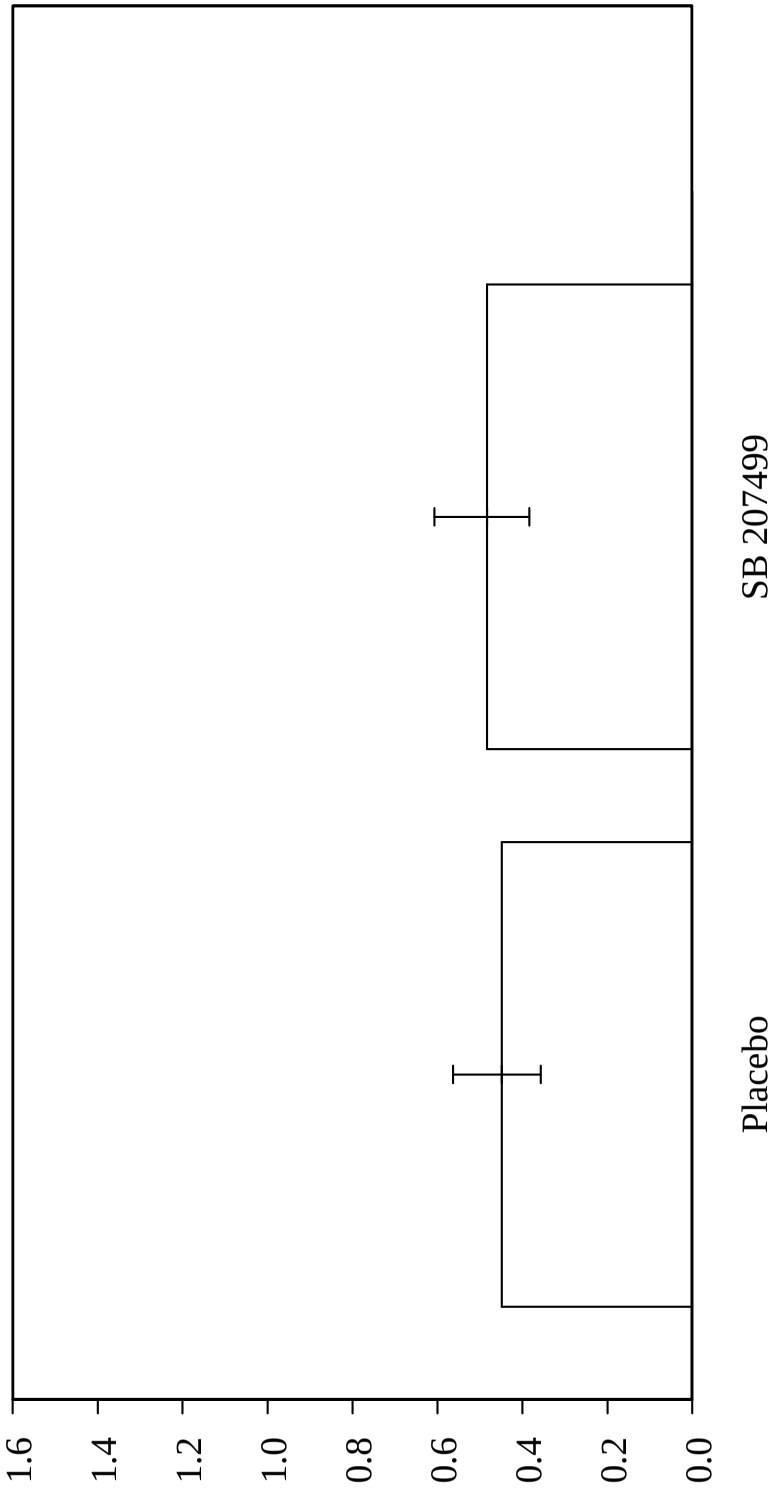


Figure 19A.7A
Kaplan-Meier Estimates of Percentage of Patients Level II/Level III Exacerbation-Free - PP
Protocol 157

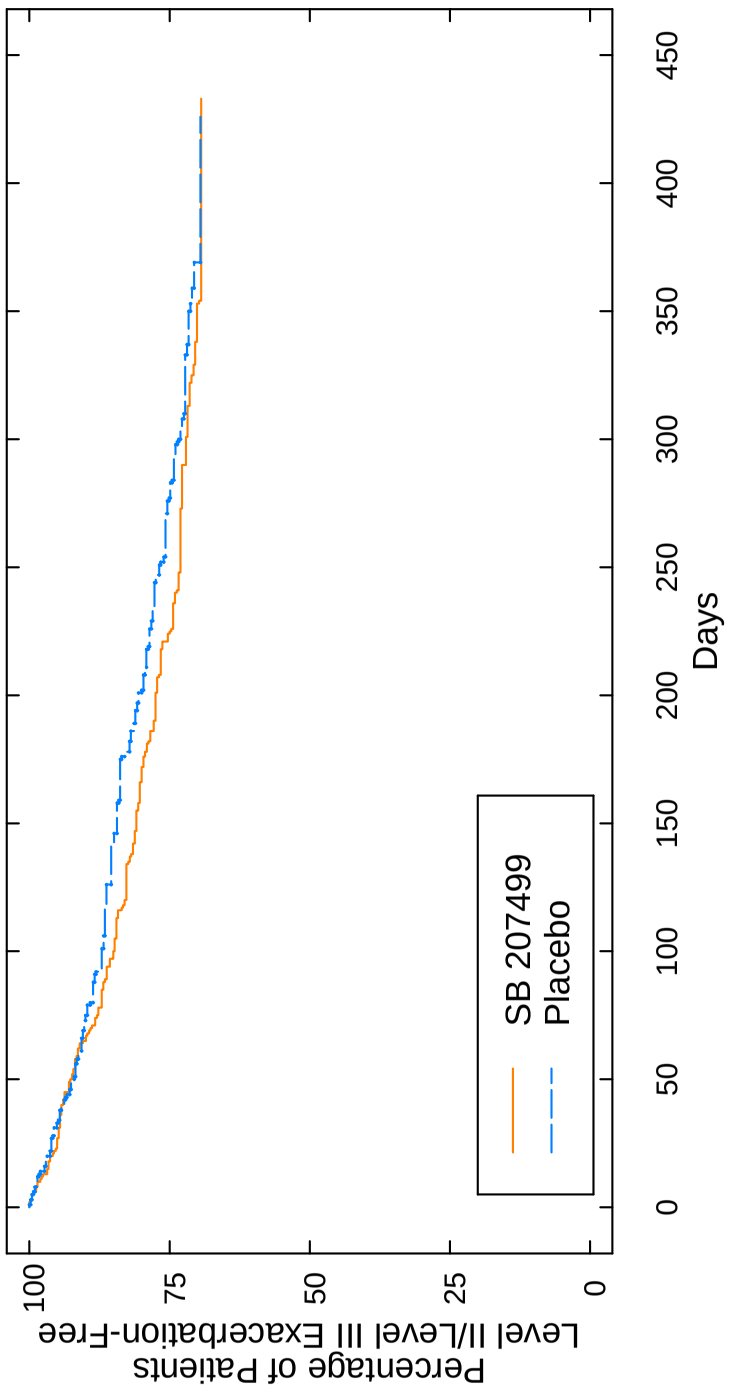


Figure 19A.7B
Kaplan-Meier Estimates of Percentage of Patients Exacerbation-Free - PP
Protocol 157

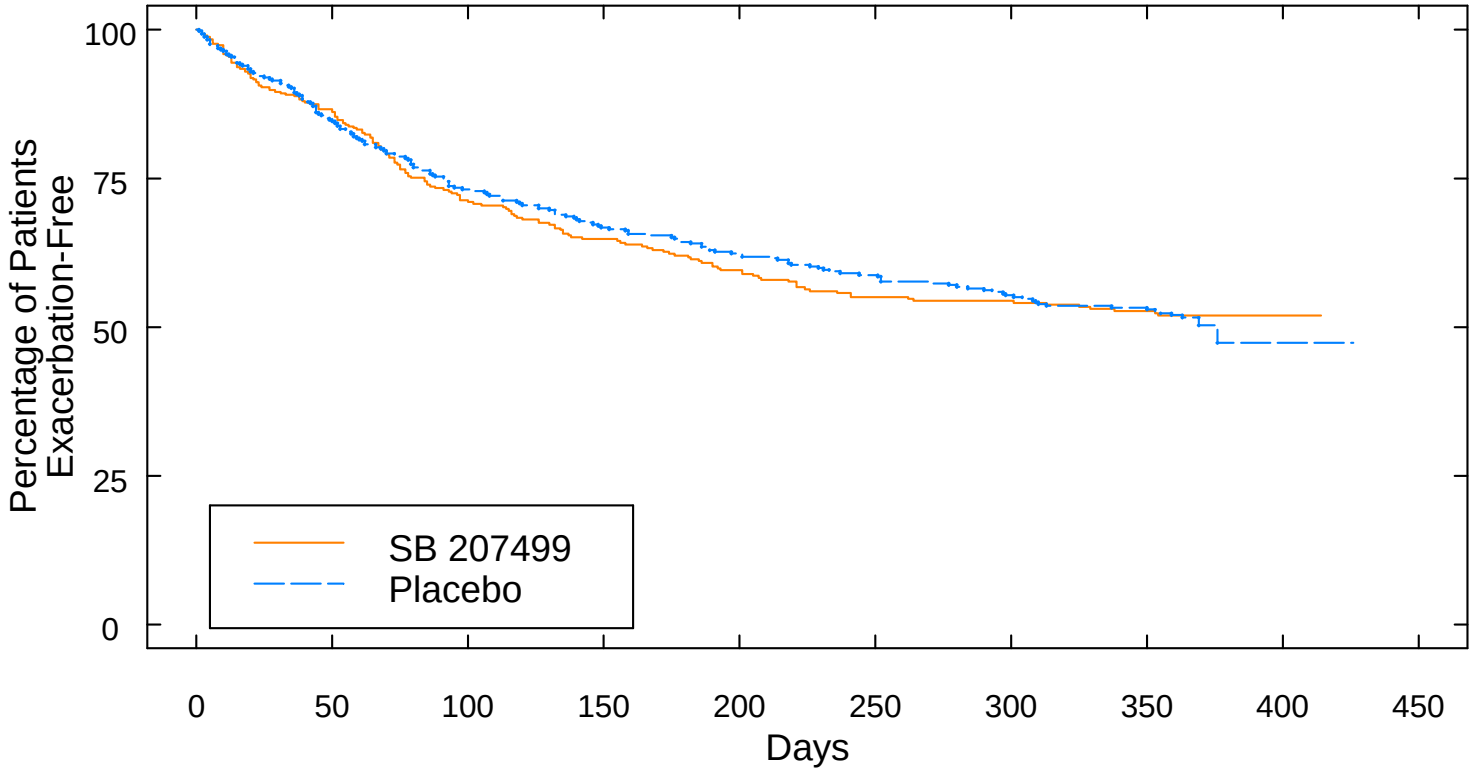


Figure 19.7C

Distribution of Level II/III Exacerbations by Treatment Group

Protocol 157

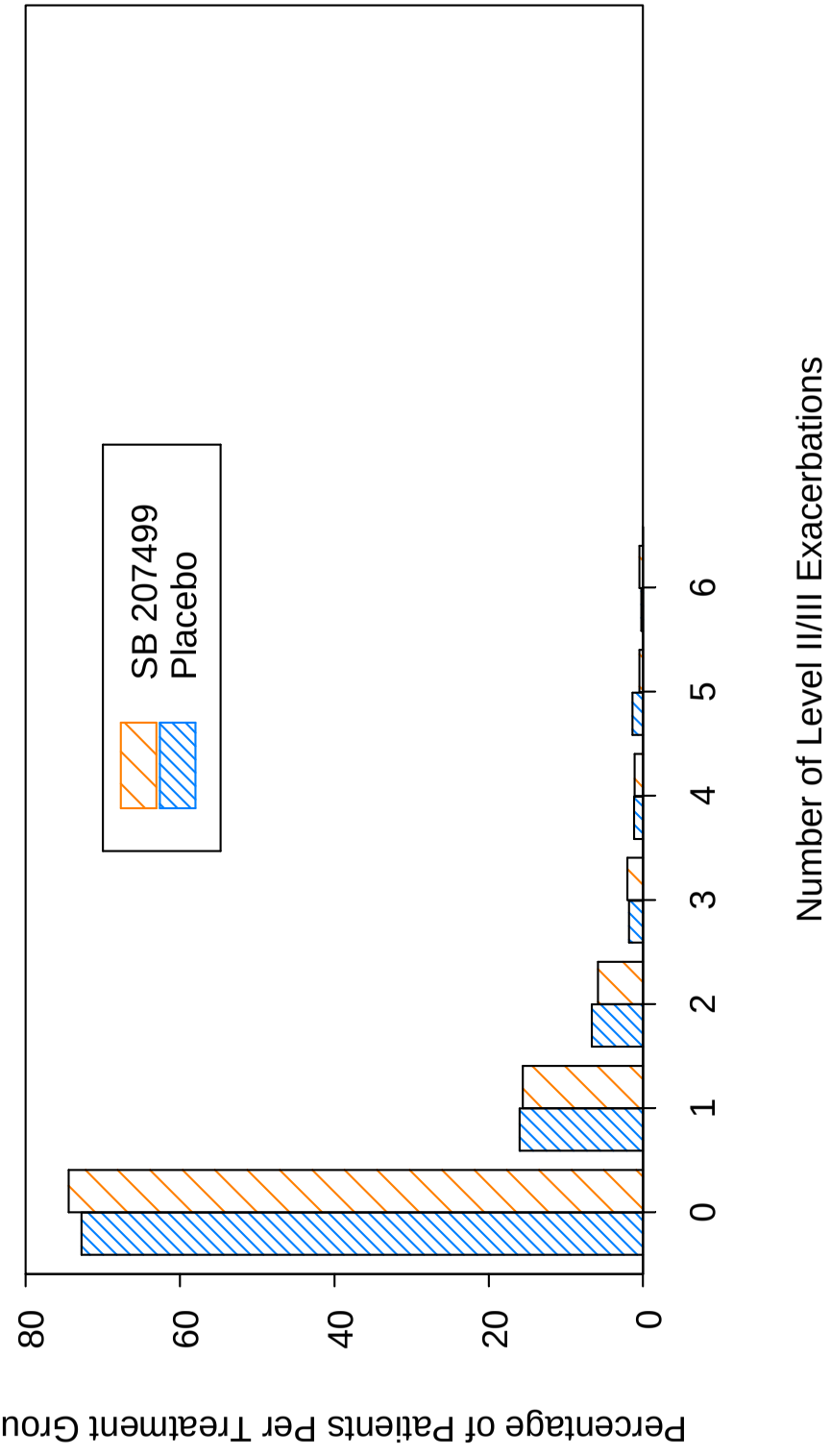


Figure 19.1E
Mean (SEM) Change from Baseline in Pre-BD FEV1(L)
ITT (Including All Essential Visits)
Protocol 157

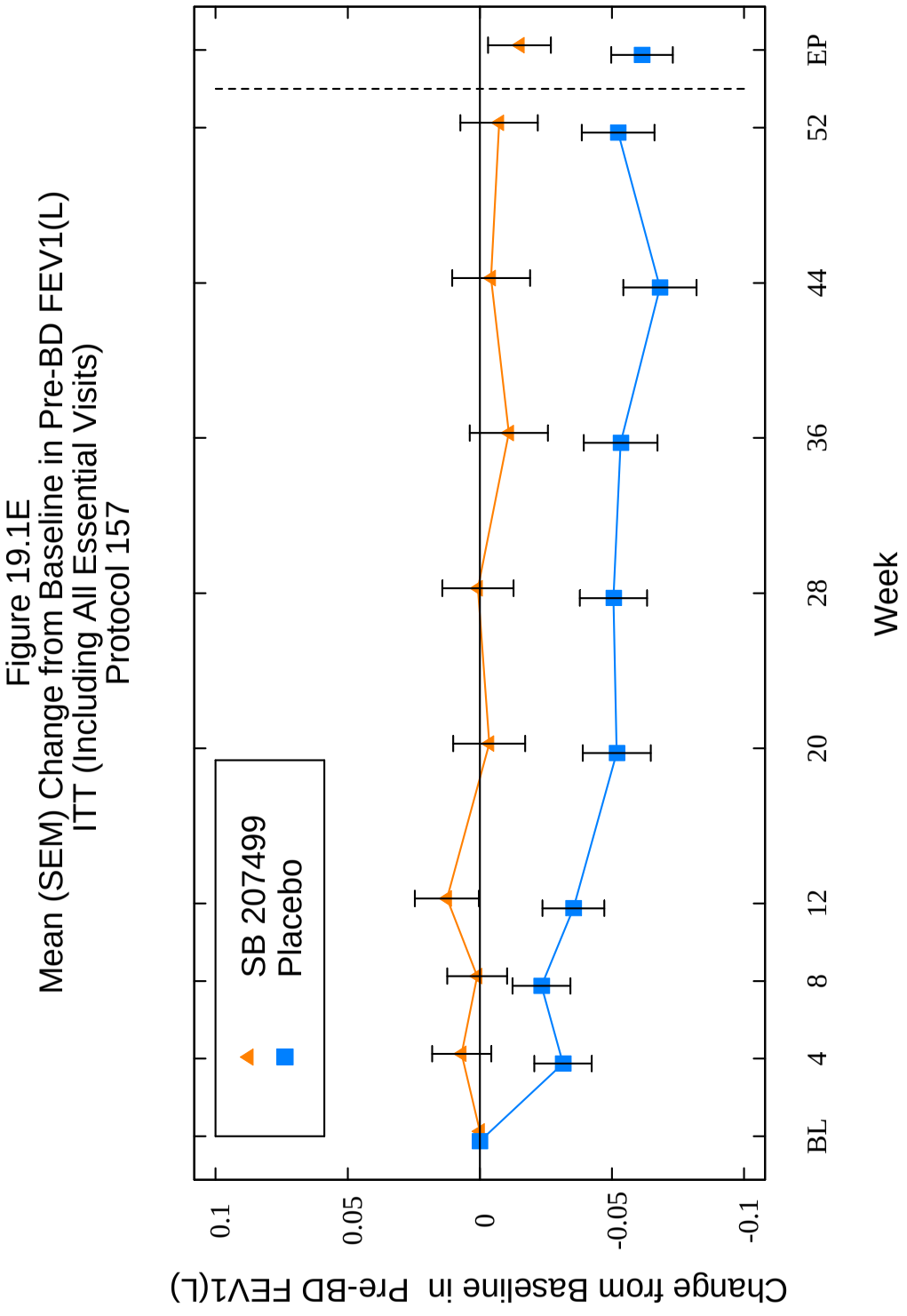


Figure 19.16
Cumulative Incidence of Abdominal Pain - ITT
By Time of Initial Onset and Treatment Group
Protocol 157

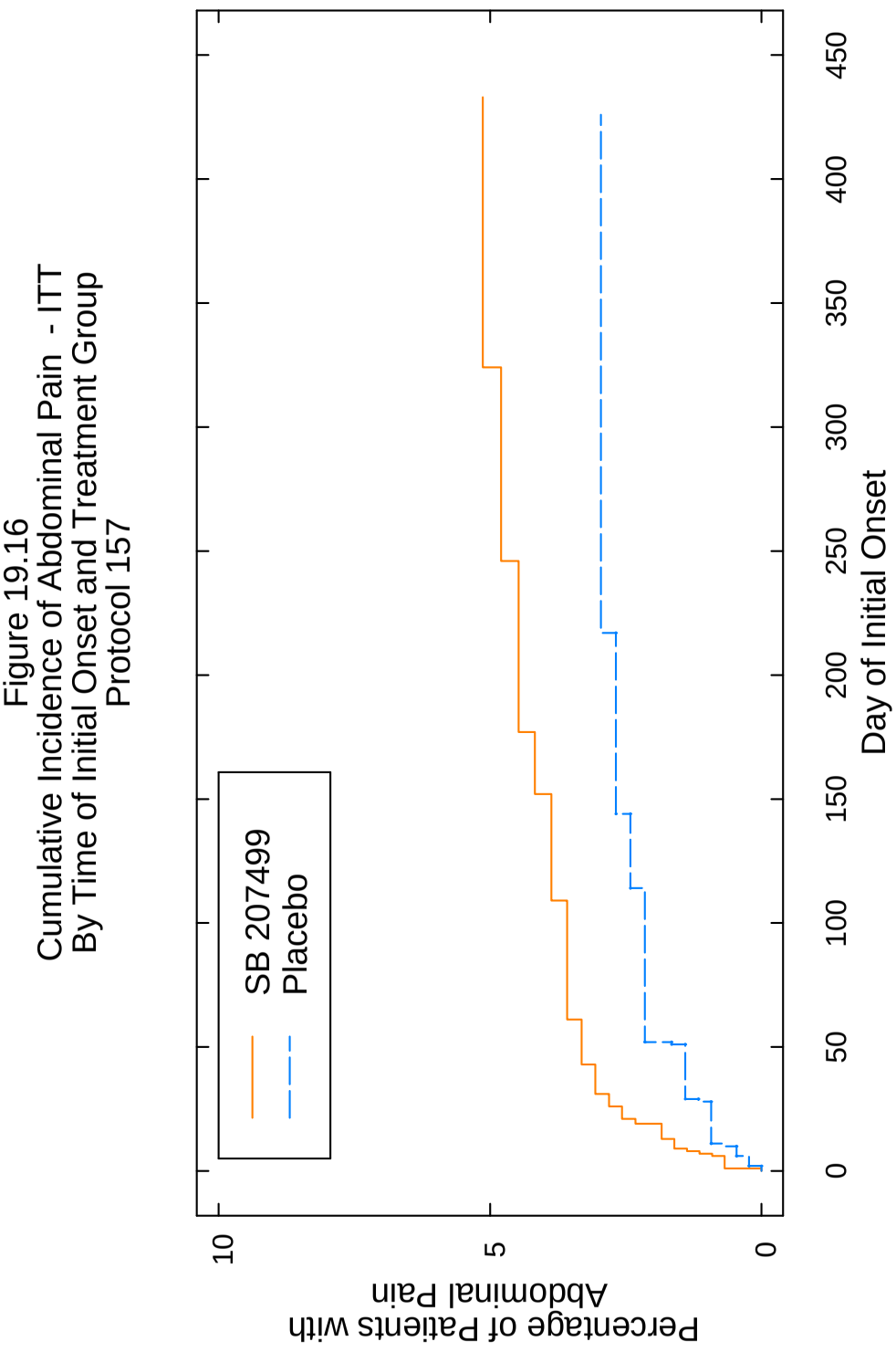


Figure 19.7D

Distribution of Exacerbations by Treatment Group

Protocol 157

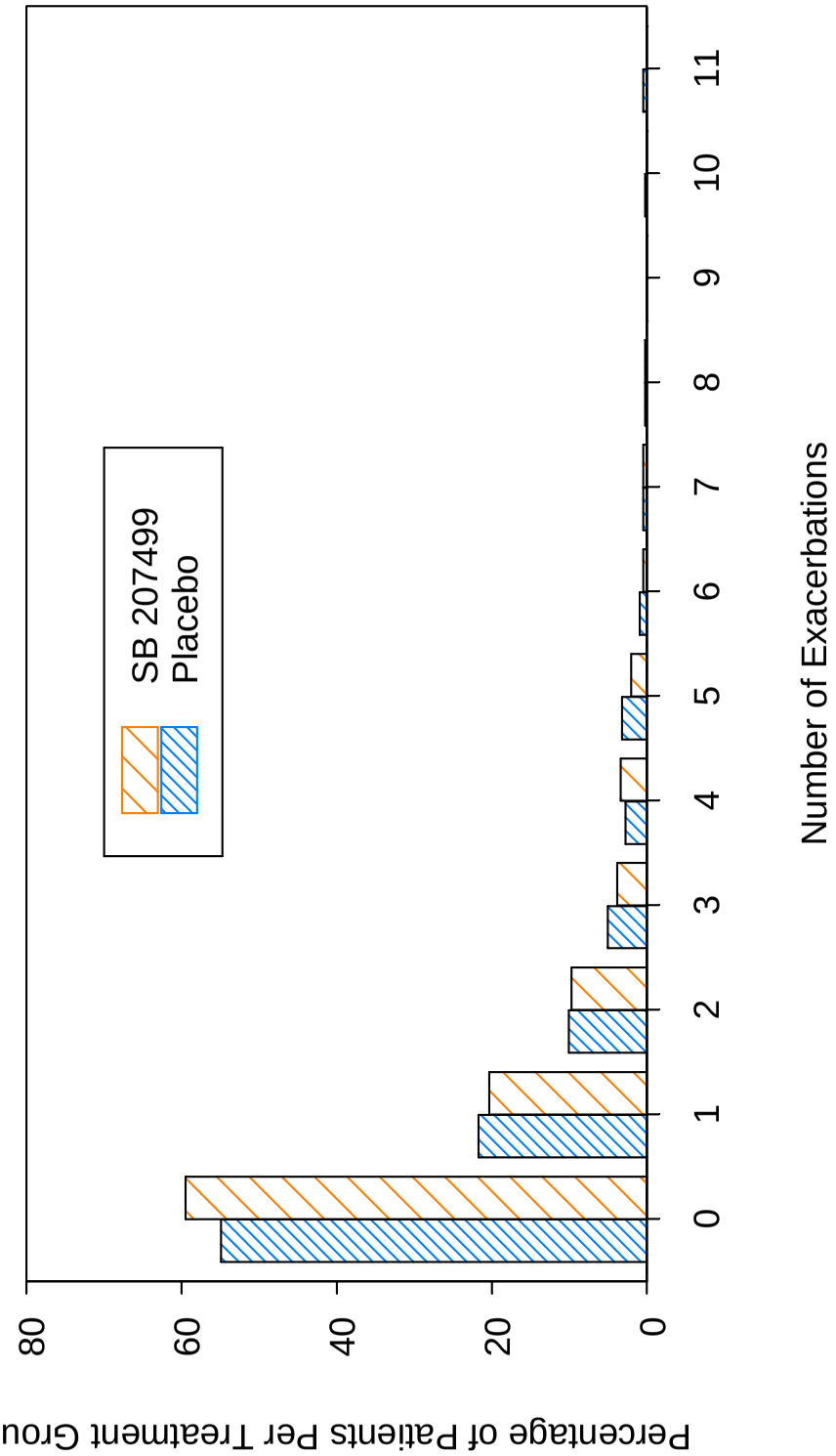


Figure 19.1G

Mean (SEM) Change from Baseline in Pre-BD FEV1 (L) Averaged Over 52 Weeks-ITT Completers

Protocol 157

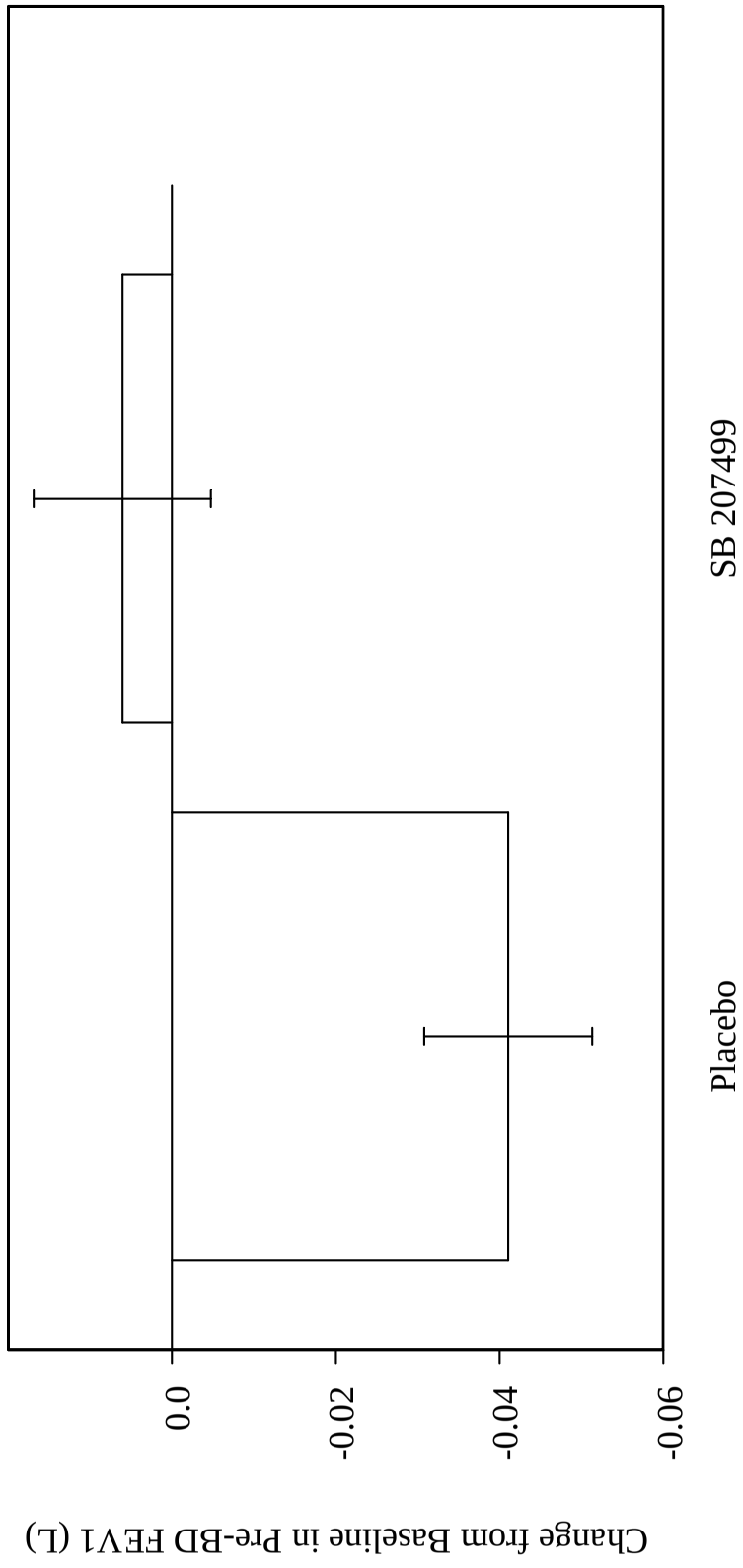


Figure 19.7A
Kaplan-Meier Estimates of Percentage of Patients Level II/Level III Exacerbation-Free - ITT
Protocol 157

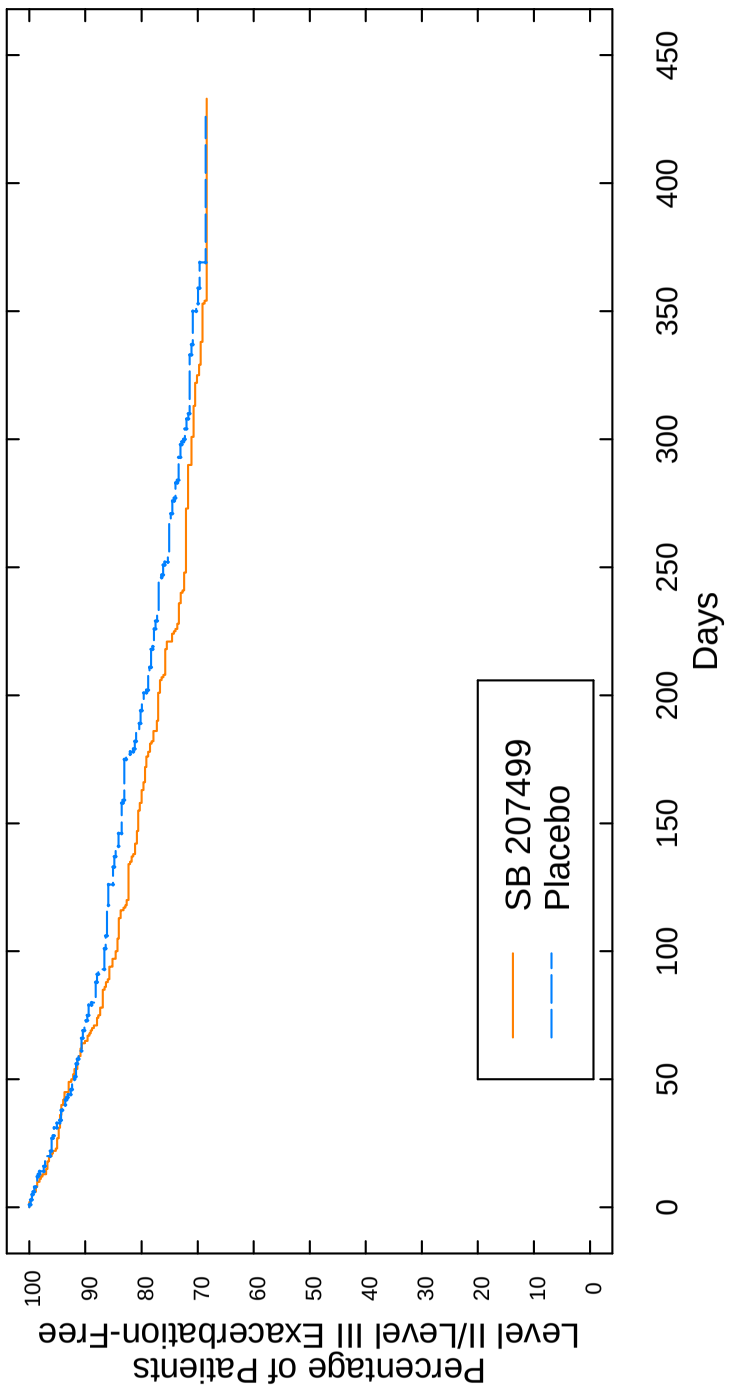


Figure 19.2F

Mean (SEM) Change from Baseline in Total SGRQ Score Averaged Over 52 Weeks-ITT

Protocol 157

Figure 19A.1A
Mean (SEM) Change from Baseline in Pre-BD FEV1(L)
- PP
Protocol 157

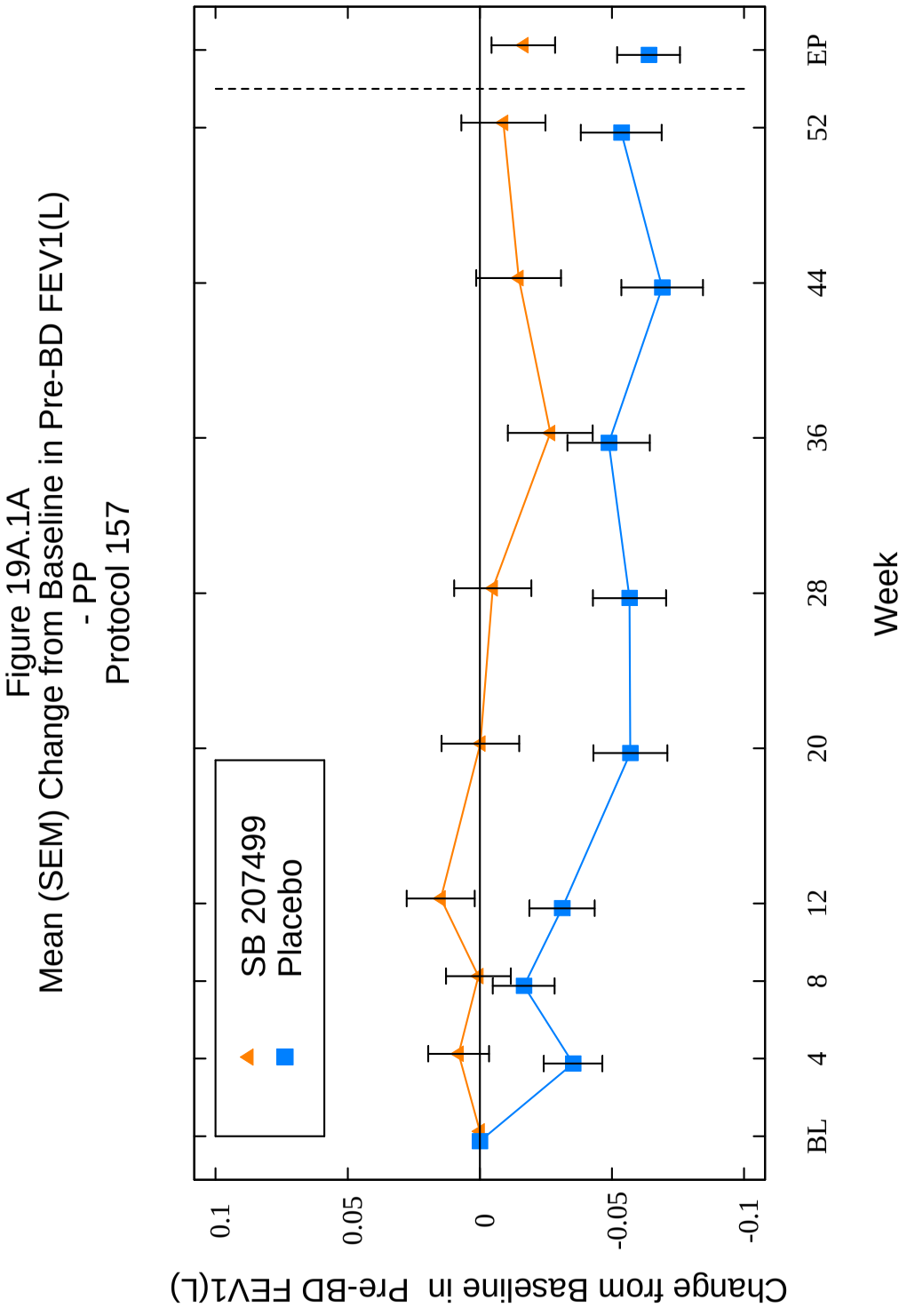


Figure 19.25
Mean (SEM) Change from Baseline in Domicilliary Cough
ITT
Protocol 157

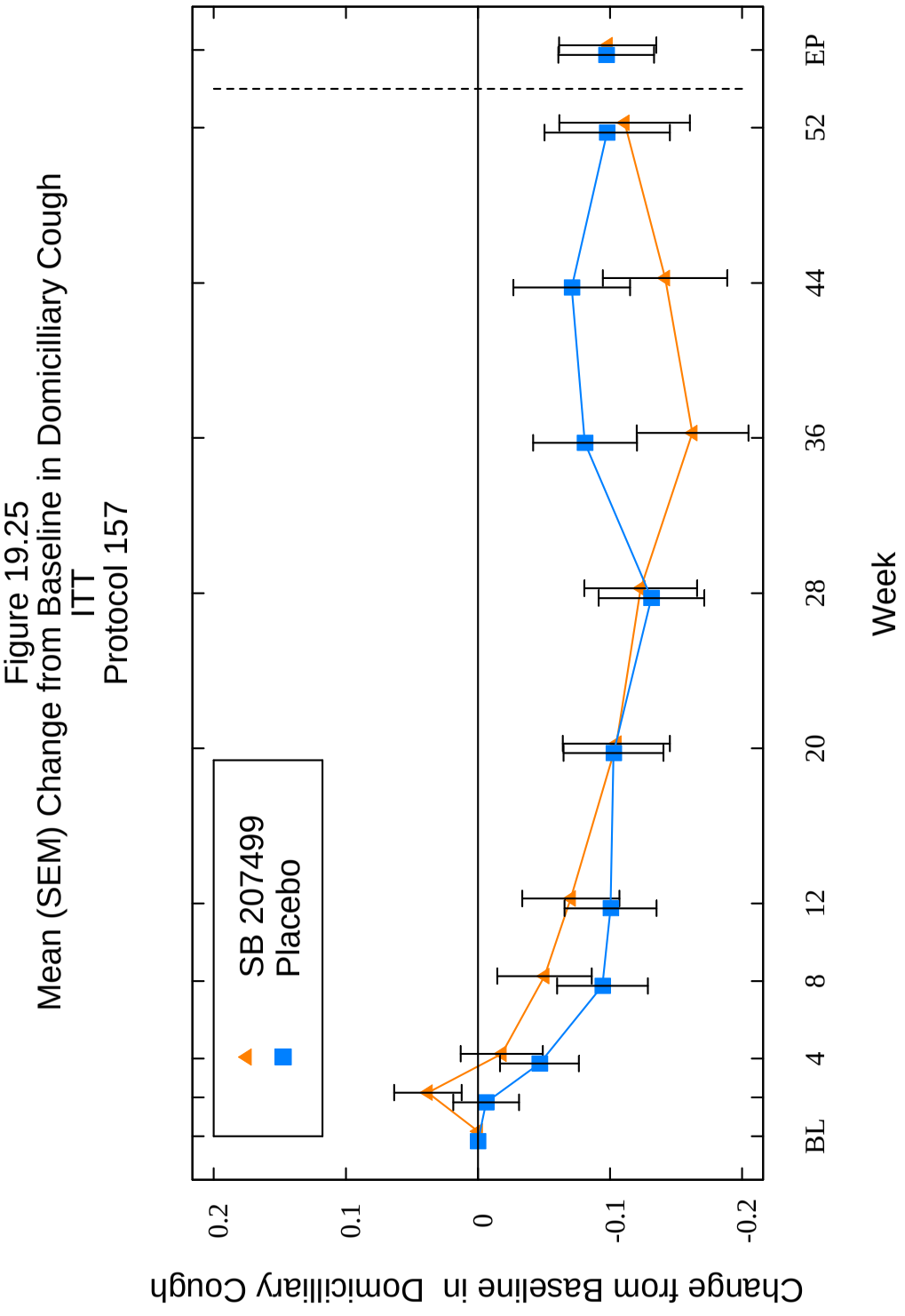


Figure 19.21
Mean (SEM) Change from Baseline in SGRQ Activity Score
ITT
Protocol 157

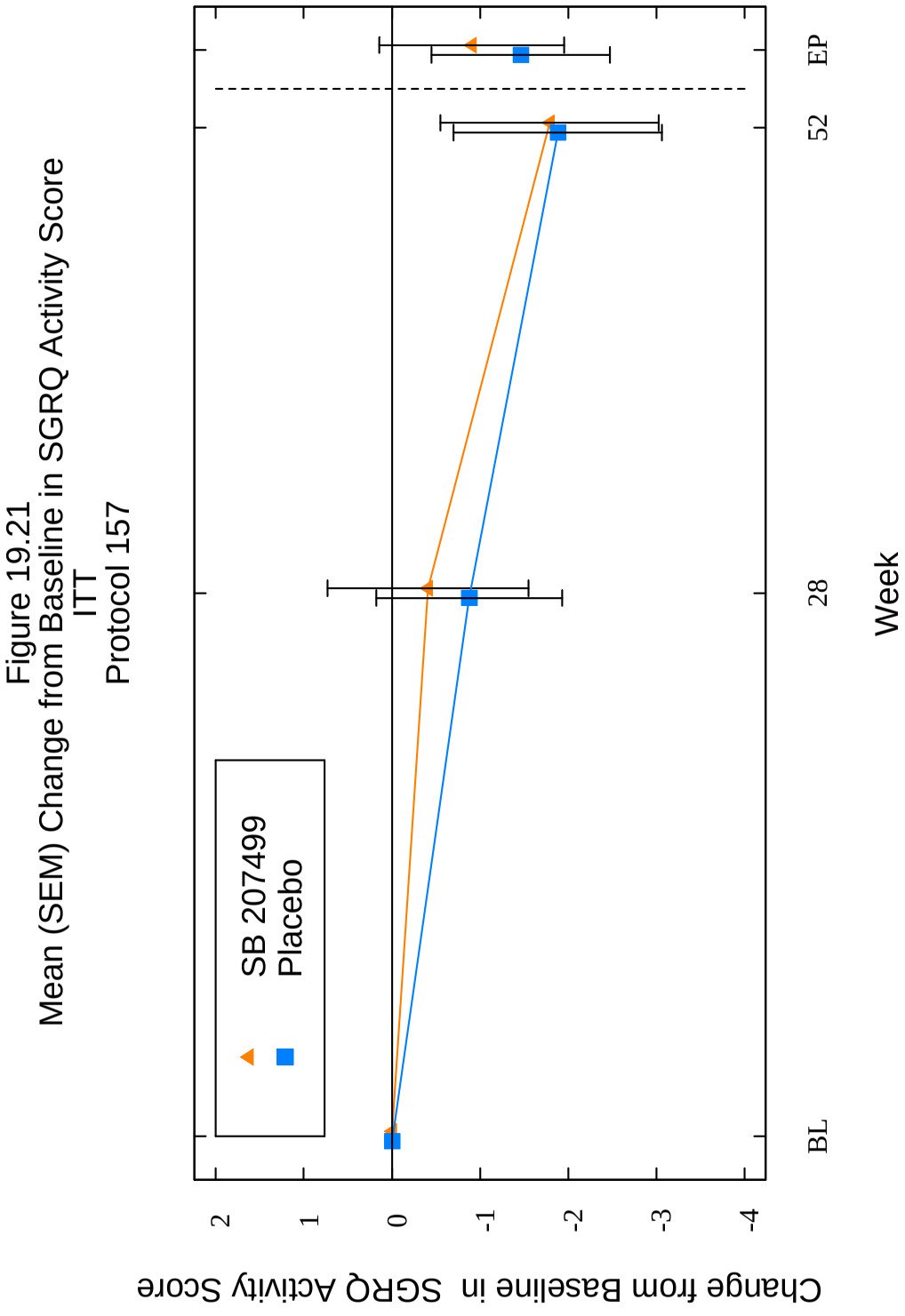


Figure 19.1B
Mean (SEM) Change from Baseline in Pre-BD FEV1(L)
ITT Completers
Protocol 157

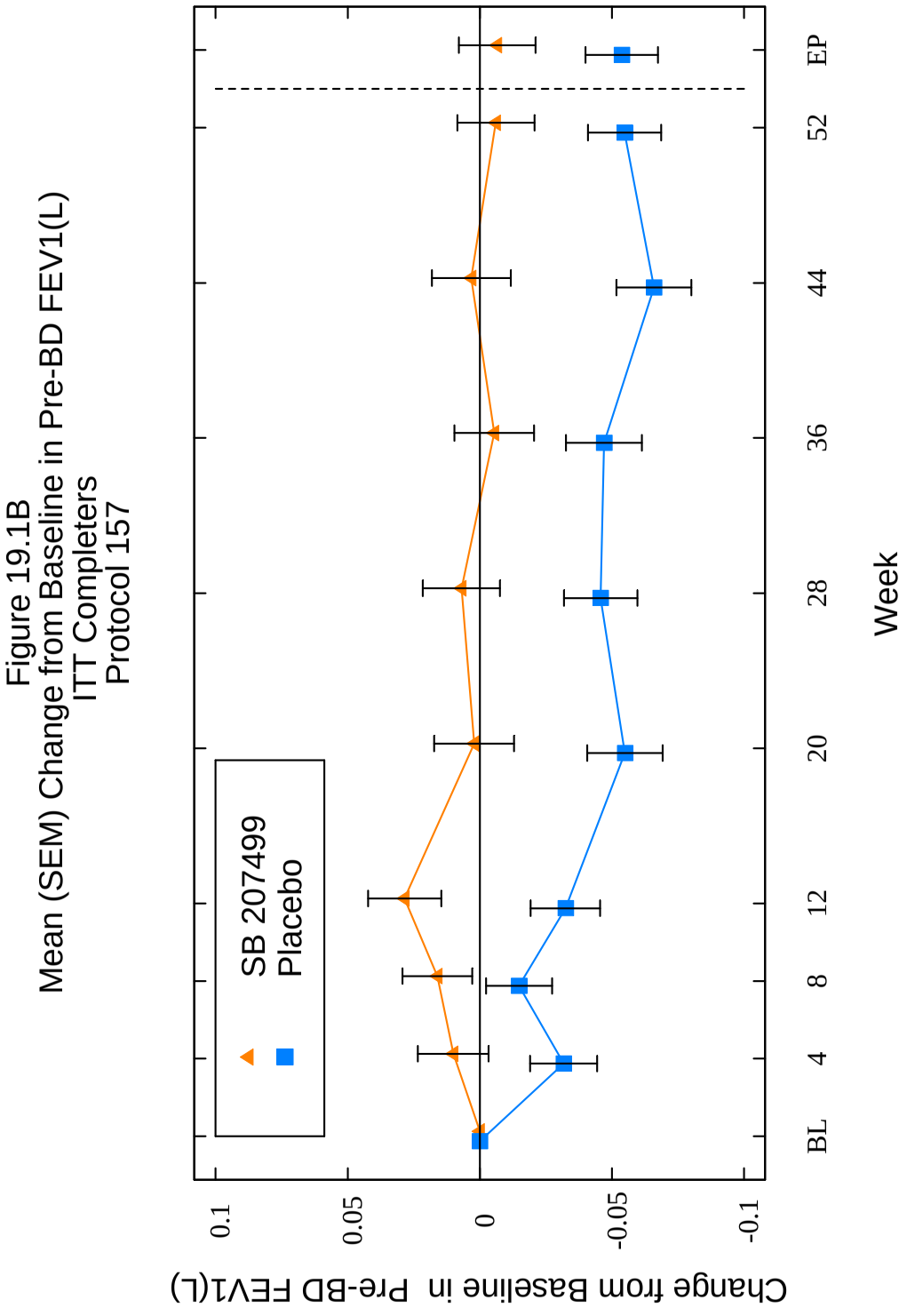


Figure 19.1A
Mean (SEM) Change from Baseline in Pre-BD FEV1(L)
ITT
Protocol 157

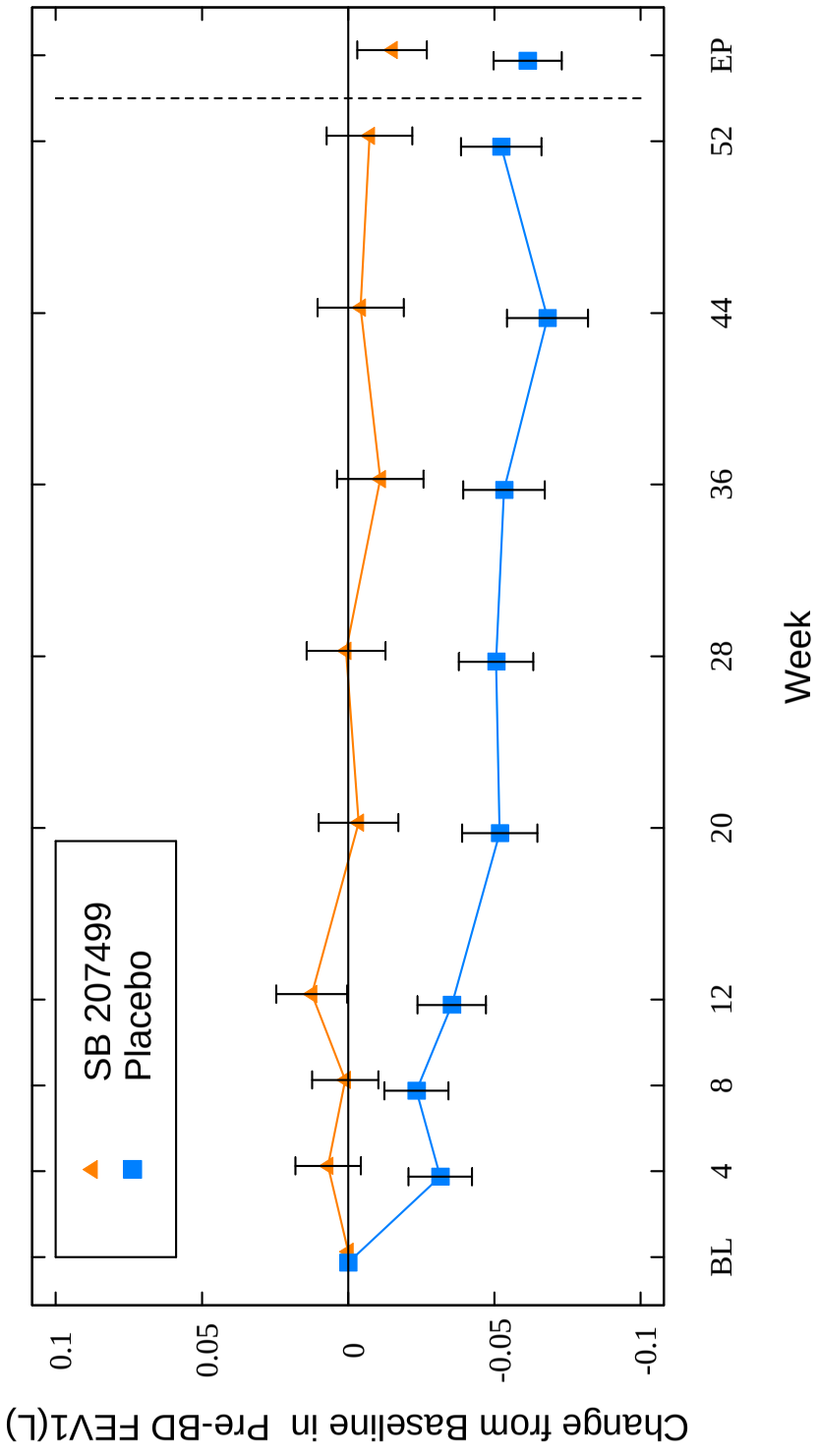


Figure 19.17
Cumulative Incidence of Diarrhea - ITT
By Time of Initial Onset and Treatment Group
Protocol 157

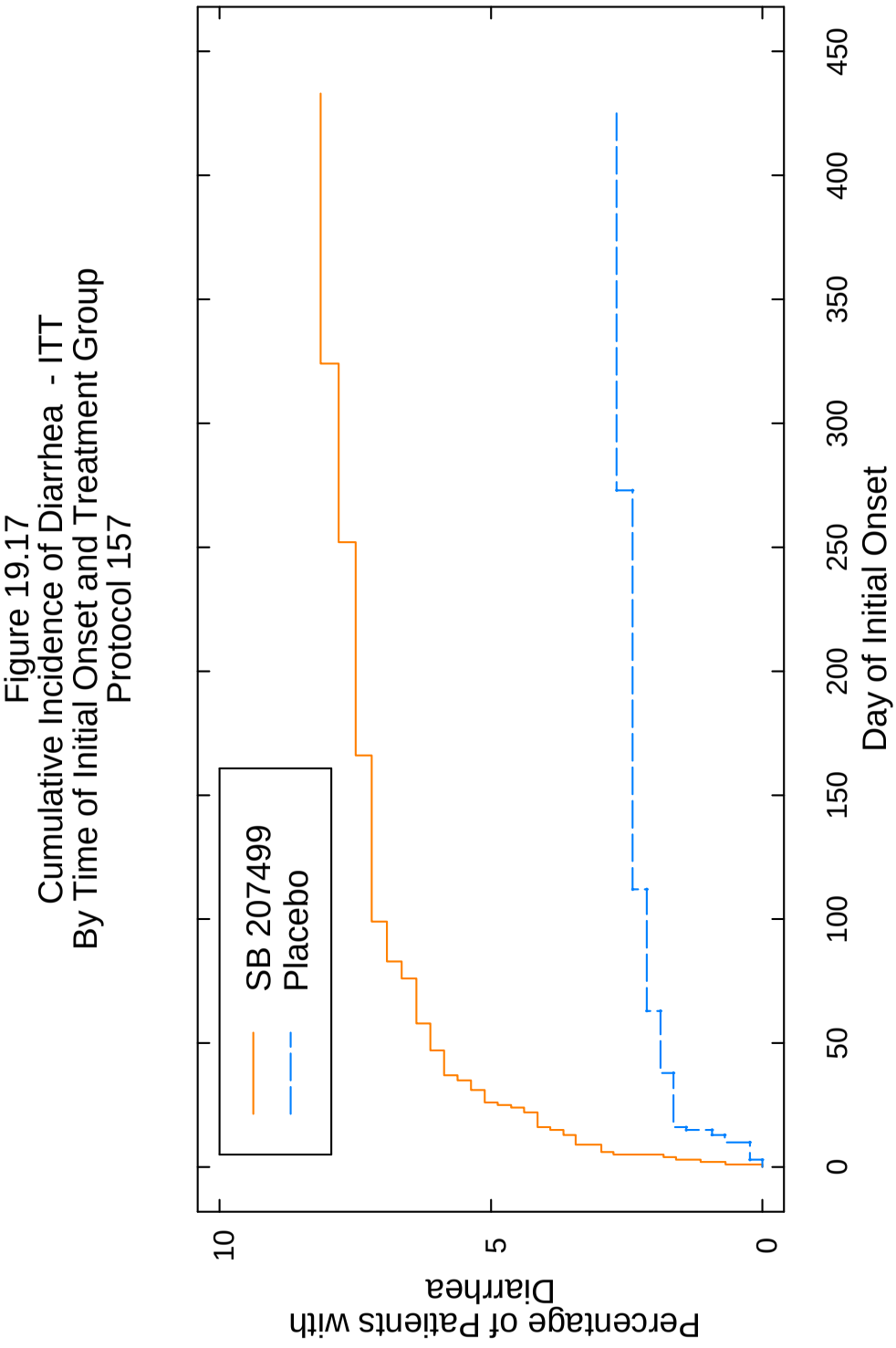


Figure 19.1F

Mean (SEM) Change from Baseline in Pre-BD FEV1 (L) Averaged Over 52 Weeks-ITT

Protocol 157

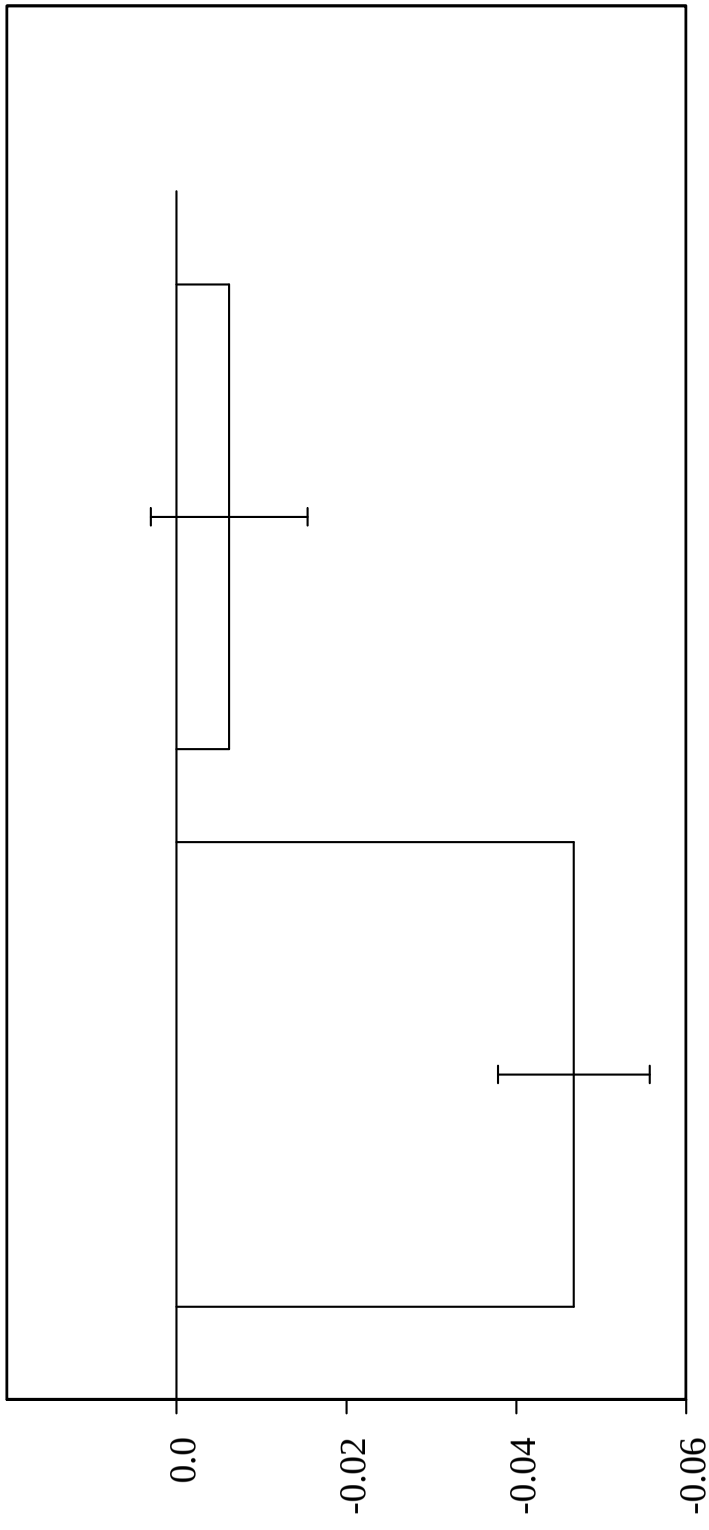


Figure 19.10
Mean (SEM) Change from Baseline in Domicilliary PEF (L/Min)
ITT
Protocol 157

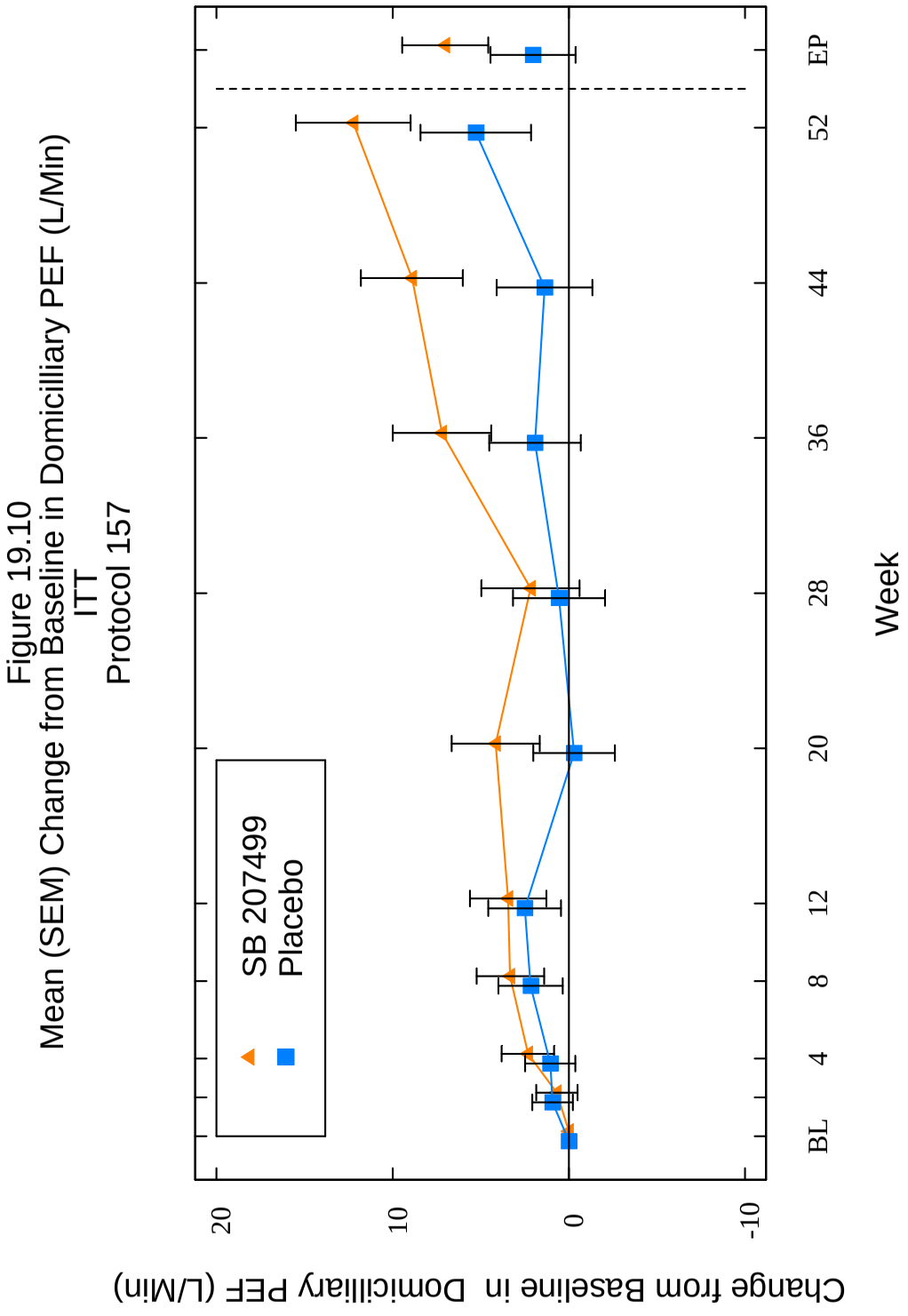


Figure 19.7B
Kaplan-Meier Estimates of Percentage of Patients Exacerbation-Free - ITT
Protocol 157

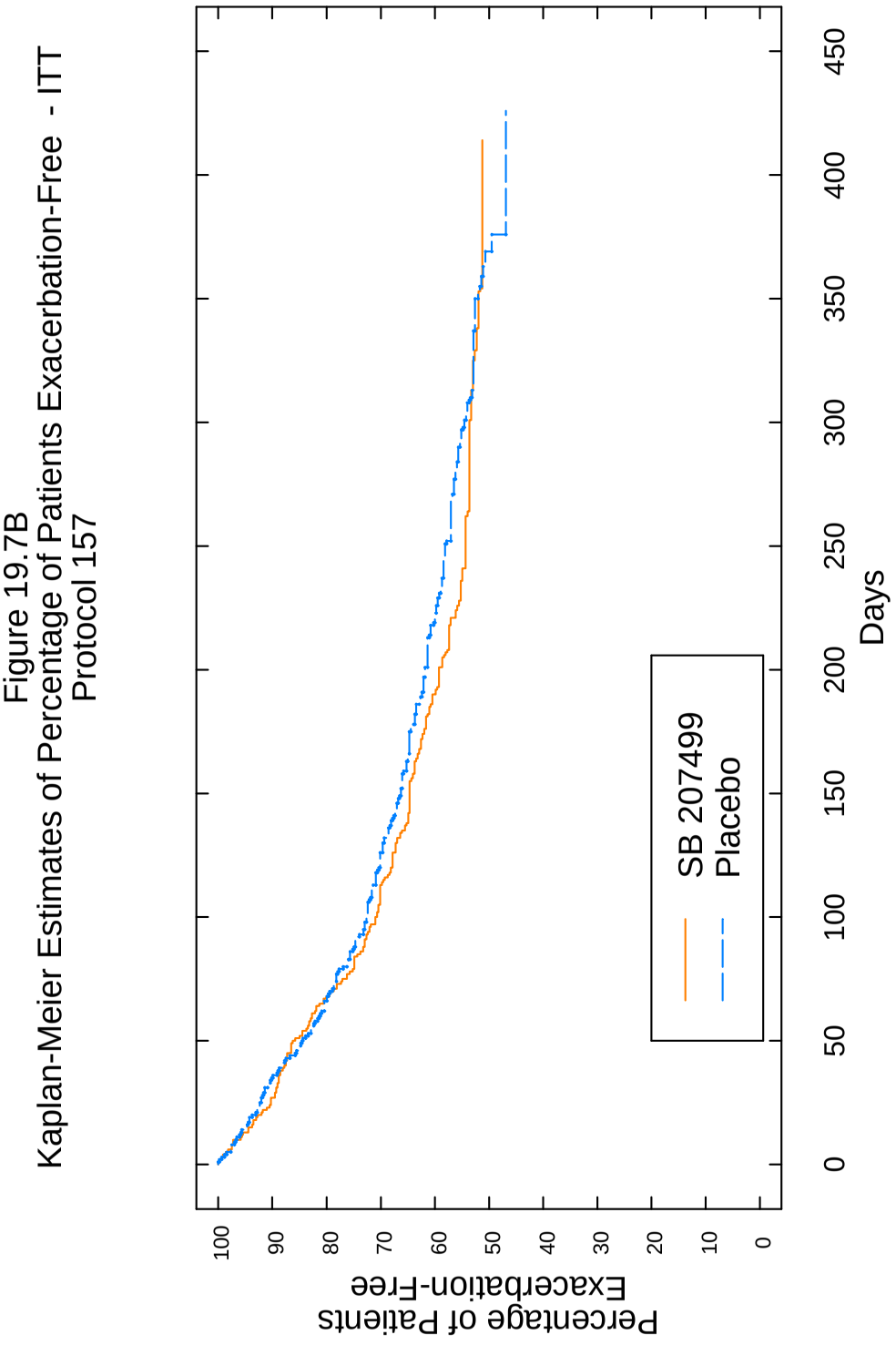


Figure 19.1H

Distribution of Change from Baseline FEV1 (L) at ITT Endpoint by Treatment Group

Protocol 157

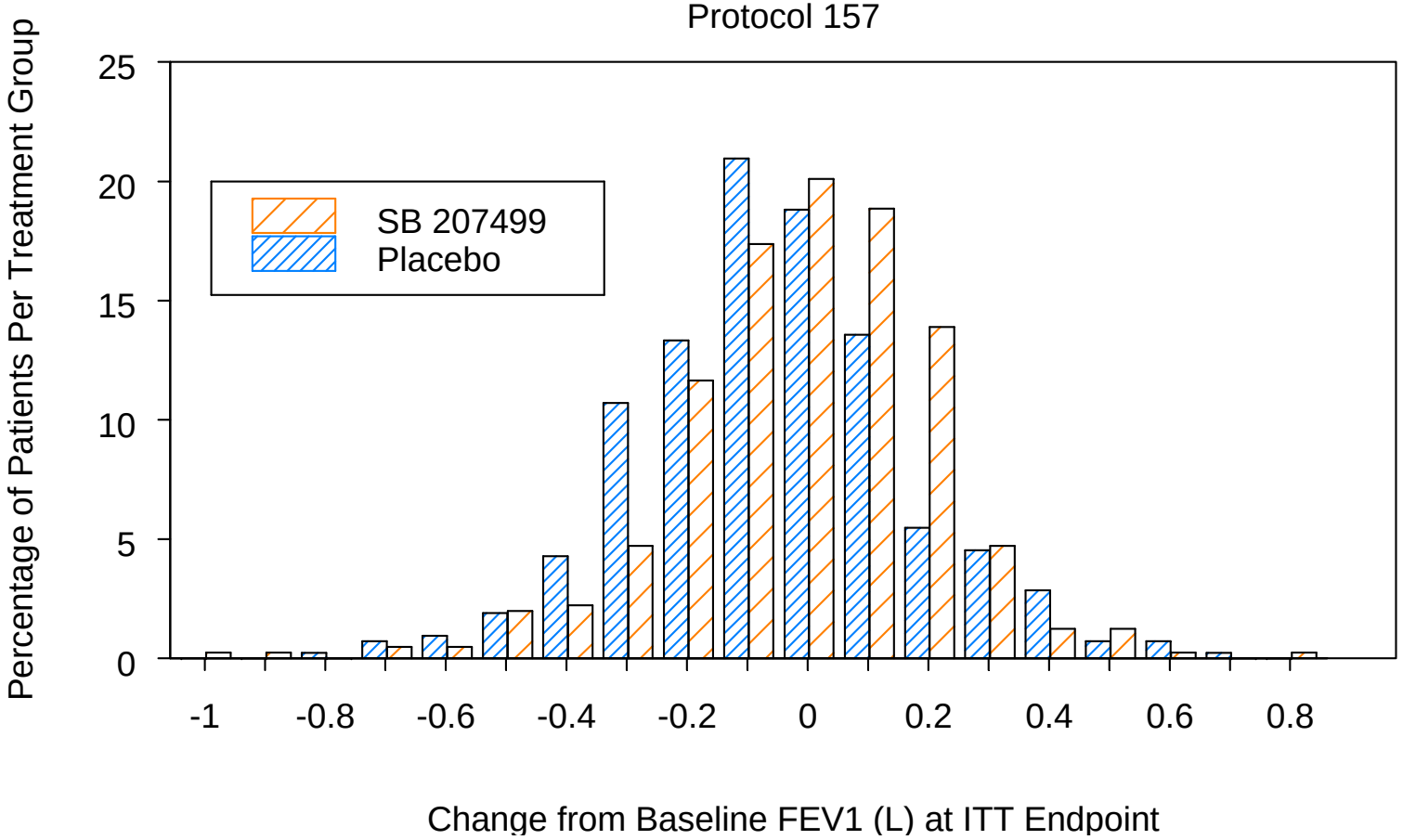


Figure 19.2B
Mean (SEM) Change from Baseline in SGRQ Total Score
ITT Completers
Protocol 157

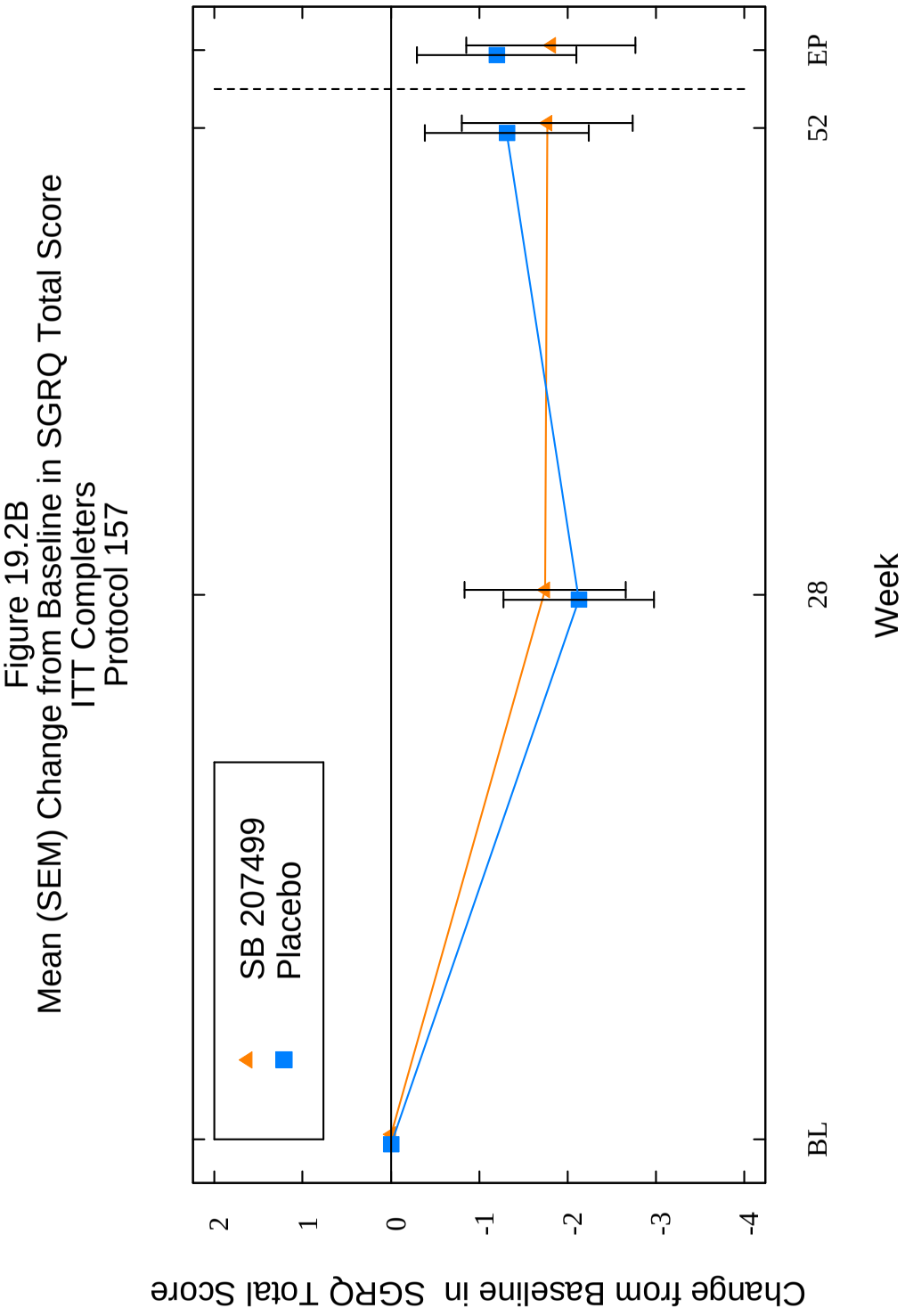


Figure 19.20
Cumulative Incidence of GI AEs - ITT
By Time of Initial Onset and Treatment Group
Protocol 157

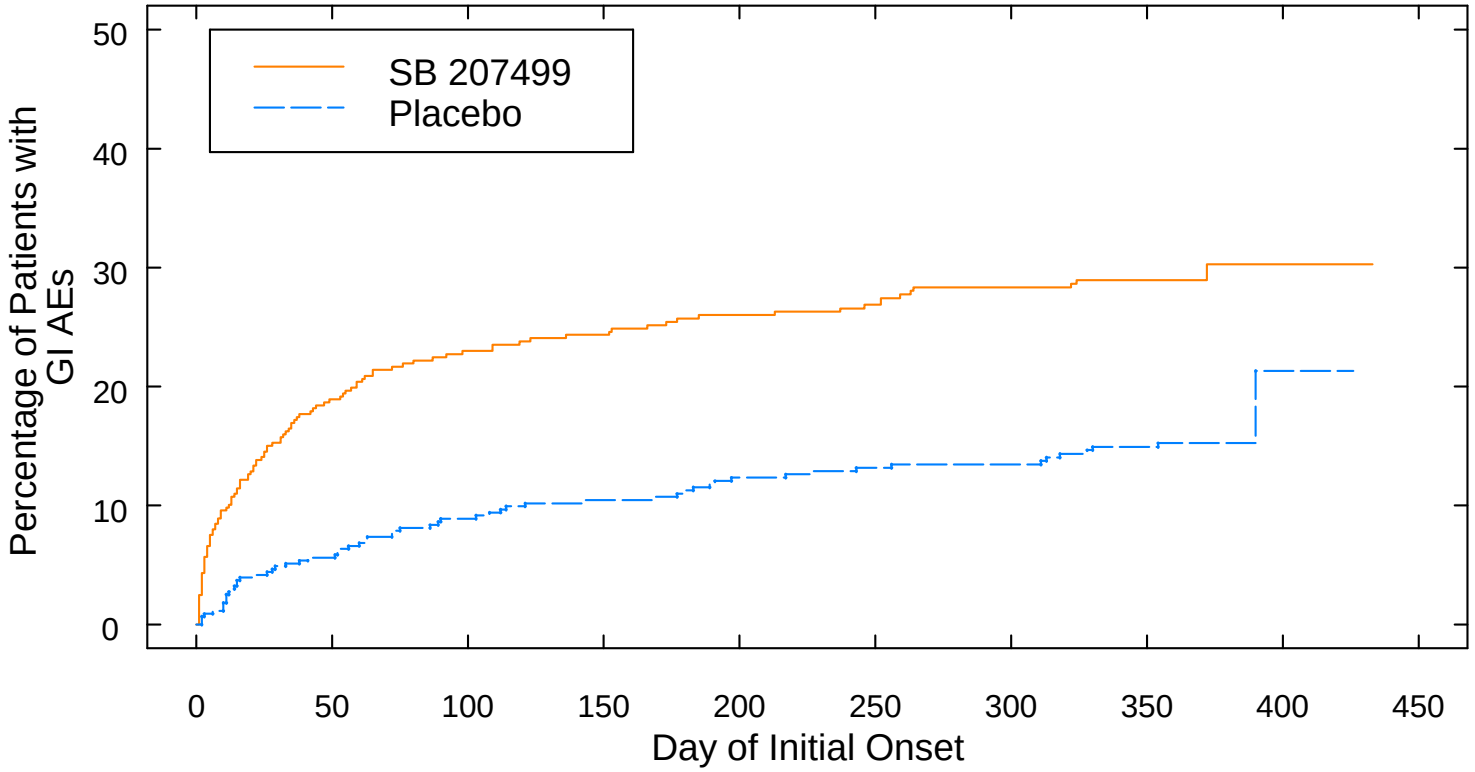


Figure 19.32
Percentage of Randomized Patients In Study
Protocol 157

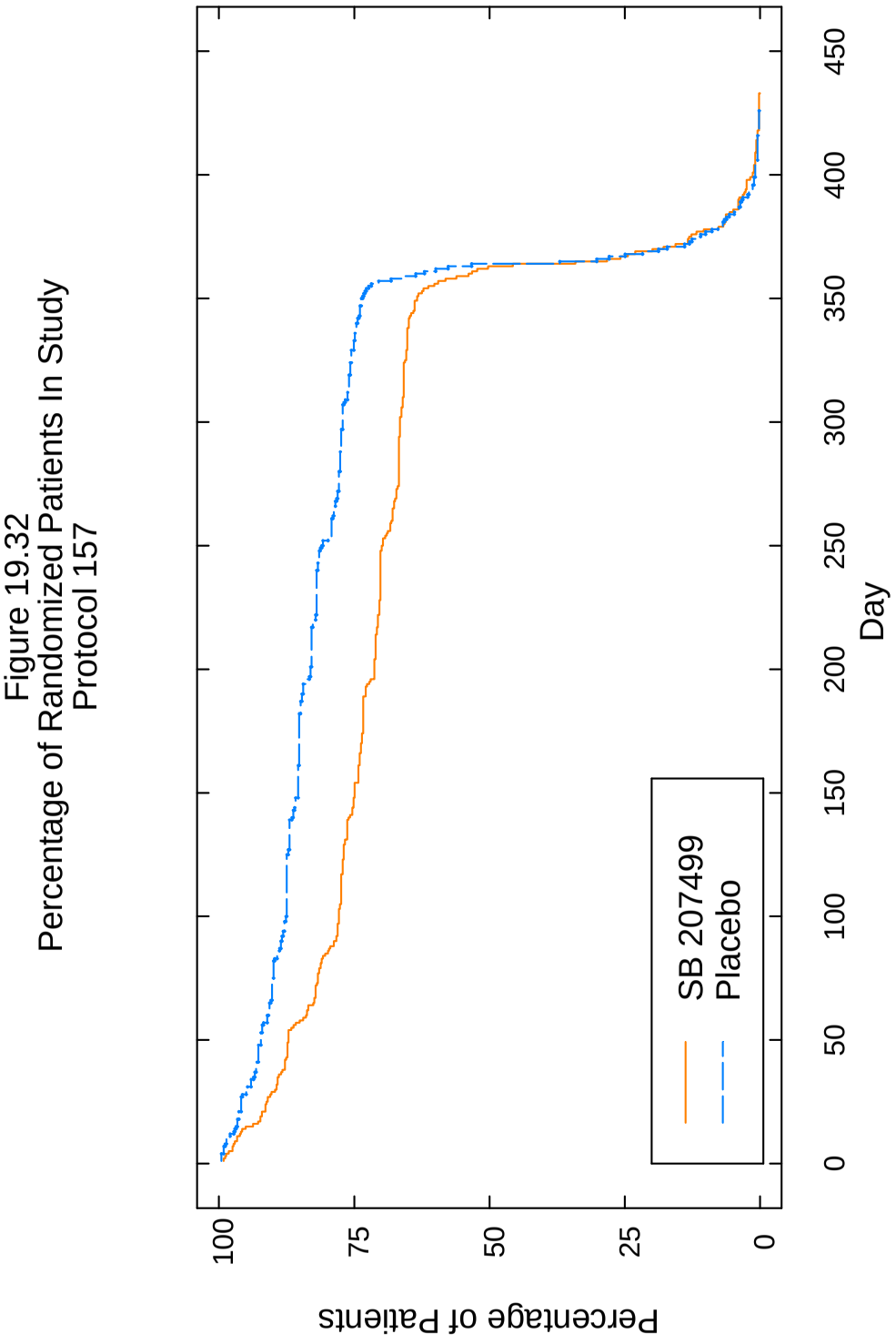


Figure 19.7F
Mean Cumulative Function for Exacberbations
By Treatment Group
All Randomized Patients
Protocol 157

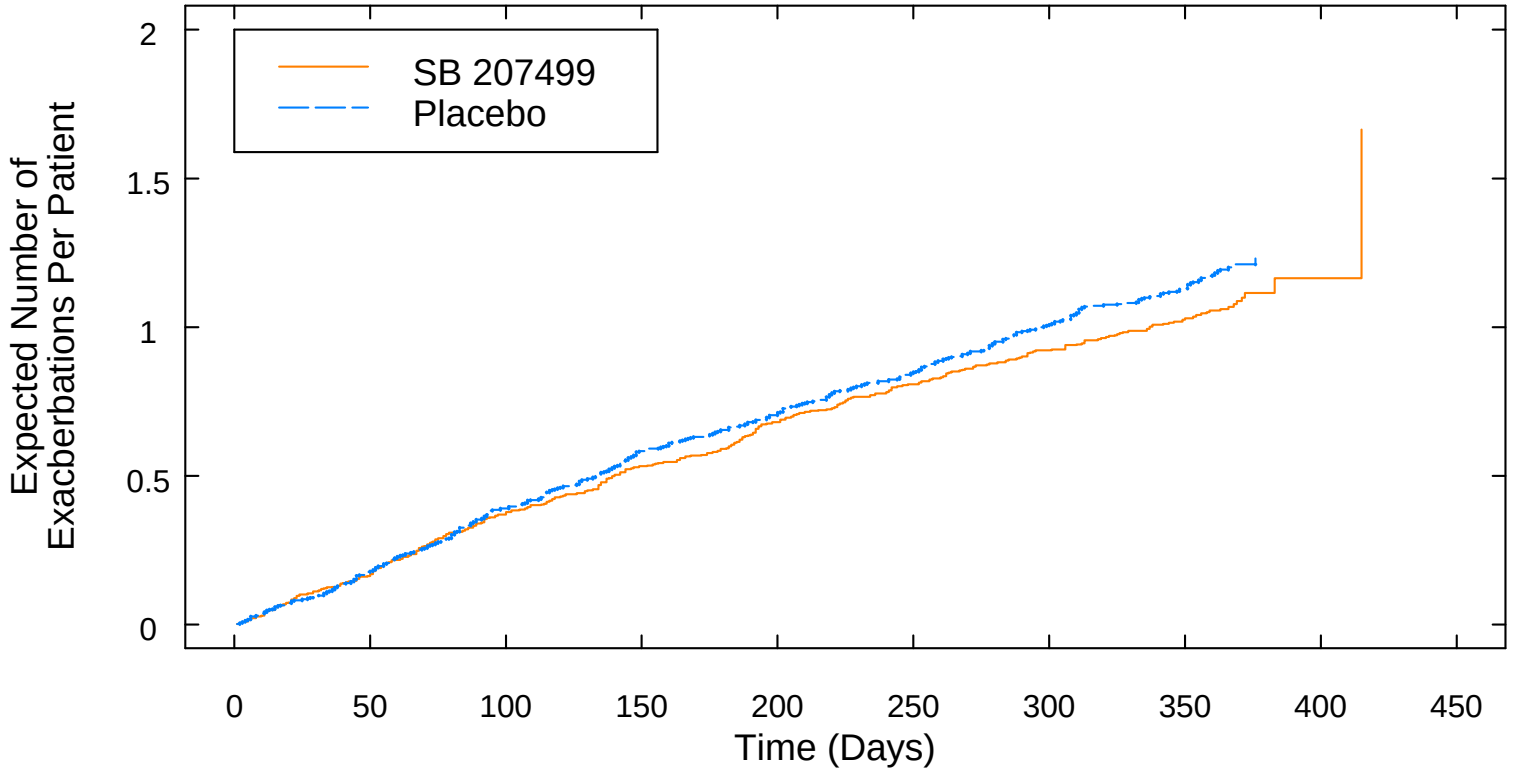
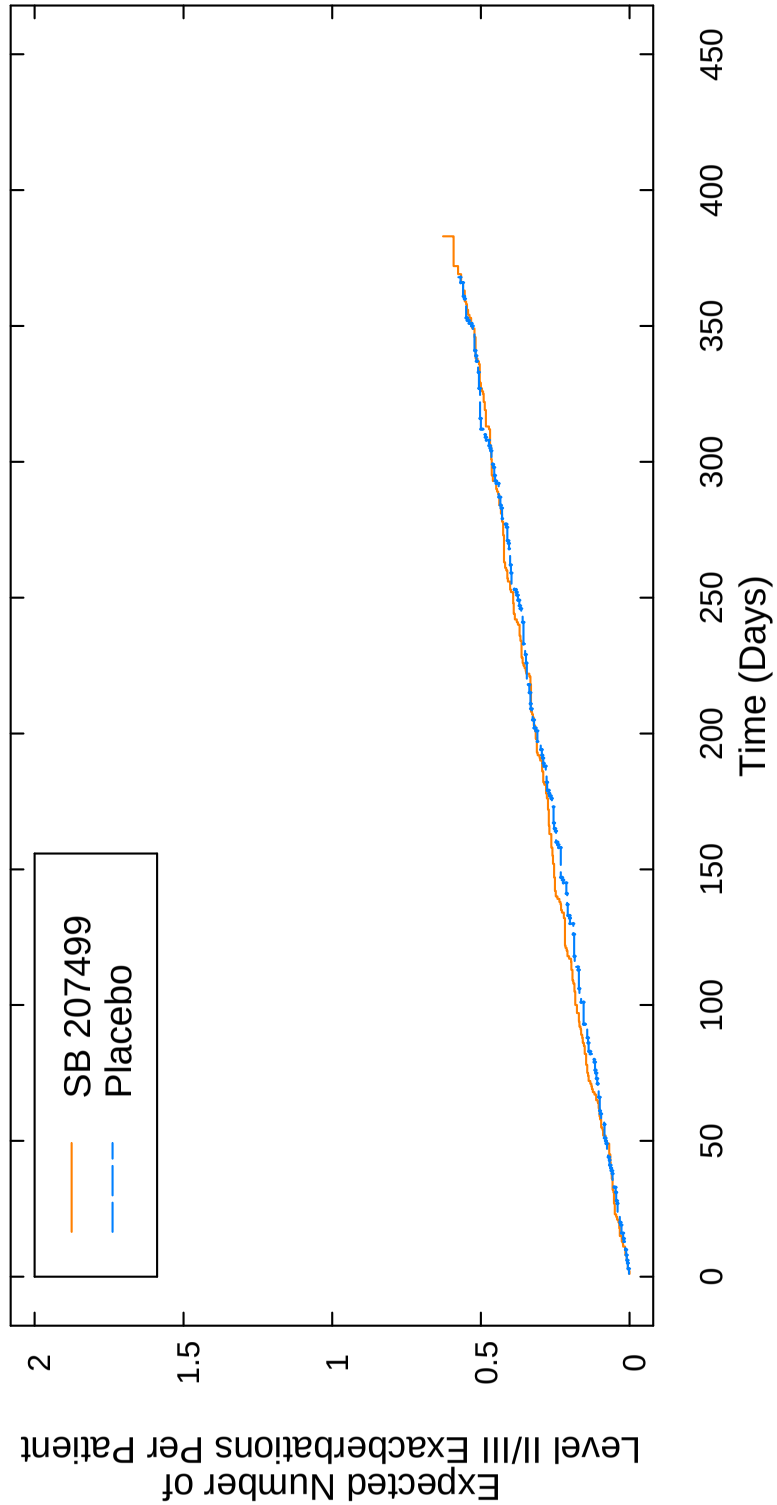


Figure 19.7E
Mean Cumulative Function for Level II/III Exacerbations
By Treatment Group
All Randomized Patients
Protocol 157



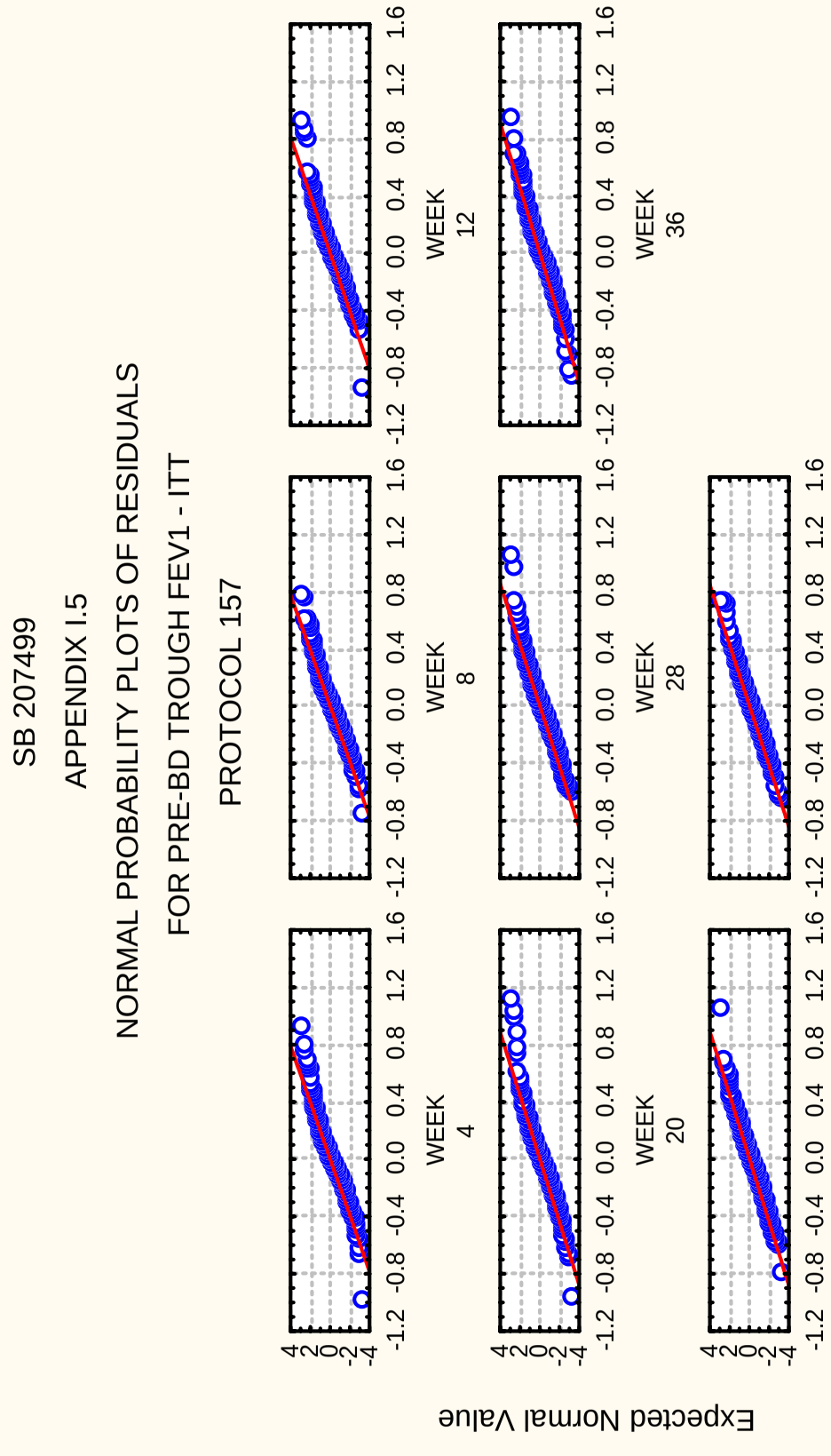
SB 207499

APPENDIX I.5

NORMAL PROBABILITY PLOTS OF RESIDUALS

FOR PRE-BD TROUGH FEV1 - ITT

PROTOCOL 157



Synopsis

Document Number: GM2004/00073/00 Study Number: SB-207499-157

Title: A Randomised, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy, Safety and Tolerability of Oral Cilomilast (15 mg bd) When Given as Maintenance Treatment for 12 Months to Subjects with Chronic Obstructive Pulmonary Disease (COPD)	
Investigator(s): This was a multicentre study.	
Study centre(s): The study was conducted in 137 centres in 18 countries (Australia, Belgium, Czech Republic, Denmark, Finland, France, Germany, Italy, Netherlands, New Zealand, Poland, Russia, Slovakia, South Africa, Spain, Sweden, Taiwan, United Kingdom).	
Publication(s): None at the time of this report	
Study period: 01Nov2001 - 09Jan2004	Phase of Development: III
Objectives: The primary objective of the study was to assess the clinical efficacy of cilomilast (15 mg bd) versus placebo as maintenance treatment for subjects with COPD by assessment of the reduction in the risk of COPD exacerbations and superior pulmonary function data (FEV_1) compared with placebo over a 52 week treatment period. The secondary objective of the study was to further define the clinical safety and tolerability of cilomilast 15mg bd versus placebo by assessment of adverse events and laboratory measures over a 52-week period in subjects with COPD.	
Methodology: This was a multicentre, multi-national, randomised, placebo-controlled, parallel group study consisting of a 4-week single blind, placebo run-in, a 52-week double-blind treatment period and a 1-week follow-up period after completion of treatment. Subjects discontinued all COPD medication on entry to the run-in period except for ipratropium bromide which they could continue at a constant dose plus as required salbutamol. Eligible subjects who completed the 4-week run in were randomised to receive either 15mg twice daily of cilomilast or placebo twice daily for 52 weeks. Assignment to study drug was stratified according to smoking status at baseline prior to randomisation for 'current smokers' and 'ex-smokers'. Subjects attended the clinic for 13 scheduled visits if they completed the study. There were two screening visits (week -4 and -2) and a baseline visit at week 0 (visit 3). During the double blind phase, visits were scheduled after 2, 4, 8, 12, 20, 28, 36, 44 and 52 weeks (visits 4 to 12). Throughout the study (Visit 1 through to Visit 12) subjects completed a daily record card (DRC) with details of morning peak expiratory flow (PEF), COPD symptoms, the use of rescue medication and health outcomes data. There were also patient and Investigator assessments of efficacy. Safety was assessed by monitoring adverse events (AEs), vital signs, clinical laboratory tests (chemistry and haematology) and 12 lead electrocardiograms (ECGs).	
Number of subjects: It was planned to randomise approximately 800 subjects to achieve 550 evaluable subjects who completed the study. 1390 subjects were recruited and 907 were randomised (455 cilomilast; 452 placebo); 619 subjects (288 cilomilast; 331 placebo) completed the study.	

Title: A Randomised, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy, Safety and Tolerability of Oral Cilomilast (15 mg bd) When Given as Maintenance Treatment for 12 Months to Subjects with Chronic Obstructive Pulmonary Disease (COPD)
Diagnosis and main criteria for inclusion: Male or female subjects aged between 40 and 80 years inclusive with a clinical diagnosis of COPD confirmed by spirometry; a pre-bronchodilator FEV_1 to FVC ratio ≤ 0.7, poor reversibility of airway obstruction defined by $\leq$10% of the predicted normal or $\leq$200 ml increase in FEV_1 (or both) after the administration of salbutamol 400 mcg and a post-salbutamol FEV_1 of ≥ 30 and $\leq$70% of predicted normal. Subjects with a smoking history of ≥ 10 pack years who in the opinion of the Investigator were not at risk of severe or life threatening exacerbations of COPD and were able to stop all COPD medications apart from short acting anti-cholinergics and salbutamol from Visit 1 were included. Subjects who successfully completed the baseline screening period and had less than 20% change (increase or decrease) in pre-bronchodilator FEV_1 assessed at screening Visit 2 and at baseline Visit 3, poor reversibility of airway obstruction defined by $\leq$10% of predicted normal or $\leq$200 ml increase in FEV_1 (or both) after the administration of salbutamol 400mcg at Visit 1 and Visit 3 and compliance of $\geq$ 80% and $\leq$ 120% in taking single-blind study medication during the placebo run-in period were eligible for randomisation and entry into the double-blind treatment period.
Treatment administration: Cilomilast Tablets containing 15 mg of cilomilast (SB 207499): Batch number [redacted] Matching placebo Tablets were provided: Batch numbers [redacted] and [redacted] Subjects in both groups took one Tablet in the morning immediately after breakfast and in the evening immediately after a meal. Metered Dose Inhalers (MDIs) of salbutamol (100 mcg/actuation, 200 actuations per canister) were provided for on-demand (prn) use during the study. Subjects in the Netherlands and Denmark were permitted to use 200mcg salbutamol per actuation via diskus devices as an alternative to the MDI device.
Criteria for evaluation: The primary efficacy endpoints were the occurrence of COPD exacerbations (Level II and III) and the change from baseline of pre-bronchodilator clinic FEV_1 at trough (> 8 hours after previous dose of study medication). Secondary efficacy endpoints included the number of subjects with mild, moderate and severe exacerbations, number of exacerbations (mild, moderate or severe), the time to the first exacerbation (any) and time to first moderate or severe exacerbation, clinic FEV_1 (post-bronchodilator) and disease-specific quality of life using the total score of the St. George's Respiratory Questionnaire (SGRQ). Safety was assessed by monitoring adverse events (AEs) with additional monitoring for gastrointestinal adverse events (GIAEs) including faecal occult blood tests, vital signs, clinical laboratory tests (chemistry and haematology) and 12 lead electrocardiograms (ECGs).

Title: A Randomised, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy, Safety and Tolerability of Oral Cilomilast (15 mg bd) When Given as Maintenance Treatment for 12 Months to Subjects with Chronic Obstructive Pulmonary Disease (COPD)

Statistical methods: Treatment differences for mean change from baseline in FEV_1 averaged over 52 weeks were analysed based on a repeated measure model with fixed effects for treatment, centre and time. The incidence of moderate or severe COPD exacerbations which occurred during the treatment period were analysed using a maximum likelihood based analysis, assuming a Poisson distribution. A Log-rank test was performed using SAS PROC LIFETEST to compare the exacerbation-free curves of a moderate or severe COPD exacerbation between cilomilast treatment group and placebo treatment group. The exacerbation-free survival rate at 52 weeks, and associated 95% confidence intervals, were estimated for each treatment group using the Kaplan-Meier product limit.

All continuous efficacy variables were also analysed using the ANOVA model with fixed effects of treatment and centre at all double-blind visits as well as endpoint. All categorical variables were tabulated using contingency Table and chi-square test. All efficacy variables were analysed for the intent to treat population with FEV_1 and exacerbation also analysed for the per protocol population as well. FEV_1 and COPD exacerbations (Level 2 and Level 3) were also analysed by subjects' smoking status.

Summary:

Efficacy: The average change from baseline in pre-bronchodilator trough FEV_1 in both the ITT and PP population was significantly greater in the cilomilast group over 52 weeks. The mean difference in both the ITT and PP populations was 0.041L ($p<0.001$) in this population of poorly reversible subjects. The difference between the groups within the ITT population was statistically significant after 4 weeks treatment and this was maintained over the 52-weeks of treatment. The improvement was significant in both non-smokers and smokers, although the largest average improvement over 52 weeks was seen in baseline smokers (0.048L) compared with baseline former smokers (0.039L). For the level of II/III COPD exacerbation rate over 52 weeks, there was no statistical difference in the rate per patient year (0.483 cilomilast; 0.448 placebo; $p=0.580$).

For secondary outcomes, there was no statistical difference between cilomilast and placebo in the number of subjects with mild, moderate and severe exacerbations, number of exacerbations (mild, moderate or severe), the time to the first exacerbation (any) and time to first moderate or severe exacerbation. Post-bronchodilator trough FEV_1 improved by 0.043L ($p=0.004$) over the 52-week period in favour of cilomilast. The difference between the groups in favour of cilomilast was significant at week 12 (0.051L; $p=0.001$), which was maintained until the end of the 52 week treatment period. The largest difference between the groups was seen at week 44 with a difference of 0.072L observed

In relation to the other endpoints there was a significant difference in the change from baseline in clinic PEF with a mean difference over 52 weeks between cilomilast and placebo of 5.50l/min ($p=0.029$), 8.84L/min at endpoint ($p=0.005$) and 8.867L/min ($p=0.024$) at week 52. FVC improved in favour of cilomilast by 0.042L $p=0.037$) on average over 52 weeks. Both the patient and investigator global assessment of efficacy resulted in more subjects being categorised as

Title: A Randomised, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy, Safety and Tolerability of Oral Cilomilast (15 mg bd) When Given as Maintenance Treatment for 12 Months to Subjects with Chronic Obstructive Pulmonary Disease (COPD)
improved in the cilomilast group compared to the placebo group. For the other tertiary endpoints there was no statistical difference in all individual domains of the SGRQ, the total number of COPD exacerbations of all severities, symptom score (cough, sputum and breathlessness), use of rescue medication and night-time awakenings, residual volume, blood CD4+/CD8+ ratio and level of serum C reactive protein at week 52. There were trends in favour of cilomilast for change from baseline in FEF_{25-75} over 52 weeks and duration of exacerbations although none of these reached statistical significance. Safety: The number of subjects experiencing an AE on-therapy was similar between subjects receiving cilomilast (77.1%) and placebo (75.9%). The most common AE in both treatment groups was an exacerbation of COPD which was experienced by 46.2% of subjects receiving placebo and 42.0% receiving cilomilast. The number of AEs considered by the investigator to be related to study medication was 10.4% in the placebo group and 21.5% in the cilomilast group. The most common treatment related events were related to the GI system which included nausea in 1.1% of subjects receiving placebo and 7.3% receiving cilomilast, diarrhoea by 1.3% and 4.4%, abdominal pain by 0.6% and 3.8% and vomiting by 0.7% and 2.4% of subjects respectively. The incidence of events which were determined by the investigator as being of severe intensity was 11.1% in both the placebo and cilomilast groups. The only events which were classified as severe in >1% of subjects in either treatment group was an exacerbation of COPD in 3.3% and 3.7% of subjects receiving placebo and cilomilast and nausea in 1.3% subjects receiving cilomilast. A total of 24 events (5.3%) in the placebo group resulted in an interruption in study medication compared to 40 events (8.8%) in the cilomilast group. Of these, three events occurred in >1% of subjects in any treatment group; nausea in 4 subjects (0.9%) receiving placebo and 6 subjects (1.3%) receiving cilomilast, exacerbation of COPD by 4 subjects (0.9%) and 6 subjects (1.3%) and headache by 3 subjects (0.7%) and 5 subjects (1.1%) respectively. A similar number of subjects experienced an on-therapy SAE in each treatment group with 12.2% of subjects receiving placebo and 11.6% receiving cilomilast. The most common SAE reported in both groups was an exacerbation of COPD which was experienced by 18 subjects (4.0%) in the placebo group and 19 subjects (4.2%) in the cilomilast group.

Title: A Randomised, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy, Safety and Tolerability of Oral Cilomilast (15 mg bd) When Given as Maintenance Treatment for 12 Months to Subjects with Chronic Obstructive Pulmonary Disease (COPD)

AEs commencing on-therapy which lead to withdrawal were reported by 40 subjects (8.8%) in the placebo group and 75 subjects (16.5%) in the cilomilast group. The most common AEs leading to withdrawal were exacerbation of COPD, nausea, diarrhoea and vomiting which were all reported by $\leq$ 4% of the subjects in either treatment group. All other AEs leading to withdrawal were reported by five subjects or less. GI events of concern were experienced in 11 (2%) of subjects receiving placebo and 32 (7%) of subjects receiving cilomilast of which one patient in the placebo group (0.2%) and 17 subjects in the cilomilast group (3.7%) were withdrawn; diarrhoea was the most common event requiring 6 subjects (1.3%) in the cilomilast group to be withdrawn from the study.

There was no difference between placebo and cilomilast in the transition to a value of either low or high concern in haematology and biochemistry analytes or vital signs and new-onset ECG changes.

Conclusions:

- There was a significant improvement in pre and post-bronchodilator trough $FEV_{1,}$ maintained over 52 weeks and pre-bronchodilator FVC and PEF.
- Cilomilast was well tolerated in the majority of subjects over 52 weeks.

Date of Report: February 2009

Confidential



Cilomilast

Cilomilast (SB 207499)

A Randomised, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy, Safety and Tolerability of Oral Cilomilast (15 mg bd) When Given as Maintenance Treatment for 12 Months to Subjects with Chronic Obstructive Pulmonary Disease (COPD)

SB 207499/157

Final Protocol

[redacted] PhD*
[redacted] MB Bs FRAC PhD*, [redacted] PhD**, [redacted] PhD**

*Clinical Development &Medical Affairs, GlaxoSmithKline, **Biostatistics and Data Sciences, GlaxoSmithKline

SB Document Number: SB-207499/RSD-101LWJ/4

Issue Date: 08 August 2001
Amended: 26 September 2001
10 August 2002
26 March 2003

Endorsements

Clinical Unit: European Respiratory Medical Affairs

Document No.: SB-207499/RSD-101LWJ/4

Drug Name: Cilomilast

Compound No: SB 207499

Protocol Title: A Randomised, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy, Safety and Tolerability of Oral Cilomilast (15 mg bd) When Given as Maintenance Treatment for 12 Months to Subjects with Chronic Obstructive Pulmonary Disease (COPD)

CPMS Number: 207499/157

GSK Site Monitor:

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

Table of Contents

Synopsis 12
1 Introduction 22
2 Objectives 26
2.1 Primary Objectives 26
2.2 Secondary Objectives 26
3 Study Design Overview 26
3.1 Study Design 26
3.2 Schedule of Assessments 30
3.3 Method of Randomisation 33
4 Study Population 33
4.1 Number of Patients/Centres 33
4.2 Inclusion Criteria 33
4.2.1 Screening Inclusion Criteria (At Screening Visit 1) 33
4.2.2 Randomisation Inclusion Criteria (at Baseline Visit 3) 35
4.3 Exclusion Criteria 35
4.3.1 Screening Exclusion Criteria (At Screening Visit 1) 35
4.3.2 Randomisation Exclusion Criteria (at Baseline Visit 3) 37
5 Conduct of the Study 37
5.1 Ethical and Regulatory Considerations 37
5.1.1 Ethics Review Committee (ERC) 37
5.1.2 Informed Consent 38
5.2 Outline of Study Procedures 39
5.2.1 Study Visits 39
5.3 Detailed Description of Study Stages/Visits 39
5.3.1 Visit 1 (Week-4): Screening and Start of 4-week Single-blind Run-in 39
5.3.2 Visit 2 (Week -2): Single-blind Run-in Period 42
5.3.3 Visit 3 (Week 0): Baseline, Start of Double-blind Treatment Phase .. 44
5.3.4 Visit 4 (End of Week 2): Double-blind Treatment Phase 48
5.3.5 Visit 5 (End of Week 4): Double-blind Treatment Phase 50
5.3.6 Visit 6 (End of Week 8): Double-blind Treatment Phase 52
5.3.7 Visit 7 (End of Week 12): Double-blind Treatment Phase 54
5.3.8 Visit 8 (End of Week 20): Double-blind Treatment Phase 57
5.3.9 Visit 9 (End of Week 28): Double-blind Treatment Phase 59
5.3.10 Visit 10 (End of Week 36): Double-blind Treatment Phase 62
5.3.11 Visit 11 (End of Week 44): Double-blind Treatment Phase 64
5.3.12 Visit 12 (End of Week 52): End of Double-blind Treatment Phase . 67
5.3.13 Early Withdrawal Assessments 68

Early Withdrawal Visit 69
5.3.14 Safety Follow-up Visit 71
5.4 Clinical Observations and Procedures 72
5.4.1 Previous Medical History and Diagnosis 72
5.4.2 Physical & Respiratory Examination and Vital Signs 73
5.4.3 Chest Radiograph 73
5.4.4 Electrocardiograph (ECG) 74
5.4.5 Pulmonary Function Tests 74
5.4.6 Residual Volume (Visits 3, 9 and 12 and Early Withdrawal - selected centres only) 75
5.4.7 Domiciliary Peak Flow Measurement 76
5.4.8 Laboratory Tests 76
5.4.9 Diary Card 78
5.4.10 Patient and Investigator Global Assessments 79
6 Study Medication and Administration 80
6.1 Study Medication 80
6.2 Dosage and Administration 81
6.3 Blinding 81
6.4 Packaging 82
6.5 Labelling and Preparation 82
6.6 Storage 83
6.7 Drug Accountability 83
6.8 Assessment of Compliance 83
6.9 Treatment of Study Medication Overdose 84
6.10 Occupational Safety 84
6.11 Concomitant Medication/Treatment 84
6.11.1 Permitted Medications 84
6.11.2 Prohibited Medications 86
6.11.3 Treatment of COPD Exacerbations 88
6.11.4 Concomitant Medication 88
7 Outcomes Research and Pharmacoeconomics 88
7.1 Outcomes Measurement and Analysis 88
7.2 Economic Data Collection and Analysis 89
7.3 Health Status Analyses 89
8 Adverse Events 90
8.1 Eliciting and Documenting Adverse Events 90
8.1.1 Adverse Event Definition 90
8.1.2 COPD Exacerbation Definitions 91
8.1.2.1 Resolution of Exacerbations 92
8.1.3 Gastrointestinal Adverse Events 93

8.1.4 Serious Adverse Event Definition 94
8.2 Recording of Adverse Events 96
8.2.1 Soliciting of Adverse Events 97
8.2.2 Evaluating the Adverse Event 97
8.2.2.1 Assessment of Intensity/Severity 97
8.2.2.2 Assessment of Causality 98
8.3 Reporting and Recording of Serious Adverse Events 99
8.3.1 Regulatory Responsibility 99
8.3.2 Recording of Serious Adverse Events 99
8.3.3 Reporting of Serious Adverse Events to GlaxoSmithKline 100
8.3.4 Follow-up of Serious AEs 101
8.4 Overdose 101
8.4.1 Reporting of Overdose 102
8.4.2 Further Information on Overdose 102
8.5 Treatment Failures 102
8.6 Post-study Events 102
8.7 Pregnancy 102
8.7.1 Reporting of Pregnancy 103
8.7.2 Follow-up of Pregnancies 103
8.7.3 Action Taken as a Result of Pregnancy 103
8.8 Unblinding Treatment Codes 103
8.9 Investigator Letters 104
9 Subject Completion and Withdrawal 104
9.1 Definitions 104
9.2 Procedures for Handling Withdrawals 104
9.3 Reasons for Withdrawal 105
10 Statistical Issues: Design and Analysis 106
10.1 Objectives 106
10.2 Hypotheses 106
10.3 Definition of Variables 107
10.3.1 Primary Efficacy Variable 107
10.3.2 Secondary Efficacy Variables 107
10.3.2 Secondary Efficacy Variables 108
10.4 Comparisons of Interest 109
10.4.1 Primary Comparisons of Interest 109
10.4.2 Other Comparisons of Interest 109
10.5 Interim Analysis 109
10.6 Target Sample Size 110
10.6.1 Sample Size Calculation 110
10.6.2 Sample Size Sensitivity 110

10.6.3 Sample Size Re-Estimation 111
10.7 Methods of Analysis 111
10.7.1 Populations of Interest 111
10.7.2 Statistical Methods 112
11 Administrative Matters 114
References 115
Appendices 117

List of Tables

Table 1 Treatment Differences for Cilomilast Phase III Studies in Primary and Secondary Parameters Intent-to-Treat Population* 24
Table 2 Overall Incidence of Most Commonly Reported On-therapy Adverse Events in Cilomilast Phase III Studies 25
Table 3 Outline of Study Procedures 31
Table 4 Examples of Permitted Medications 85
Table 5 Prohibited Medications 87

List of Figures

Figure 1 Schematic Representation of Study Design..... 29

List of Appendices

Appendix A Declaration of Helsinki 118
Appendix B Administrative Matters 122
Appendix C Sample Informed Consent 127
Appendix D Prediction Equations 139
Appendix E The EQ-5D Questionnaire 141
Appendix F The St. George's Respiratory Questionnaire 147
Appendix G Gastrointestinal Adverse Event Monitoring 164

List of Abbreviations & Definitions

Abbreviations

AE	adverse event
ALP	alkaline phosphatase
ALAT (SGPT)	alanine aminotransferase
ASAT (SGOT)	aspartate aminotransferase
bd	twice daily
BP	blood pressure
BTPS	body temperature and pressure standard
cyclic AMP	cyclic adenosine monophosphate
CI	confidence interval
cm	Centimetre
CO	carbon monoxide
COPD	chronic obstructive pulmonary disease
CRF	case report form
DMPK	drug metabolism and pharmacokinetics
DRC	daily record card
ECG	Electrocardiogram
ER	Emergency Room
ERC	ethics review committee
FEF_{25-75}	forced expiratory flow at 25-75% vital capacity
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
GGT	gamma-glutamyl transferase
GSK	GlaxoSmithKline
HR	heart rate
ICS	inhaled corticosteroids
ITT	intent-to-treat
IUD	intrauterine device
LTOT	long-term oxygen therapy
mcg	Microgram
MDI	metered dose inhaler
mg	Milligram
ml	Millilitre
mmHg	millimetres of mercury
PCO_2	arterial carbon dioxide tension
PDE4	phosphodiesterase 4
PEF	peak expiratory flow rate
PFT	pulmonary function test
PK	Pharmacokinetic
PO_2	arterial oxygen tension

prn	pro re nata (as needed)
RV	residual volume
R&D	research and development
SaO_2	transcutaneous oxygen saturation
SB	SmithKline Beecham
SGRQ	St. George's Respiratory Questionnaire

Definitions

adverse event	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
serious adverse event	any event which is fatal, life-threatening, disabling or incapacitating or results in hospitalisation, prolongs a hospital stay, a congenital abnormality, or is associated with cancer or overdose (either accidental or intentional), and pregnancy. In addition, any event which the Investigator regarded as serious based on appropriate medical judgement

Synopsis

Compound/Protocol No.

SB 207499/157

Protocol Title

A Randomised, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy, Safety and Tolerability of Oral Cilomilast (15 mg bd) When Given as Maintenance Treatment for 12 Months to Subjects with Chronic Obstructive Pulmonary Disease (COPD)

Rationale

Chronic obstructive pulmonary disease (COPD) is a disease state characterised by progressive development of airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response to the lungs to noxious particles or gases[1]. COPD comprises both chronic bronchitis and emphysema and is characterised by inflammatory abnormalities in small airways.

COPD is one of the leading causes of death worldwide, fourth or fifth highest in developed countries, with an increasing prevalence and mortality [2] and is projected to be the third leading cause of death worldwide by 2020 [3].

Patients typically have chronic symptoms, particularly breathlessness on exertion, and a productive cough, accompanied by progressive deterioration in lung function, interspersed by exacerbations of their disease. This combination leads to substantial impairment in the patient's health related quality of life [4]. Long term evaluation of the disease is based on rate of decline in lung function over time, exacerbations, and health status.

Many definitions of COPD exist but in general most definitions include some combination of the following clinical findings: decrease in lung function, worsening of dyspnoea, increase in sputum purulence, and increase in sputum volume. Following an exacerbation, most patients are expected to experience at least a temporary decrease in functional status and quality of life [5] and 50% of those hospitalised for the condition are expected to be re-admitted at least once in the ensuing 6 months [6][7].

Stopping smoking is the single most effective means of improving prognosis in patients with COPD [8] and is associated with a reduction in the accelerated rate of decline in FEV_1 [9]. None of the existing medications for COPD has been shown to modify the long-term decline in lung function. Therefore, pharmacotherapy for COPD is used predominantly to decrease symptoms and minimise number and severity of exacerbations. The vast majority of patients are treated with inhaled or oral bronchodilators alone, including anticholinergics, short- and long- acting β_2 agonists and theophyllines. Regular treatment with inhaled corticosteroids is recommended for symptomatic patients with a spirometric response to ICS or those with FEV_1< 50% predicted normal value and repeated exacerbations requiring treatment with antibiotics or oral corticosteroids [1].

Cilomilast is a potent and selective phosphodiesterase type 4 (PDE4) inhibitor currently under development for the treatment of COPD. 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 activities, along with the knowledge that PDE 4 is the major cyclic AMP-hydrolysing isozyme in these cells [10].

In two of the recently completed Phase III studies (Studies 039 and 091), administration of cilomilast was shown to result in a dramatic diminution of exacerbation rates over the 24 weeks of treatment. Treatment with cilomilast reduced the risk of having an exacerbation by 39% relative to placebo ($P = 0.002$) and the risk of an exacerbation requiring treatment by a physician or hospitalisation by 45% ($P = 0.001$) in Study 039. Similarly, in Study 091, the risk of having an exacerbation was reduced by 30% ($P = 0.005$) and the risk of an exacerbation requiring treatment by a physician or hospitalisation by 32% ($P = 0.010$). A similar impact on exacerbations was not observed in the third Phase III study, Study 042. Resource utilisation-free survival associated with COPD exacerbation was significantly higher in the cilomilast group (88.1%) than in the placebo group (76.9%; P = 0.004) in Study 039. In this study, the cilomilast-treated group had a higher percentage of patients that were utilisation-free in terms of physician visits, ER/urgent care visits and hospitalisations over the entire 24-week treatment period. Similar trends were observed in Studies 042 and 091.

Study 157 is being conducted as a pivotal Phase III study to assess the efficacy and safety of cilomilast versus placebo over a longer timeframe as maintenance treatment in patients with COPD and to confirm and extend the results observed

in studies 039 and 091. The study design of Study 157 is similar to that of Studies 039, 042, and 091. However, in Study 157, there will be two co-primary efficacy parameters based on COPD exacerbations and Clinic FEV_1. Patients will be treated with randomised study medication for 52 weeks.

As of 15 February 2001, 717 patients have been treated with cilomilast in 32 Phase I clinical pharmacology studies; 1100 patients in six Phase II dose-ranging studies (633 and 467 patients, respectively with asthma and COPD); and 1891 patients with COPD in three double-blind, placebo-controlled Phase III studies, long-term open extension studies and mechanism of action studies. Two Phase III studies are currently ongoing.

Three Phase III randomised, double-blind, placebo-controlled studies (039, 042, and 091) have recently completed. Patients with COPD were characterised by a % predicted FEV_1 ≥30% and ≤70% post-bronchodilator, a FEV_1/FVC of ≤0.7, and fixed airway obstruction differentiated by ≤15% reversibility following administration of a $beta_2$-agonist. Study 039 was conducted in North America, 091 in Europe, and 042 Internationally. In each of the phase III, placebo-controlled studies, patients with COPD entered a 4-week single-blind run-in phase and then were randomised to receive cilomilast 15 mg bd or placebo in a ratio of 2 to 1. A total of 1374 patients were treated with cilomilast 15 mg bd. Efficacy data from the three Phase III studies are presented in the following table.

Treatment Differences for Cilomilast Phase III Studies in Primary and Secondary Parameters Intent-to-Treat Population*

	039		042		091	
Randomised Patients	**Placebo 213**	**Cilomilast 425**	**Placebo 226**	**Cilomilast 474**	**Placebo 242**	**Cilomilast 469**
FEV_1(trough)**	40 ml (0.002) [0.01, 0.06]		30 ml (0.044) [0.00, 0.06]		30 ml (0.055) [-0.00, 0.06]	
SGRQ**†	-4.1 (<0.001) [-6.0, -2.2]		0.7 (NS) [-1.2, 2.6]		-0.4 (NS) [-2.4, 1.6]	
FVC (trough)	50 ml (0.049) [0.00, 0.10]		50 ml (0.047) [0.00, 0.09]		20 ml (NS) [-0.03, 0.06]	
Dyspnoea	-0.24 (0.029) [-0.45, -0.02]		-0.20 (0.068) [-0.41, 0.01]		-0.16 (NS) [-0.36, 0.04]	
Exacerbations Relative Risk††	0.61 (0.002) [0.45, 0.83]		1.07 (NS) [0.83, 1.40]		0.70 (0.005) [0.55, 0.90]	

* Mean change from baseline based on the comparison to placebo averaged over 24 weeks. *P* values are provided in parentheses. Lower/Upper 95% CI are provided in brackets.
** Primary Endpoint; alpha = 0.025.
† St. Georges Respiratory Questionnaire.
†† Cilomilast relative to placebo.
NS not significant.

The maintenance of pulmonary function demonstrated in Study 039 is supported by the results of Studies 042 and 091, in which modest improvements in both FEV_1 and FVC were demonstrated when averaged over 24 weeks of treatment. Although the primary endpoint in Studies 042 and 091 did not achieve statistical significance, comparisons of the least square mean differences over placebo for both FEV_1 and FVC in these three studies suggest that cilomilast maintains and may slightly improve pulmonary function in patients with moderate to severe "fixed" COPD (approximately 45% of which are active smokers) over a six-month period, while placebo-treated patients experience a linear decline in FEV_1.

In these three Phase III studies, the most common on-therapy adverse experiences reported in more than 5% of patients are displayed by decreasing frequency in the following table.

Overall Incidence of Most Commonly Reported On-therapy Adverse Events in Cilomilast Phase III Studies

	All Randomised Patients			
	Placebo		Cilomilast	
Adverse Event*	**(N = 684)**		**(N = 1374)**	
(Preferred Term)	**N**	**%**	**N**	**%**
Chronic obstructive airways disease	266	38.9	422	30.7
Diarrhoea	41	6.0	175	12.7
Nausea	28	4.1	172	12.5
Abdominal pain	39	5.7	157	11.4
Upper respiratory tract infection	51	7.5	111	8.1
Headache	43	6.3	101	7.4
Dyspepsia	17	2.5	83	6.0
Vomiting	7	1.0	76	5.5

* Includes adverse events reported for >5% of patients in either of the treatment groups.

Chronic obstructive airways disease (i.e. exacerbations) was reported more frequently in patients who received placebo while diarrhoea, nausea, abdominal pain, dyspepsia and vomiting were reported more frequently in patients who received cilomilast. The majority of the events were considered mild or moderate in severity by the Investigators. The gastrointestinal adverse experiences reported more frequently in patients who received cilomilast were generally mild and expected side effects of the known pharmacology of the drug. Most of these gastrointestinal adverse experiences were self-limiting and occurred during the initial period of treatment. Few of the events were considered serious. In Studies 039 and 091, patients who received placebo had a higher incidence of exacerbations of their underlying disease. This effect was not seen in Study 042.

There was no evidence of any adverse effect on laboratory parameters, vital sign values, or electrocardiographic parameters.

Please refer to the Investigator's Brochure for more detailed pre-clinical and clinical information. [11]

Objectives

The primary objective of the study is to assess the clinical efficacy of cilomilast (15 mg bd) versus placebo as maintenance treatment for patients with COPD by assessment of the reduction in the risk of COPD exacerbations and improvement in pulmonary function (FEV_1) over a 52 week treatment period.

The secondary objective of the study is to further define the clinical safety and tolerability of cilomilast 15 mg bd versus placebo by assessment of adverse events and laboratory measures over a 52 week period in subjects with COPD

Study Population

Approximately 800 patients will be randomised to achieve 550 evaluable patients to complete the study. Up-to 100 centres in Europe and Australia/New Zealand are expected to participate, with each centre aiming to enrol between 8 and 24 patients.

Study Design

This Phase III study is a double-blind, placebo controlled, randomised, parallel group study requiring a maximum of 13 visits over a 57-week period. Subjects meeting the Visit 1 inclusion criteria are entered into a 4 week single-blind placebo run-in period to collect baseline data. During the run-in period subjects are permitted to take ipratropium bromide (constant dose) and salbutamol (prn) for the treatment of COPD. At the end of this 4 week period, subjects complying with inclusion/exclusion criteria will be eligible for continuation into the double-blind phase of the study for 52 weeks. Subjects will be randomly allocated to either cilomilast 15mg bd or placebo bd. Study medication will be administered immediately after breakfast and evening meal. Assignment to study drug will be stratified according to smoking status at Baseline prior to randomisation for 'current smokers' and 'ex-smokers'.

Throughout the study (Visit 1 - through to Visit 12) subjects complete a daily record card with details of morning PEF, COPD symptoms and the use of rescue medication. In the event of early discontinuation of study treatment, subjects will be urged to continue to complete their daily record cards and to attend the remaining scheduled clinic visits for essential assessments (for the 52 week treatment period). The number and severity of COPD exacerbations will be assessed by the Investigator at each clinic visit by reviewing the diary card entries as well as specific questioning. Each COPD exacerbation will be categorised according to one of the three levels of severity.

Level 1 (Mild-self treated): Acute worsening of COPD that is self-managed by the patient at home by increasing the dose of relief salbutamol medication by > 2 occassions/24 hour period on two or more consecutive days compared with their baseline (baseline = mean of last 10 days of run-in period) or use of other additional bronchodilator medication

Level 2 (Moderate- physician, investigator treated): Acute worsening of symptoms (cough, sputum production, breathlessness) requiring treatment with oral corticosteroids prescribed by a physician or primary care doctor, or as a result of hospital out-patient visit (including Emergency Room).

Exacerbations requiring oral corticosteroids will be treated with a standardised course of prednisolone or prednisone tablets 30mg/day for 10 days, or methylprednisolone tablets 24mg/day for 10 days.

Level 3 (Severe - attendance at hospital): Acute worsening of COPD that requires the patient to be admitted to hospital for treatment.

If appropriate, courses of antibiotics may be prescribed to treat an infection (Level 1, 2 or 3)

Details of all exacerbations will be recorded in the COPD Exacerbation Section in the CRF as follows: dates of onset and resolution; outcome and severity. In addition any information collected during the exacerbation should be recorded in the CRF (e.g. lung function tests, other laboratory tests, change in alertness, malaise, insomnia, fatigue, depression, confusion, symptoms associated with URTI, ankle swelling, heart rate, respiratory rate, pulse oximetry (arterial blood gases) and blood sample for serum C Reactive Protein).

The time of resolution of an exacerbation will be determined by the investigator and/or subject. However, some guidance for distinguishing recurrence of a single exacerbation from distinct exacerbation episodes is provided as follows.

- Level 2 exacerbations treated with oral corticosteroids will be classified as separate exacerbations only if the courses of treatment are administered more than one week apart. A course of oral corticosteroids started within one week of finishing a previous course will be considered a continuation of the exacerbation.

- Likewise hospitalisation for an exacerbation within a week of completing a course of oral corticosteroids or initiation of a course oral corticosteroids within a week of discharge from hospital for an exacerbation will be considered a single continuous (Level 3) exacerbation.

Where a Level 1 exacerbation is immediately preceded or followed (within 1 week) by an exacerbation of any level, the investigator and/or subject will consider the possibility that this represents a continuation of the exacerbation.

Pulmonary function tests will be performed at all visits (with the exception of Visit 4). At these visits pulmonary function (FEV_1, FVC, FEF_{25-75} and PEF) will be measured before and after a standard dose of salbutamol (400 mcg), at trough levels of study drug except at the second visit, Week –2, when pulmonary function tests will be performed before and after ipratropium (80 mcg). To ensure consistency of pulmonary function data, spirometry equipment will be standardised and pulmonary function data reviewed centrally throughout the study. At selected centres, residual volume (RV) will be measured pre- and post-salbutamol at Baseline, Visit 9 (Week 28) and Visit 12 (Week 52).

The impact of COPD on patient health status will be assessed by the SGRQ and EQ-5D at Baseline, Week 28 and Week 52. A Patient and Investigator Global Assessment will be elicited at Baseline, Visit 9 (Week 28) and Visit 12 (Week 52).

Safety assessments will include adverse events, vital signs, ECGs, and clinical laboratory tests. Additional monitoring will be provided for gastrointestinal adverse events. Gastrointestinal adverse events of concern are defined as symptoms (i.e., bloody or black stool, abdominal discomfort such as pain or cramps, diarrhoea, vomiting) which cause the patient concern or interfere with daily activities (including eating or sleeping), and will be assessed by the Investigator within 24 hours of occurrence. A standardised clinical and laboratory assessment will be completed. Further investigation and review will be arranged as clinically appropriate at the Investigator's discretion. All events should be followed to resolution. Any patient who has a gastrointestinal adverse experience of concern **and** a positive faecal occult blood test or melena during the randomised treatment phase of the study will be referred to a gastroenterologist

for a **complete** colonoscopy that emphasises visualisation of the transverse colon. Biopsies should be taken if appropriate.

Patients who complete Study 157 or who withdraw before the end of Week 52 will be asked to return for essential assessments only at the scheduled visit dates. Patients who do not wish to return for further scheduled visits will be asked to return for a safety follow-up visit 7 ± 3 days after the last dose of study medication.

Efficacy Parameters

The **primary** efficacy variables are:

- Occurrence of COPD exacerbations, Level 2 and 3.
- Change from baseline of pre-bronchodilator Clinic FEV_1 at trough ($\geq$ 8 hours after previous dose of study medication).

The **secondary** efficacy variables are listed below:

- COPD exacerbations - (Number of subjects with mild, moderate and severe exacerbations, number of exacerbations (mild, moderate or severe) and the time to the first exacerbation (any) and time to first moderate or severe exacerbation).
- Clinic FEV_1 (post-bronchodilator).
- Disease-specific quality of life using the total score of the St. George's Respiratory Questionnaire (SGRQ).

The **tertiary** efficacy variables are listed below:

- Pulmonary function parameters (Clinic FVC, clinic FEV_{25-75}, morning PEF from Daily Diary Cards and clinic PEF).
- Use of relief medication and number of days with no need for rescue medication (salbutamol)
- Duration of exacerbations
- Symptom scores and symptom free days (24 hour period)
- Nighttime awakenings
- Number of withdrawals (NB as far as possible subjects discontinuing study medication should remain in the study for assessments for completion of the 12 month treatment period).
- Disease-specific quality of life: SGRQ subscales (symptoms, activity and impact)

- Generic Health Status (EQ-5D)
- Health Outcomes Endpoints: resource utilisation and indirect costs
- Time off work/normal activities due to COPD
- Plethysmography measurements including clinic trough residual volume (RV), pre and post salbutamol – conducted at selected sites only
- Global Subject Assessment
- Global Investigator Assessment
- Blood CD4+/CD8+ ratio
- Serum C Reactive Protein

Safety Parameters

- Incidence of adverse events (with additional monitoring for gastrointestinal adverse events)
- Vital signs.
- Clinical laboratory tests (chemistry and haematology)
- Electrocardiograms (12-lead ECGs)

Statistical Evaluation

Treatment differences for mean change from baseline in FEV_1 averaged over 52 weeks will be analysed based on a repeated measure model with fixed effects for treatment, centre and time.

The incidence of a moderate or severe COPD exacerbations occurring during the treatment period will be analysed using a maximum likelihood based analysis, assuming a Poisson distribution.

A Log-rank test will be performed using SAS PROC LIFETEST® to compare the exacerbation-free curves of a moderate or severe COPD exacerbation between cilomilast treatment group and placebo treatment group.

The exacerbation-free survival rate at 52 weeks, and associated 95% confidence intervals, will be estimated for each treatment group using the Kaplan-Meier product limit.

All continuous efficacy variables will also be analysed using the ANOVA model with fixed effects treatment, centre at all double-blind visits as well as endpoint. All categorical variables will be tabulated using contingency table and chi-square test.

All efficacy variables will be analyzed for the intent to treat population with FEV1 and exacerbation being analysed for the per protocol population as well.

FEV_1 and COPD exacerbations (Level 2 and Level 3) will also be analysed by patients' smoking status.

Evaluation of safety data will include all randomised patients and will be based on comparisons of patient experience by assigned medication regimen. Adverse events will be tabulated by relationship to study medication, severity, time of initial onset, and action taken. Contingency tables will be provided to evaluate the number of patients with clinical laboratory results, vital signs and ECGs of concern.

1 Introduction

Chronic obstructive pulmonary disease (COPD) is a disease state characterised by progressive development of airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response to the lungs to noxious particles or gases[1]. COPD comprises both chronic bronchitis and emphysema and is characterised by inflammatory abnormalities in small airways.

COPD is one of the leading causes of death worldwide, fourth or fifth highest in developed countries, with an increasing prevalence and mortality [2] and is projected to be the third leading cause of death worldwide by 2020 [3].

Patients typically have chronic symptoms, particularly breathlessness on exertion, and a productive cough, accompanied by progressive deterioration in lung function, interspersed by exacerbations of their disease. This combination leads to substantial impairment in the patient's health related quality of life [4]. Long term evaluation of the disease is based on rate of decline in lung function over time, exacerbations, and health status.

Many definitions of COPD exist but in general most definitions include some combination of the following clinical findings: decrease in lung function, worsening of dyspnoea, increase in sputum purulence, and increase in sputum volume. Following an exacerbation, most patients are expected to experience at least a temporary decrease in functional status and quality of life [5] and 50% of those hospitalised for the condition are expected to be re-admitted at least once in the ensuing 6 months [6][7].

Stopping smoking is the single most effective means of improving prognosis in patients with COPD [8] and is associated with a reduction in the accelerated rate of decline in FEV_1 [9]. None of the existing medications for COPD has been shown to modify the long-term decline in lung function. Therefore, pharmacotherapy for COPD is used predominantly to decrease symptoms and minimise number and severity of exacerbations. The vast majority of patients are treated with inhaled or oral bronchodilators alone, including anticholinergics, short- and long- acting β_2 agonists and theophyllines. Regular treatment with inhaled corticosteroids is recommended for symptomatic patients with a spirometric response to ICS or those with FEV_1< 50% predicted normal value and repeated exacerbations requiring treatment with antibiotics or oral corticosteroids [1].

Cilomilast is a potent and selective phosphodiesterase type 4 (PDE4) inhibitor currently under development for the treatment of COPD. 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 activities, along with the knowledge that PDE 4 is the major cyclic AMP-hydrolysing isozyme in these cells [10].

In two of the recently completed Phase III studies (Studies 039 and 091), administration of cilomilast was shown to result in a dramatic diminution of exacerbation rates over the 24 weeks of treatment. Treatment with cilomilast reduced the risk of having an exacerbation by 39% relative to placebo ($P = 0.002$) and the risk of an exacerbation requiring treatment by a physician or hospitalisation by 45% ($P = 0.001$) in Study 039. Similarly, in Study 091, the risk of having an exacerbation was reduced by 30% ($P = 0.005$) and the risk of an exacerbation requiring treatment by a physician or hospitalisation by 32% ($P = 0.010$). A similar impact on exacerbations was not observed in the third Phase III study, Study 042. Resource utilisation-free survival associated with COPD exacerbation was significantly higher in the cilomilast group (88.1%) than in the placebo group (76.9%; P = 0.004) in Study 039. In this study, the cilomilast-treated group had a higher percentage of patients that were utilisation-free in terms of physician visits, ER/urgent care visits and hospitalisations over the entire 24-week treatment period. Similar trends were observed in Studies 042 and 091.

Study 157 is being conducted as a pivotal Phase III study to assess the efficacy and safety of cilomilast versus placebo over a longer timeframe as maintenance treatment in patients with COPD and to confirm and extend the results observed in studies 039 and 091. The study design of Study 157 is similar to that of Studies 039, 042, and 091. However, in Study 157, there will be two co-primary efficacy parameters based on COPD exacerbations and Clinic FEV_1. Patients will be treated with randomised study medication for 52 weeks.

As of 15 February 2001, 717 patients have been treated with cilomilast in 32 Phase I clinical pharmacology studies; 1100 patients in six Phase II dose-ranging studies (633 and 467 patients, respectively with asthma and COPD); and 1891 patients with COPD in three double-blind, placebo-controlled Phase III studies, long-term open extension studies and mechanism of action studies. Two Phase III studies currently ongoing.

Three Phase III randomised, double-blind, placebo-controlled studies (039, 042, and 091) have recently completed. Patients with COPD were characterised by a % predicted FEV_1 ≥30% and ≤70% post-bronchodilator, a FEV_1/FVC of ≤0.7, and fixed airway obstruction differentiated by ≤15% reversibility following administration of a $beta_2$-agonist. Study 039 was conducted in North America, 091 in Europe, and 042 Internationally. In each of the phase III, placebo-controlled studies, patients with COPD entered a 4-week single-blind run-in phase and then were randomised to receive cilomilast 15 mg bd or placebo in a ratio of 2 to 1. A total of 1374 patients were treated with cilomilast 15 mg bd. Efficacy data from the three Phase III studies are presented in Table 1.

Table 1 Treatment Differences for Cilomilast Phase III Studies in Primary and Secondary Parameters Intent-to-Treat Population*

	039		042		091	
Randomised	**Placebo**	**Cilomilast**	**Placebo**	**Cilomilast**	**Placebo**	**Cilomilast**
Patients	**213**	**425**	**226**	**474**	**242**	**469**
FEV_1(trough)**	40 ml (0.002)		30 ml (0.044)		30 ml (0.055)	
	[0.01, 0.06]		[0.00, 0.06]		[-0.00, 0.06]	
SGRQ**†	-4.1 (<0.001)		0.7 (NS)		-0.4 (NS)	
	[-6.0, -2.2]		[-1.2, 2.6]		[-2.4, 1.6]	
FVC (trough)	50 ml (0.049)		50 ml (0.047)		20 ml (NS)	
	[0.00, 0.10]		[0.00, 0.09]		[-0.03, 0.06]	
Dyspnoea	-0.24 (0.029)		-0.20 (0.068)		-0.16 (NS)	
	[-0.45, -0.02]		[-0.41, 0.01]		[-0.36, 0.04]	
Exacerbations	0.61 (0.002)		1.07 (NS)		0.70 (0.005)	
Relative Risk††	[0.45, 0.83]		[0.83, 1.40]		[0.55, 0.90]	

* Mean change from baseline based on the comparison to placebo averaged over 24 weeks. *P* values are provided in parentheses. Lower/Upper 95% CI are provided in brackets.
** Primary Endpoint; alpha = 0.025.
† St. Georges Respiratory Questionnaire.
†† Cilomilast relative to placebo.
NS not significant.

The maintenance of pulmonary function demonstrated in Study 039 is supported by the results of Studies 042 and 091, in which modest improvements in both FEV_1 and FVC were demonstrated when averaged over 24 weeks of treatment. Although the primary endpoint in Studies 042 and 091 did not achieve statistical significance, comparisons of the least square mean differences over placebo for both FEV_1 and FVC in these three studies suggest that cilomilast maintains and may slightly improve pulmonary function in patients with moderate to severe "fixed" COPD (approximately 45% of which are active smokers) over a six-month period, while placebo-treated patients experience a linear decline in FEV_1.

In these three Phase III studies, the most common on-therapy adverse experiences reported in more than 5% of patients are displayed by decreasing frequency in Table 2.

Table 2 Overall Incidence of Most Commonly Reported On-therapy Adverse Events in Cilomilast Phase III Studies

	All Randomised Patients			
	Placebo		Cilomilast	
Adverse Event*	**(N = 684)**		**(N = 1374)**	
(Preferred Term)	**N**	**%**	**N**	**%**
Chronic obstructive airways disease	266	38.9	422	30.7
Diarrhoea	41	6.0	175	12.7
Nausea	28	4.1	172	12.5
Abdominal pain	39	5.7	157	11.4
Upper respiratory tract infection	51	7.5	111	8.1
Headache	43	6.3	101	7.4
Dyspepsia	17	2.5	83	6.0
Vomiting	7	1.0	76	5.5

* Includes adverse events reported for >5% of patients in either of the treatment groups.

Chronic obstructive airways disease (i.e. exacerbations) was reported more frequently in patients who received placebo while diarrhoea, nausea, abdominal pain, dyspepsia and vomiting were reported more frequently in patients who received cilomilast. The majority of the events were considered mild or moderate in severity by the Investigators. The gastrointestinal adverse experiences reported more frequently in patients who received cilomilast were generally mild and expected side effects of the known pharmacology of the drug. Most of these gastrointestinal adverse experiences were self-limiting and occurred during the initial period of treatment. Few of the events were considered serious. In Studies 039 and 091, patients who received placebo had a higher incidence of exacerbations of their underlying disease. This effect was not seen in Study 042.

There was no evidence of any adverse effect on laboratory parameters, vital sign values, or electrocardiographic parameters.

Please refer to the Investigator's Brochure for more detailed pre-clinical and clinical information. [11]

2 Objectives

2.1 Primary Objectives

The primary objective of the study is to assess the clinical efficacy of oral cilomilast 15 mg bd as maintenance treatment for patients with COPD. This will be demonstrated over a 52 week treatment period in subjects with COPD who are poorly reversible to bronchodilators by assessment of:

- Reduction in the risk of the occurrence of exacerbations of COPD for subjects treated with cilomilast 15 mg bd compared with placebo and
- Superior pulmonary function data (FEV_1) for subjects treated with cilomilast 15 mg bd compared with placebo

2.2 Secondary Objectives

To further define the clinical safety and tolerability of cilomilast 15 mg bd versus placebo as maintenance treatment by assessment of adverse events and laboratory measures over a 52 week period in subjects with COPD

3 Study Design Overview

3.1 Study Design

This Phase III study is a double-blind, placebo controlled, randomised, parallel group study requiring a maximum of 13 visits over a 57-week period. A 4-week single-blind placebo run-in period will be followed by 52 weeks of treatment with double-blind study medication. Patients who complete the double-blind period will be asked to return for a safety follow-up visit 7 ± 3 days after the last dose of study medication. Patients who withdraw from the study before Visit 12 (Week 52) will be asked to return for essential assessments only at the previously scheduled visit dates. If these patients do not wish to return for scheduled visits, they will be asked to return for a safety follow-up visit 7 ± 3 days after the last dose of study medication. Patients eligible to enter the double-blind period must meet the Randomisation Criteria and will be randomised in a 1:1 ratio to receive either cilomilast 15 mg or matching placebo tablets twice daily. Study medication will be administered immediately after breakfast and evening meal. Assignment

to study drug will be stratified according to smoking status at Baseline prior to randomisation for 'current smokers' and 'ex-smokers'.

Throughout the study (Visit 1 - through to Visit 12) subjects complete a daily record card with details of morning PEF, COPD symptoms and the use of rescue medication. In the event of early discontinuation of study treatment, subjects will be urged to continue to complete their daily record cards and to attend the remaining scheduled clinic visits for essential assessments (for the 52 week treatment period). The number and severity of COPD exacerbations will be assessed by the Investigator at each clinic visit by reviewing the diary card entries as well as specific questioning. Each COPD exacerbation will be categorised according to one of the three levels of severity.

Level 1 (Mild-self treated): Acute worsening of COPD that is self-managed by the patient at home by increasing the dose of relief salbutamol medication by > 2 occassions/24 hour period on two or more consecutive days compared with their baseline (baseline = mean of last 10 days of run-in period) or use of other additional bronchodilator medication

Level 2 (Moderate- physician, investigator treated): Acute worsening of symptoms (cough, sputum production, breathlessness) requiring treatment with oral corticosteroids prescribed by a physician or primary care doctor, or as a result of hospital out-patient visit (including Emergency Room).

Exacerbations requiring oral corticosteroids will be treated with a standardised course of prednisolone or prednisone tablets 30mg/day for 10 days, or methylprednisolone tablets 24mg/day for 10 days.

Level 3 (Severe - attendance at hospital): Acute worsening of COPD that requires the patient to be admitted to hospital for treatment.

If appropriate, courses of antibiotics may be prescribed to treat an infection (Level 1, 2 or 3).

Details of all exacerbations will be recorded in the COPD Exacerbation Section in the CRF as follows: dates of onset and resolution; outcome and severity. In addition any information collected during the exacerbation should be recorded in the CRF (e.g. lung function tests, other laboratory tests, change in alertness, malaise, insomnia, fatigue, depression, confusion, symptoms associated with URTI, ankle swelling, heart rate, respiratory rate, pulse oximetry (arterial blood gases) and blood sample for serum C Reactive Protein).

The time of resolution of an exacerbation will be determined by the investigator and/or subject. However, some guidance for distinguishing recurrence of a single exacerbation from distinct exacerbation episodes is provided as follows.

- Level 2 exacerbations treated with oral corticosteroids will be classified as separate exacerbations only if the courses of treatment are administered more than one week apart. A course of oral corticosteroids started within one week of finishing a previous course will be considered a continuation of the exacerbation.

- Likewise hospitalisation for an exacerbation within a week of completing a course of oral corticosteroids or initiation of a course oral corticosteroids within a week of discharge from hospital for an exacerbation will be considered a single continuous (Level 3) exacerbation.

Where a Level 1 exacerbation is immediately preceded or followed (within 1 week) by an exacerbation of any level, the investigator and/or subject will consider the possibility that this represents a continuation of the exacerbation.

Pulmonary function tests will be performed at all visits (with the exception of one safety-only visit at Visit 4 (Week 2)). At these visits pulmonary function (FEV_1, FVC, FEF_{25-75} and PEF) will be measured at trough levels of study drug, before and after a standard dose of salbutamol (400 mcg) except at Visit 2 (Week –2) when pulmonary function tests will be performed before and after a standard dose of ipratropium (80mcg). To ensure consistency and standardisation of pulmonary function data, spirometry equipment will be standardised and pulmonary function data reviewed centrally throughout the study.

The impact of COPD on patient health status will be assessed by the SGRQ and EQ-5D at Baseline, Visit 9 (Week 28) and Visit 12 (Week 52). Investigator and Patient Global Assessments will also be completed at these timepoints.

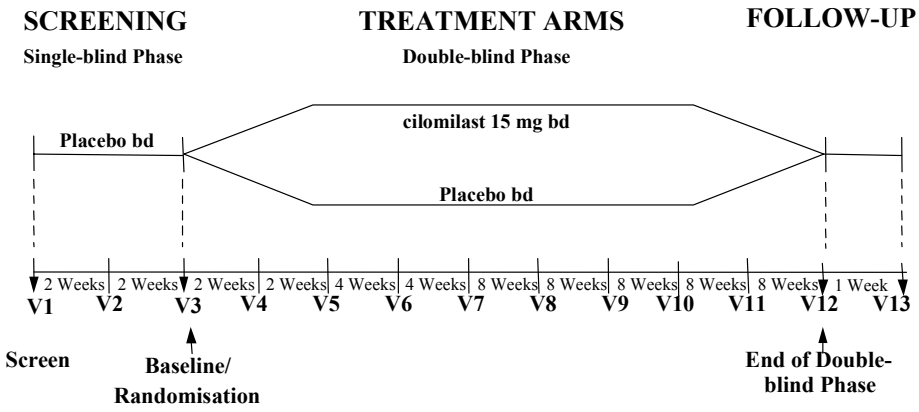
Safety assessments will include adverse events, vital signs, ECGs, and clinical laboratory tests. Additional monitoring will be provided for gastrointestinal adverse events. Gastrointestinal adverse events of concern are defined as symptoms (i.e., bloody or black stool, abdominal discomfort such as pain or cramps, diarrhoea, vomiting) which cause the patient concern or interfere with daily activities (including eating or sleeping), and will be assessed by the Investigator within 24 hours of occurrence. A standardised clinical and laboratory assessment will be completed. Further investigation and review will be arranged as clinically appropriate at the Investigator's discretion. All events should be followed to resolution. Any patient who has a gastrointestinal adverse experience of concern and a positive faecal occult blood test or melena during the

randomised treatment phase of the study will be referred to a gastroenterologist for a **complete** colonoscopy that emphasises visualisation of the transverse colon. Biopsies will be taken if appropriate.

Patients who complete Study 157 will be asked to return for a safety follow-up visit 7 ± 3 days after the last dose of study medication. Patients who withdraw from the study before Visit 12 (Week 52) will be asked to return for essential assessments only at the previously scheduled visit dates. If these patients do not wish to return for scheduled visits, they will be asked to return for a safety follow-up visit 7 ± 3 days after the last dose of study medication.

The study design is presented in Figure 1.

Figure 1 Schematic Representation of Study Design



A stable dose of anticholinergic medication via a metered dose inhaler (MDI) or salbutamol (on an "as needed" basis) via MDI with or without a spacer (according to the patient's usual practice) are the only COPD medications permitted during the study period from Visit 1 through Visit 12 with the exception of additional medication allowed for the treatment of exacerbations. Combination products (e.g., a combined salbutamol and ipratropium bromide formulation) are **not** permitted. Patients using a combined anticholinergic-beta$_2$-agonist must be changed to separate single therapies prior to or at Visit 1; patients should maintain equivalent doses of the component bronchodilators.

If clinically indicated, oral steroids or antibiotics may be administered for a short course (<14 days) for the treatment of an exacerbation of COPD. COPD exacerbations are categorised as Level 1, 2, or 3, based on the Investigator's

judgement and on the treatment received by the patient for the exacerbation (Section 8.1.2). Patients who take any corticosteroids or are hospitalised for the treatment of a COPD exacerbation during the run-in phase will be withdrawn from the study prior to randomisation (see Sections 6.11.3 and 8.1.2).

At **all** visits, the following restrictions apply:

- Patients should not have smoked for 2 hours prior to presentation to the clinic.

- At Visits 1 and 2, patients should not have taken inhaler therapy (i.e., salbutamol and/or anticholinergic agent) for a minimum of **8 hours prior** to the clinic visit. If this time period has not been observed, the visit should be deferred to the next day and the patient should refrain from using these medications for at least 8 hours before pulmonary function tests are performed.

- For all other visits (3 – 12) the patient must refrain from taking salbutamol and/or anticholinergic medication for a minimum of 4 hours prior to presentation to the clinic. If this time period has not been observed, 4 hours must elapse before pulmonary function tests are performed.

3.2 Schedule of Assessments

Study assessments are represented in Table 3.

Table 3 Outline of Study Procedures

Visit	1	2	3	4	5	6	7	8	9	10	11	12		13
	Screen		Base-line									End of DB	Early Withdrawal	Follow -up
Time relative to baseline (weeks)[1]	-4	-2	0	+2	+4	+8	+12	+20	+28	+36	+44	+52		+53
Signed written informed consent	x													
Medical & surgical history	x													
Pulmonary symptoms	x													
Postero-anterior chest X-ray[2]	x													
Medication history including flu vaccination[3]	x													
Health Status Assessments: SGRQ and EQ-5D			x						x			x	x	
Patient global assessment			x						x			x	x	
Investigator global assessment			x						x			x	x	
Physical examination [4]	x		x									x	x	x[5]
Smoking status	x	x	x	x	x	x	x	X	x	x	X	x	x	x
Exacerbation assessment	x	x	x	x	x	x	x	X	x	x	X	x	x	x
Resource utilisation				x	x	x	x	X	x	x	X	x	x	x
Diary Card Review		x	x	x	x	x	x	X	x	x	X	x	x	
Baseline signs and symptoms [6]	x	x	x											
Adverse experiences [6]			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
Study medication compliance		x	x	x	x	x	x	X	x	x	X	x	x	
Resting 12-lead ECG	x		x				x		x			x	x	x[5]
Vital signs (BP, HR)[7]	x[7]	x	x[7]	x	x	x	x[7]	X	x[7]	x	X	x[7]	x[7]	x
PFTs pre and post salbutamol: Pre-dose [8]	X		x		x	x	x	X	x	x	X	x	x	x
PFTs: salbutamol reversibility [9]	X		X											
PFTs: ipratropium reversibility		x												
Residual Volume (body box) pre-/post-salbutamol Selected sites only			X						x			x	x	
Laboratory tests	X		X[10]		x	x	x	X	x	x	X	x[10]	x[10]	x[5]
Faecal occult blood test[11]	X	x									X[17]	x	x	
Dispense single-blind med	x[12]	x[13]												
Dispense double-blind med			x[14]	x[13]	x[15]	x[15]	x[15]	x[15]	x[15]	x[15]	X[15]			
Study conclusion record														x[16]

1	All visit dates must be scheduled at the visit interval listed here using the Baseline visit as Day 0.
2	Chest X-ray to be taken at entry to the run-in period or in the 3 months prior to entry to the run-in period
3	Details of 'flu vaccinations will be recorded at every visit

4	Includes respiratory examination.
5	Only if abnormalities are present at Visit 12.
6	Does not include COPD exacerbations
7	Orthostatic vital signs to be measured at Visits 1, 3, 7, 9, and 12
8	Includes FEV_1, FVC, FEF_{25-75} and PEF measured by spirometry by the same study personnel at each visit before dose of study medication is taken.
9	Includes FEV_1, FVC, FEF_{25-75} and PEF measured by spirometry by the same study personnel at each visit 30 minutes after administration of 400 mcg of salbutamol via MDI with or without a spacer, and before dose of study medication is taken.
10	Includes Blood CD4+/CD8+ ratio and serum C Reactive Protein
11	In addition to the usual laboratory tests, three faecal occult blood tests will be performed between Visits 1 and 3, at visit 11(with additional consent) and at the end of the treatment period and at Early Withdrawal
12	Register the patient with RAMOS.
13	The container of study medication issued at the previous visit will be re-issued at this visit
14	Call RAMOS to randomise the patient and to obtain study medication assignment and container number.
15	Call RAMOS to obtain study medication container number(s)
16	Or earlier if the subject withdraws from the study prior to Visit 12.
17	FOB test at visit 11 is optional and should only be collected if patient has signed a specific consent

RSD-101LWJ/4
CONFIDENTIAL
GM2004/00073/00
SB-207499/157

3.3 Method of Randomisation

The GlaxoSmithKline Registration and Medication Ordering System (GSK RAMOS) will be used to allocate treatment to patients. At Visit 3, after a patient has satisfied the inclusion and exclusion criteria, the investigator will access RAMOS by telephone to receive the patient's randomisation number and initial study medication container number. Patients will be randomised to receive cilomilast or placebo in a 1:1 ratio for the duration of the treatment period. Assignment to study drug will be stratified according to smoking status at Baseline prior to randomisation for 'current smokers' and 'ex-smokers' and randomisation will be balanced within each stratum. To ensure balance with respect to the number of patients assigned to each treatment group, the allocation schedule will be generated in blocks using the GSK Coding Memo System. All trial medications will be packaged to be indistinguishable irrespective of treatment. Randomised patients will be identified throughout the study by their CRF number.

The master randomisation list will be held by GlaxoSmithKline

4 Study Population

4.1 Number of Patients/Centres

Approximately 800 patients will be randomised to achieve 550 evaluable patients to complete the study. Up-to 100 centres in Europe and Australia/New Zealand are expected to participate, with each centre aiming to enrol between 8 and 24 patients.

4.2 Inclusion Criteria

4.2.1 Screening Inclusion Criteria (At Screening Visit 1)

Subjects who fulfil all of the following criteria will be eligible for inclusion in the study:

- Male or female adults between 40 and 80 years of age, inclusive.

Note: Women of childbearing potential must be using effective contraceptive measures (i.e., oral contraceptives, Norplant®, an IUD, a diaphragm with

spermicide or Depo-Provera®) for at least 1 month prior to Visit 1 and should continue using the same contraceptive method during the study.

- Subjects with a clinical diagnosis of COPD, as defined by GOLD guidelines [1]. (A diagnosis of COPD should be considered in any patient who has symptoms of cough, sputum production, or dyspnoea, and/or a history of exposure to risk factors for the disease. The diagnosis is confirmed by spirometry. The presence of a post-bronchodilator FEV_1 < 80% of the predicted value in combination with an FEV_1/FVC <70% confirms the presence of airflow limitation that is not fully reversible).

- Subjects with a smoking history of ≥ 10 pack years (1 pack year = 20 cigarettes smoked per day for 1 year or equivalent). (Ex-smokers are defined as those who have stopped smoking for at least 6 months prior to Visit 1. Ex-smokers are eligible to enter the study provided they have at least 10 pack years smoking history).

- Subjects with a pre-bronchodilator FEV_1 to FVC ratio (FEV_1:FVC) ≤ 0.7 at Visit 1.

- Subjects with poor reversibility of airway obstruction, defined by ≤10% of the predicted normal or ≤200 ml (or both) increase in FEV_1 after the administration of salbutamol 400 mcg via MDI at Visit 1 (Screening).

- Subjects with a post-salbutamol FEV_1 of ≥ 30 and ≤ 70% of predicted normal for height, age and gender at Visit 1. Subjects will be assessed 30 (± 5) minutes after the administration of 400 mcg salbutamol (via MDI with or without a spacer). Predicted normal values will be taken from the report of the working party of the European Community for Coal and Steel [12]

- Subjects in the opinion of the investigator who are not at risk of severe or life threatening exacerbations of COPD and will be able to stop all COPD medications apart from short acting anti-cholinergics and salbutamol from Visit 1.

- Subjects who are willing and able to complete a Daily Record Card (DRC) and use a peak expiratory flow meter satisfactorily.

- Subjects who give their signed and dated written informed consent to participate.

4.2.2 Randomisation Inclusion Criteria (at Baseline Visit 3)

Subjects who fulfil the Inclusion Criteria below at end of 4 week run-in period (Visit 3) may enter the double-blind treatment phase of the study:

- Less than 20% change (increase or decrease) in pre-bronchodilator FEV_1 assessed at Screening Visit 2 and at Baseline Visit 3.

- Subjects with poor reversibility of airway obstruction, defined by ≤10% of predicted normal or ≤200 ml (or both) increase in FEV_1 after the administration of salbutamol 400mcg via MDI at Visit 1 and Visit 3

- Medication Compliance: ≥ 80% and ≤ 120% compliance in taking single-blind study medication during the placebo run-in period.

4.3 Exclusion Criteria

4.3.1 Screening Exclusion Criteria (At Screening Visit 1)

The following subjects are not eligible for inclusion into the study:

- Women who are pregnant or lactating.

- Subjects with asthma as the main component of their obstructive airways disease.

- Subjects with poorly controlled COPD, defined as the occurrence of a Level 2 or Level 3 exacerbation of COPD, or a hospitalisation or emergency room visit for the treatment of COPD, in the 2 weeks prior to Visit 1.

- Subjects with clinically significant orthostatic changes in blood pressure or heart rate at Visit 1.

- Subjects with a diagnosis or suspicion of sleep apnoea.

- Subjects with known active tuberculosis, lung cancer, clinically overt bronchiectasis, or other known specific pulmonary disease.

- Subjects with sinusitis which in the investigator's opinion may interfere with the study objectives.

- Subjects with a chest X-ray indicating diagnosis other than COPD that might interfere with the study (chest X-ray to be taken at entry to the run-in period or in the 3 months prior to entry to the run-in period).

- Subjects with clinically significant cardiovascular, neurological, renal, endocrine, gastrointestinal, hepatic or haematological abnormalities that are uncontrolled on permitted therapy.

- Subjects with clinically significant gastrointestinal or hepatic abnormalities.

- Subjects who have participated in the acute phase of a Pulmonary Rehabilitation Program within 4 weeks prior to Visit 1 (Screening) or who will enter a Pulmonary Rehabilitation Program during the study.

- Subjects with a history of hypersensitivity to PDE4 inhibitors.

- Subjects with a history (or suspected history) of alcohol abuse or any other recreational substance abuse.

- Subjects receiving treatment with inhaled cromolyn sodium or nedocromil, inhaled long-acting beta$_2$-agonists, and/or oral beta$_2$-agonists, combination short acting beta$_2$-agonists and anticholinergics, xanthines, leukotriene modifiers, mucolytics or oral/inhaled corticosteroids. **All COPD medications except short-acting anticholinergic medication or salbutamol via MDI should be withdrawn prior to or at Visit 1 (Screening) (Section 6.11.2).**

- Subjects receiving treatment with long term oxygen therapy (LTOT) or those subjects who require supplemental oxygen more often than on an occasional (prn) basis, or subjects who require nocturnal positive pressure for sleep apnoea.

- Subjects who have received an investigational drug within 30 days of entry into this study (Visit 1), or within 5 drug half-lives of the investigational drug (whichever is longer).

- Subjects who have previously participated in a cilomilast study and who received double-blind or open-label study medication.

- Subjects who are unable or unwilling to comply with all protocol specified procedures, including the completion of the quality of life questionnaires.

Note: Subjects who fulfil all of the Inclusion and Exclusion Criteria at Screening Visit 1 may enter the single-blind placebo run-in phase of the study.

4.3.2 Randomisation Exclusion Criteria (at Baseline Visit 3)

Subjects who fulfil any of the following Exclusion Criteria at the end of the 4-week run-in period (Visit 3) are not eligible to enter the double-blind treatment phase of the study:

- Subjects who have had any changes to their COPD medication (other than 'as required' use of salbutamol), received corticosteroids (oral or inhaled) for respiratory disease, or hospitalised for COPD/lower respiratory tract infections during the run-in period.

- Subjects receiving any other medication during the run-in period which in the opinion of the investigator, is judged as likely to affect baseline assessments

- Subjects with a positive faecal occult blood test result between Visits 1 and 3.

- Subjects with clinically significant orthostatic changes in blood pressure or heart rate at Visit 3.

5 Conduct of the Study

5.1 Ethical and Regulatory Considerations

The study will be conducted according to Good Clinical Practice guidelines and the Declaration of Helsinki (Appendix A).

5.1.1 Ethics Review Committee (ERC)

ERCs 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 their written unconditional approval obtained and submitted to the sponsor before commencement of the study. GSK will supply relevant data for the Investigator to submit to the hospital/university/independent ERC for the protocol's review and approval. Verification of the ERC's unconditional approval of the protocol and the written informed consent statement and written information to be given to the subjects will be transmitted to the GSK Study Monitor prior to shipment of drug supplies and 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 must be informed by the Investigator of all subsequent protocol amendments and of serious or unexpected adverse experiences occurring during the study which are likely to affect the safety of the patients or the conduct of the study. Approval for such changes must be transmitted in writing to the GSK Study Monitor via the Investigator.

5.1.2 Informed Consent

The principles of informed consent in the current edition of the 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. Subjects, their relatives, guardians or, if necessary, legal representatives must be given ample opportunity to enquire about details of the study.

The consent form generated by the investigator with the assistance of GSK, must be approved (along with the protocol) by the ERC and be acceptable to GSK. 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 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 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 and consider it before it is signed.

Consent must be documented either by the dated signature of the subject or the subject's legally authorised representative. 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 GSK professional and Regulatory Compliance persons.

A sample informed consent statement is presented in Appendix C.

5.2 Outline of Study Procedures

5.2.1 Study Visits

Patients are required to refrain from using inhaled $beta_2$-agonists or anticholinergic medication during the 4-hour period preceding each visit (except at Visits 1 and 2 when patients should refrain from using these medications for at least 8 hours prior to the visit). Patients who smoke must not smoke 2 hours prior to each visit.

Visits must be scheduled at the same time of day (± 2 hours) for any patient but this must be at least 8 hours after the last dose of study medication. This will ensure that trough measurements are obtained. Smoking and the use of inhaled $beta_2$-agonists or anticholinergic treatment must be avoided during the clinic stay if at all possible.

5.3 Detailed Description of Study Stages/Visits

5.3.1 Visit 1 (Week-4): Screening and Start of 4-week Single-blind Run-in

Patients considered by the Investigator as potential candidates for entry into the study will attend the clinic for a screening visit. They must have refrained from taking inhaled $beta_2$-agonists and anticholinergic medication for at least 8 hours prior to the visit and refrained from smoking for at least 2 hours prior to the visit. **If this has not occurred, the specified period must elapse before pulmonary function tests are performed and the patient must return to clinic the following day, if appropriate.**

The Investigator should perform the following procedures at Visit 1:

- Obtain written informed consent from the patient.
- Perform a full medical and surgical history (including alcohol consumption) and physical examination (including respiratory examination), (Section 5.4.1 and Section 5.4.2).
- Document the patient's cigarette smoking history and current smoking status. As per usual care, patients should be offered normal advice to stop smoking. (Note: Current smokers may participate in the study.)
- Document the patient's pulmonary history and symptoms (Section 5.4.1).

- Review a current postero-anterior (PA) chest radiograph (performed within the 12 weeks prior to assessment). If such a radiograph is not available for review, a new radiograph must be performed and available for review at Visit 3 (Section 5.4.3).

- Perform an assessment of COPD exacerbations. If the patient has experienced a Level 2 or Level 3 exacerbation of COPD during the two weeks prior to Visit 1, he/she is not eligible to participate in the study. Additionally, patients experiencing any level exacerbation who self medicate with corticosteroids during the two weeks prior to Visit 1 are not eligible to participate (Section 8.1.2).

- Record all medication for COPD, including inhalers, taken during the 3 months preceding this visit, together with all other medications taken within 2 weeks of the visit. Prohibited respiratory medications should be discontinued (Section 6.11.2).

- Document details of influenza vaccinations within the past 12 months.

Greater than 8 hours after the patient's last salbutamol administration:

- Perform a resting 12-lead electrocardiogram after the patient has been semisupine for 5 minutes (Section 5.4.4).

- Measure blood pressure and heart rate after the patient has been sitting for 5 minutes. After the patient has been in a supine position for 5 minutes followed by sitting with legs dependent for 1 minute, measure orthostatic changes in heart rate and blood pressure. If the patient experiences a decrease in systolic blood pressure of ≥20 mmHg or a decrease in diastolic blood pressure of ≥10 mmHg or an increase in heart rate of ≥20 beats/minute, he/she is not eligible to participate in the study (Section 5.4.2).

- Perform the pulmonary function tests before and 30 minutes after administration of salbutamol (Section 5.4.5). Salbutamol reversibility should also be calculated at this visit.

Following completion of the above procedures, complete the checklist of the inclusion and exclusion criteria. If the patient is eligible to enter the study the following should be performed:

- Take blood and urine samples for routine haematology, biochemistry, (including beta-HCG for women of childbearing potential) and urinalysis (Section 5.4.8).

- Issue a 35-day supply of single-blind study medication (Section 6.1), a salbutamol MDI for 'as-needed' use and a spacer. The first dose of study medication should be taken in the clinic with food. Patients will be instructed to take one tablet each morning immediately after breakfast and a second tablet immediately after the evening meal.

- Register the patient with the Registration and Medication Ordering System (RAMOS) (Section 6.1)

- Issue a miniWright Peak Flow Meter for determination of home morning peak expiratory flow rates. Demonstrate the procedure for measuring and recording PEF.

- Issue and explain the diary card which will be used by the patient to record daily PEF measurements, relief medication use and COPD symptoms (Section 5.4.7, Section 5.4.9).

- Review the procedure for reporting gastrointestinal adverse events with the patient (Section 8.1.3).

- Issue a faecal occult blood kit and ask the patient to follow the instructions on the kit and to return it at the next visit (Section 5.4.8).

Patients will be asked to return to the clinic for Visit 2 in 14 (± 3) days at the same time of day and reminded:

- **not** to take the study medication at least 8 hours before their next clinic visit.

- to refrain from using salbutamol or anticholinergic medication during the 8 hours immediately preceding Visit 2.

- to refrain from smoking for 2 hours immediately preceding the next visit.

- to bring any remaining study medication tablets, all study medication containers, the salbutamol inhaler and spacer, and the diary card with them to the next visit.

- to continue taking their anticholinergic medication, if prescribed, at a constant dose and salbutamol when needed to control symptoms.

5.3.2 Visit 2 (Week -2): Single-blind Run-in Period

At this visit the Investigator will complete the following assessments:

- Document if the patient has taken salbutamol or anticholinergic medication during the 8 hours immediately preceding the visit or smoked during the 2 hours immediately preceding the visit.
- Record any changes or additions to the patient's concomitant medication in the CRF (Section 6.11.4).
- Document details of influenza vaccinations the patient may have had since the last visit.
- Document any changes in the patient's smoking status since the last visit (Section 5.4.1).
- Determine if the patient has entered a Pulmonary Rehabilitation Program since the last visit.
- Determine the patient's compliance in taking study medication since the last visit (Section 6.8). Emphasise the importance of compliance to patients whose compliance is <80% or >120%.
- Collect and review the patient's diary card and check that it has been completed correctly. Review the domiciliary PEF and use of relief medication (Section 5.4.7 and Section 5.4.9) and record details in the CRF of all relief medication taken since the last visit.
- Record any adverse events which have occurred since the last visit on the Baseline Signs and Symptoms page of the CRF and follow up, as appropriate (Section 8).
- Perform a COPD exacerbation assessment to determine if the patient has experienced any exacerbations or been hospitalised during the period between Visits 1 and 2. Patients who have taken any corticosteroids or are hospitalised for the treatment of a COPD exacerbation during the run-in phase will not be randomised to double-blind medication and should be withdrawn from the study (Section 8.1.2). For any patients who discontinue from the study, the continuation/withdrawal page of the CRF should be completed.

- Review the patient's faecal occult blood test kit or, if no sample was provided to remind patient of the necessity of providing faecal occult blood samples by visit 3.

Greater than 8 hours after the patient's last salbutamol administration:

- Measure blood pressure and heart rate after the patient has been sitting for 5 minutes (Section 5.4.2).

- Perform the pulmonary function tests before and 30 minutes after administration of 80 mcg ipratropium and before administration of the next dose of study medication in the clinic. Calculate ipratropium reversibility (Section 5.4.5).

For patients who are continuing in the study:

Re-dispense the same container of single-blind study medication (Section 6.1). The next dose of study medication should be taken in the clinic with food. Instruct the patient to take one tablet each morning immediately after breakfast and a second tablet immediately after the evening meal. Remind the patient not to take their study medication at least 8 hours prior to their next clinic visit.

- Check the patient's supply of salbutamol relief medication and if necessary explain that this must only be used as needed to relieve symptoms; issue a new salbutamol inhaler if required.

- Issue the patient a new diary card with instructions to complete the card each morning.

- Review the procedure for reporting gastrointestinal adverse events with the patient.

Patients will be asked to return to the clinic for Visit 3 in 14 (± 3) days at the same time of day. Patients will be reminded:

- **not** to take the study medication at least 8 hours before their next clinic visit.

- to refrain from using salbutamol or anticholinergic medication during the 4 hours immediately preceding Visit 3.

- to refrain from smoking for 2 hours immediately preceding the next visit.

- to bring any remaining study medication tablets, all study medication containers, the salbutamol inhaler and spacer, and the diary card with them to the next visit.

- to continue taking their anticholinergic medication, if prescribed, at a constant dose and salbutamol when needed to control symptoms.

5.3.3 Visit 3 (Week 0): Baseline, Start of Double-blind Treatment Phase

The following assessments will be made **BEFORE the dose of double-blind study medication is administered in the clinic**.

- Document if the patient has taken salbutamol or used anticholinergic medication during the 4 hours immediately preceding the visit or smoked during the 2 hours immediately preceding the visit.

- Ask the patient to complete two health status questionnaires (EQ-5D and SGRQ) before performing all other assessments (Section 7.3, Appendix E and Appendix F).

- Record Investigator and Patient Global Assessments in the CRF (Section 5.4.10).

- Record any changes or additions to the patient's concomitant medication in the CRF (Section 6.11.4).

- Document details of influenza vaccinations the patient may have had since the last visit.

- Document any changes in the patient's smoking status (Section 5.4.1).

- Determine if the patient has entered a Pulmonary Rehabilitation Program since the last visit.

- Determine the patient's compliance in taking study medication since the previous visit (Section 6.8). Emphasise the importance of compliance to patients whose compliance is <80% or >120%.

- Perform a physical examination, including a respiratory examination (Section 5.4.2).

- Collect and review the patient's diary card and check that it has been completed correctly. Review the domiciliary PEF and use of relief medication

(Section 5.4.7, Section 5.4.9) and record details in the CRF of all relief medication taken since the last visit.

- Record any adverse events which have occurred since the last visit on the Baseline Signs and Symptoms page of the CRF and follow up, as appropriate (Section 8).

- Perform a COPD exacerbation assessment to determine if the patient has experienced any exacerbations or been hospitalised during the period between Visits 2 and 3. Patients who have taken any corticosteroids or are hospitalised for the treatment of a COPD exacerbation during the run-in phase will not be randomised to double-blind medication (Section 8.1.2). For any patients who discontinue from the study, the continuation/withdrawal page of the CRF should be completed.

- Review the patient's faecal occult blood test kit.

Greater than 4 hours after the patient's last salbutamol administration:

- Perform a 12-lead electrocardiogram after the patient has been semisupine for 5 minutes (Section 5.4.4).

- Measure heart rate and blood pressure after the patient has been in a sitting position for 5 minutes. After the patient has been in a supine position for 5 minutes followed by sitting with legs dependent for 1 minute, measure orthostatic changes in heart rate and blood pressure. Patients with clinically significant orthostatic changes in blood pressure or heart rate (decrease in systolic blood pressure or diastolic blood pressure of 20 mm Hg or 10 mm Hg, respectively, or increase in heart rate of 20 beats/minute) will not be randomised to double-blind medication (Section 5.4.2). For any patients who discontinue from the study, the continuation/withdrawal page of the CRF should be completed.

- Perform the baseline pulmonary function tests before and 30 minutes after administration of salbutamol and before taking the clinic dose of double-blind study medication (Section 5.4.5).

- Measure Residual Volume (RV) using body plethysmography (Section 5.4.6) **(at selected centres only)**

Randomisation Criteria

Inclusion Criteria

- Less than 20% change (increase or decrease) in pre-bronchodilator FEV_1 assessed at Screening Visit 2 and at Baseline Visit 3.

- Subjects must have been compliant (medication compliance is defined as ≥ 80% and ≤ 120% for the visit interval) in taking study medication during the placebo run-in period.

- Subjects with poor reversibility of airway obstruction, defined by ≤10% of predicted normal or ≤200 ml (or both) increase in FEV_1 after the administration of salbutamol 400mcg via MDI at Visit 1 and Visit 3

Exclusion Criteria

- Subjects who have had any changes to their COPD medication (other than 'as required' use of salbutamol), received corticosteroids (oral or inhaled) for respiratory disease, or hospitalised for COPD/lower respiratory tract infections during the run-in period.

- Subjects receiving any other medication during the run-in period which in the opinion of the investigator, is judged as likely to affect baseline assessments

- Subjects with a positive faecal occult blood test result between Visits 1 and 3.

- Subjects with clinically significant orthostatic changes in blood pressure or heart rate at Visit 3.

Patients who do not meet these randomisation criteria must be withdrawn from the study.

For patients continuing into the double-blind phase of the study, the Investigator should carry-out the following:

- Collect blood and urine samples for routine haematology (including CD4+/CD8+ ratio and serum C Reactive Protein), biochemistry, (including beta-HCG for women of childbearing potential) and urinalysis (Section 5.4.8).

- Contact RAMOS to randomise the patient and obtain a study medication container number (Section 6.1). Locate the correct container of double-blind study medication and dispense the next dose which the patient should take in

the clinic with food. Give the assigned container of study medication to the patient with instructions to allow at least 8 hours before taking the next dose. Remind the patient to take one tablet after breakfast and one tablet after the evening meal each day until the next scheduled visit.

- Check the patient's supply of salbutamol relief medication and if necessary explain that this must only be used as needed to relieve symptoms; issue a new salbutamol inhaler if required.
- Issue the patient a new diary card with instructions to complete the card each morning.
- Review the procedure for reporting gastrointestinal adverse events with the patient.

Schedule Visit 4 at the same time of day in 14 (± 3) days time and remind the patient:

- to allow at least 8 hours before taking the next dose of study medication with food.
- **not** to take the study medication at least 8 hours before their next clinic visit.
- to refrain from using salbutamol or anticholinergic medication during the 4 hours immediately preceding 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, the salbutamol inhaler and spacer, and diary card with them to the next visit.
- to continue taking their anticholinergic medication, if prescribed, at a constant dose and salbutamol when needed to control symptoms.

Note: If results of any assessment made at Visit 3 are not available at the time of randomisation and subsequently preclude continuation in the study, the patient must be withdrawn immediately and a Safety Follow-up Visit scheduled (Section 5.3.14).

5.3.4 Visit 4 (End of Week 2): Double-blind Treatment Phase

At this visit, the following procedures will be completed:

- Document if the patient has taken salbutamol or used anticholinergic medication during the 4 hours immediately preceding the visit or smoked during the 2 hours immediately preceding the visit.
- Record any changes or additions to the patient's concomitant medication in the CRF (Section 6.11.4).
- Document details of influenza vaccinations the patient may have had since the last visit.
- Document any changes in the patient's smoking status (Section 5.4.1).
- Determine if the patient has entered a Pulmonary Rehabilitation Program since the last visit.
- Determine the patient's compliance in taking study medication (Section 6.8). Emphasise the importance of compliance to patients whose compliance is <80% or >120%.
- Collect and review the patient's diary card and check that it has been completed correctly. Review the domiciliary PEF and use of relief medication (Section 5.4.7 Section 5.4.9) and record details in the CRF of all relief medication taken since the last visit.
- Record any adverse events which have occurred since the last visit on the Adverse Experiences page of the CRF and follow up, as appropriate (Section 8).
- Perform a COPD exacerbation assessment to determine if the patient has experienced any exacerbations during the period between Visits 3 and 4. (Section 8.1.2) and record details in the CRF.
- Perform an assessment of resource utilisation for COPD since the patient's last visit and record details in the CRF. (Section 7.1 and Section 7.2).

Greater than 4 hours after the patient's last salbutamol administration:

- Measure heart rate and blood pressure after the patient has been in a sitting position for 5 minutes. (Section 5.4.2).

Patients who withdraw from the study during the visit should complete all scheduled visit assessments including pulmonary function tests, the EQ-5D and SGRQ questionnaires, Investigator and Patient Global Assessment, a physical

examination, orthostatic changes in blood pressure and heart rate, 12-lead ECG and haematology tests for CD4+/CD8+ lymphocyte ratio and serum C Reactive Protein (Section 5.3.13).

For patients who are continuing in the study:

- Dispense the next dose, which the patient should take in the clinic with food, from the same container assigned to the patient at Visit 3. Return the container of study medication to the patient with instructions to allow at least 8 hours before taking the next dose. Remind the patient to take one tablet after breakfast and one tablet after the evening meal each day until the next scheduled visit.

- Check the patient's supply of salbutamol relief medication and if necessary issue a new salbutamol inhaler.

- Issue the patient a new diary card with instructions to complete the card each morning.

- Review the procedure for reporting gastrointestinal adverse events with the patient.

Schedule Visit 5 at the same time of day in 14 (± 3) days time and remind the patient:

- to allow at least 8 hours before taking the next dose of study medication with food.

- **not** to take the study medication at least 8 hours before their next clinic visit.

- to refrain from using salbutamol or anticholinergic medication during the 4 hours immediately preceding 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, the salbutamol inhaler and spacer, and diary card with them to the next visit.

- to continue taking their anticholinergic medication, if prescribed, at a constant dose and salbutamol when needed to control symptoms.

5.3.5 Visit 5 (End of Week 4): Double-blind Treatment Phase

- Document if the patient has taken salbutamol or used anticholinergic medication during the 4 hours immediately preceding the visit or smoked during the 2 hours immediately preceding the visit.
- Record any changes or additions to the patient's concomitant medication in the CRF (Section 6.11.4).
- Document details of influenza vaccinations the patient may have had since Visit 2.
- Document any changes in the patient's smoking status (Section 5.4.1).
- Determine if the patient has entered a Pulmonary Rehabilitation Program since the last visit.
- Determine the patient's compliance in taking study medication (Section 6.8). Emphasise the importance of compliance to patients whose compliance is <80% or >120%.
- Collect and review the patient's diary card and check that it has been completed correctly. Review the domiciliary PEF and use of relief medication (Section 5.4.7 Section 5.4.9) and record details in the CRF of all relief medication taken since the last visit.
- Record any adverse events which have occurred since the last visit on the Adverse Experiences page of the CRF and follow up, as appropriate (Section 8).
- Perform a COPD exacerbation assessment to determine if the patient has experienced any exacerbations during the period between Visits 4 and 5 and record details in the CRF (Section 8.1.2).
- Perform an assessment of resource utilisation for COPD since the patient's last visit and record details in the CRF. (Section 7.1 and Section 7.2).
- Collect blood and urine samples for routine haematology, biochemistry, (including beta-HCG for women of childbearing potential) and urinalysis (Section 5.4.8).

Greater than 4 hours after the patient's last salbutamol administration:

- Measure heart rate and blood pressure after the patient has been in a sitting position for 5 minutes. (Section 5.4.2).

- Perform the pulmonary function tests before and 30 minutes after administration of salbutamol and before dispensing the clinic dose of double-blind study medication (Section 5.4.5).

Patients who withdraw from the study during the visit should complete all scheduled visit assessments, the EQ-5D and SGRQ questionnaires, Investigator and Patient Global Assessment, a physical examination, orthostatic changes in blood pressure and heart rate, 12-lead ECG and haematology tests for CD4+/CD8+ lymphocyte ratio and serum C Reactive Protein (Section 5.3.13).

For patients who are continuing in the study:

- Contact RAMOS to obtain a study medication container number (Section 6.1). Locate the correct container of study medication and dispense the next dose which the patient should take in the clinic with food. Give the assigned container of study medication to the patient with instructions to allow at least 8 hours before taking the next dose. Remind the patient to take one tablet after breakfast and one tablet after the evening meal each day until the next scheduled visit.

- Check the patient's supply of salbutamol relief medication and if necessary issue a new salbutamol inhaler.

- Issue the patient a new diary card with instructions to complete the card each morning.

- Review the procedure for reporting gastrointestinal adverse events with the patient.

Schedule Visit 6 at the same time of day in 28 (± 6) days time and remind the patient:

- to allow at least 8 hours before taking the next dose of study medication with food.

- **not** to take the study medication at least 8 hours before their next clinic visit.

- to refrain from using salbutamol or anticholinergic medication during the 4 hours immediately preceding 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, the salbutamol inhaler and spacer, and diary card with them at the next visit.
- to continue taking their anticholinergic medication, if prescribed, at a constant dose and salbutamol when needed to control symptoms.

5.3.6 Visit 6 (End of Week 8): Double-blind Treatment Phase

At this visit, the following assessments will be performed:

- Document if the patient has taken salbutamol or used anticholinergic medication during the 4 hours immediately preceding the visit or smoked during the 2 hours immediately preceding the visit.
- Record any changes or additions to the patient's concomitant medication in the CRF (Section 6.11.4).
- Document details of influenza vaccinations the patient may have had since the last visit.
- Document any changes in the patient's smoking status (Section 5.4.1).
- Determine if the patient has entered a Pulmonary Rehabilitation Program since the last visit.
- Determine the patient's compliance in taking study medication (Section 6.8). Emphasise the importance of compliance to patients whose compliance is <80% or >120%.
- Collect and review the patient's diary card and check that it has been completed correctly. Review the domiciliary PEF and use of relief medication (Section 5.4.7 Section 5.4.9) and record details in the CRF of all relief medication taken since the last visit.
- Record any adverse events which have occurred since the last visit on the Adverse Experiences page of the CRF and follow up, as appropriate (Section 8).

- Perform a COPD exacerbation assessment to determine if the patient has experienced any exacerbations during the period between Visits 5 and 6 and record details in the CRF (Section 8.1.2)

- Perform an assessment of resource utilisation for COPD since the patient's last visit and record details in the CRF. (Section 7.1 and Section 7.2).

- Collect blood and urine samples for routine haematology, biochemistry, (including beta-HCG for women of childbearing potential) and urinalysis (Section 5.4.8).

Greater than 4 hours after the patient's last salbutamol administration:

- Measure heart rate and blood pressure after the patient has been in a sitting position for 5 minutes. (Section 5.4.2).

- Perform the pulmonary function tests before and 30 minutes after administration of salbutamol and before dispensing the clinic dose of double-blind study medication (Section 5.4.5).

Patients who withdraw from the study during the visit should complete all scheduled visit assessments including the EQ-5D and SGRQ questionnaires, Investigator and Patient Global Assessment, a physical examination, orthostatic changes in blood pressure and heart rate, 12-lead ECG and haematology tests for CD4+/CD8+ lymphocyte ratio and serum C Reactive Protein. (Section 5.3.13).

For patients who are continuing in the study:

- Contact RAMOS to obtain a study medication container number (Section 6.1). Locate the correct container of study medication and dispense the next dose which the patient should take in the clinic with food. Give the assigned container of study medication to the patient with instructions to allow at least 8 hours before taking the next dose. Remind the patient to take one tablet after breakfast and one tablet after the evening meal each day until the next scheduled visit.

- Check the patient's supply of salbutamol relief medication and if necessary issue a new salbutamol inhaler.

- Issue the patient a new diary card with instructions to complete the card each morning.

- Review the procedure for reporting gastrointestinal adverse events with the patient.

Schedule Visit 7 at the same time of day in 28 (± 6) days time and remind the patient:

- to allow at least 8 hours before taking the next dose of study medication with food.
- **not** to take the study medication at least 8 hours before their next clinic visit.
- to refrain from using salbutamol or anticholinergic medication during the 4 hours immediately preceding 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, the salbutamol inhaler and spacer, and diary card with them at the next visit.
- to continue taking their anticholinergic medication, if prescribed, at a constant dose and salbutamol when needed to control symptoms.

5.3.7 Visit 7 (End of Week 12): Double-blind Treatment Phase

The following procedures will be performed at this visit:

- Document if the patient has taken salbutamol or used anticholinergic medication during the 4 hours immediately preceding the visit or smoked during the 2 hours immediately preceding the visit.
- Record any changes or additions to the patient's concomitant medication in the CRF (Section 6.11.4).
- Document details of influenza vaccinations the patient may have had since the last visit.
- Document any changes in the patient's smoking status (Section 5.4.1).
- Determine if the patient has entered a Pulmonary Rehabilitation Program since the last visit.

- Determine the patient's compliance in taking study medication (Section 6.8). Emphasise the importance of compliance to patients whose compliance is <80% or >120%.

- Collect and review the patient's diary card and check that it has been completed correctly. Review the domiciliary PEF and use of relief medication (Section 5.4.7 Section 5.4.9) and record details in the CRF of all relief medication taken since the last visit.

- Record any adverse events which have occurred since the last visit on the Adverse Experiences page of the CRF and follow up, as appropriate (Section 8).

- Perform a COPD exacerbation assessment to determine if the patient has experienced any exacerbations during the period between Visits 6 and 7 and record details in the CRF (Section 8.1.2)

- Perform an assessment of resource utilisation for COPD since the patient's last visit and record details in the CRF. (Section 7.1 and Section 7.2).

- Collect blood and urine samples for routine haematology, biochemistry, (including beta-HCG for women of childbearing potential) and urinalysis (Section 5.4.8).

Greater than 4 hours after the patient's last salbutamol administration:

- Perform a 12-lead electrocardiogram after the patient has been semisupine for 5 minutes (Section 5.4.4).

- Measure heart rate and blood pressure after the patient has been in a sitting position for 5 minutes. After the patient has been in a supine position for 5 minutes followed by sitting with legs dependent for 1 minute, measure orthostatic changes in heart rate and blood pressure (Section 5.4.2).

- Perform the pulmonary function tests before and 30 minutes after administration of salbutamol and before taking the clinic dose of double-blind study medication (Section 5.4.5).

- Patients who withdraw from the study during the visit should complete all scheduled visit assessments including the EQ-5D and SGRQ questionnaires, Investigator and Patient Global Assessments, a physical examination and

haematology tests for CD4+/CD8+ lymphocyte ratio and serum C Reactive Protein (Section 5.3.13).

For patients who are continuing in the study:

- Contact RAMOS to obtain two study medication container numbers (Section 6.1). Locate the correct containers of study medication and dispense the next dose which the patient should take in the clinic with food. Give the assigned containers of study medication to the patient with instructions to allow at least 8 hours before taking the next dose. Remind the patient to take one tablet after breakfast and one tablet after the evening meal each day until the next scheduled visit.

- Check the patient's supply of salbutamol relief medication and if necessary issue a new salbutamol inhaler.

- Issue the patient a new diary card with instructions to complete the card each morning.

- Review the procedure for reporting gastrointestinal adverse events with the patient.

Schedule Visit 8 at the same time of day in 56 (± 6) days time and remind the patient:

- to allow at least 8 hours before taking the next dose of study medication with food.

- **not** to take the study medication at least 8 hours before their next clinic visit.

- to refrain from using salbutamol or anticholinergic medication during the 4 hours immediately preceding 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, the salbutamol inhaler and spacer, and diary card with them at the next visit.

- to continue taking their anticholinergic medication, if prescribed, at a constant dose and salbutamol when needed to control symptoms.

5.3.8 Visit 8 (End of Week 20): Double-blind Treatment Phase

At this visit, the following assessments will be performed:

- Document if the patient has taken salbutamol or used anticholinergic medication during the 4 hours immediately preceding the visit or smoked during the 2 hours immediately preceding the visit.
- Record any changes or additions to the patient's concomitant medication in the CRF (Section 6.11.4).
- Document details of influenza vaccinations the patient may have had since the last visit.
- Document any changes in the patient's smoking status (Section 5.4.1).
- Determine if the patient has entered a Pulmonary Rehabilitation Program since the last visit.
- Determine the patient's compliance in taking study medication (Section 6.8). Emphasise the importance of compliance to patients whose compliance is <80% or >120%.
- Collect and review the patient's diary card and check that it has been completed correctly. Review the domiciliary PEF and use of relief medication (Section 5.4.7 Section 5.4.9) and record details in the CRF of all relief medication taken since the last visit.
- Record any adverse events which have occurred since the last visit on the Adverse Experiences page of the CRF and follow up, as appropriate (Section 8).
- Perform a COPD exacerbation assessment to determine if the patient has experienced any exacerbations during the period between Visits 7 and 8 and record details in the CRF (Section 8.1.2)
- Perform an assessment of resource utilisation for COPD since the patient's last visit and record details in the CRF. (Section 7.1 and Section 7.2).
- Collect blood and urine samples for routine haematology, biochemistry, (including beta-HCG for women of childbearing potential) and urinalysis (Section 5.4.8).

Greater than 4 hours after the patient's last salbutamol administration:

- Measure heart rate and blood pressure after the patient has been in a sitting position for 5 minutes. (Section 5.4.2).

- Perform the pulmonary function tests before and 30 minutes after administration of salbutamol and before dispensing the clinic dose of double-blind study medication (Section 5.4.5).

Patients who withdraw from the study during the visit should complete all scheduled visit assessments including the EQ-5D and SGRQ questionnaires, Investigator and Patient Global Assessment, a physical examination, orthostatic changes in blood pressure and heart rate, resting 12-lead ECG and haematology tests for CD4+/CD8+ lymphocyte ratio and serum C Reactive Protein (Section 5.3.13).

For patients who are continuing in the study:

- Contact RAMOS to obtain two study medication container numbers (Section 6.1). Locate the correct containers of study medication and dispense the next dose which the patient should take in the clinic with food. Give the assigned containers of study medication to the patient with instructions to allow at least 8 hours before taking the next dose. Remind the patient to take one tablet after breakfast and one tablet after the evening meal each day until the next scheduled visit.

- Check the patient's supply of salbutamol relief medication and issue a new salbutamol inhaler if necessary

- Issue the patient a new diary card with instructions to complete the card each morning.

- Review the procedure for reporting gastrointestinal adverse events with the patient.

Schedule Visit 9 at the same time of day in 56 (± 6) days time and remind the patient:

- to allow at least 8 hours before taking the next dose of study medication with food.

- **not** to take the study medication at least 8 hours before their next clinic visit.

- to refrain from using salbutamol or anticholinergic medication during the 4 hours immediately preceding 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, the salbutamol inhaler and spacer, and diary card with them at the next visit.
- to continue taking their anticholinergic medication, if prescribed, at a constant dose and salbutamol when needed to control symptoms.

5.3.9 Visit 9 (End of Week 28): Double-blind Treatment Phase

The following procedures will be performed at this visit:

- Document if the patient has taken salbutamol or used anticholinergic medication during the 4 hours immediately preceding the visit or smoked during the 2 hours immediately preceding the visit.
- Ask the patient to complete two health status questionnaires (EQ-5D and SGRQ) before performing all other assessments (Section 7.3, Appendix E and Appendix F).
- Record Investigator and Patient Global Assessments in the CRF (Section 5.4.10).
- Record any changes or additions to the patient's concomitant medication in the CRF (Section 6.11.4).
- Document details of influenza vaccinations the patient may have had since the last visit.
- Document any changes in the patient's smoking status (Section 5.4.1).
- Determine if the patient has entered a Pulmonary Rehabilitation Program since the last visit.
- Determine the patient's compliance in taking study medication (Section 6.8). Emphasise the importance of compliance to patients whose compliance is <80% or >120%.

- Collect and review the patient's diary card and check that it has been completed correctly. Review the domiciliary PEF and use of relief medication (Section 5.4.7 Section 5.4.9) and record details in the CRF of all relief medication taken since the last visit.

- Record any adverse events which have occurred since the last visit on the Adverse Experiences page of the CRF and follow up, as appropriate (Section 8).

- Perform a COPD exacerbation assessment to determine if the patient has experienced any exacerbations during the period between Visits 8 and 9 and record details in the CRF (Section 8.1.2)

- Perform an assessment of resource utilisation for COPD since the patient's last visit and record details in the CRF. (Section 7.1 and Section 7.2).

- Collect blood and urine samples for routine haematology, biochemistry, (including beta-HCG for women of childbearing potential) and urinalysis (Section 5.4.8).

Greater than 4 hours after the patient's last salbutamol administration:

- Perform a 12-lead electrocardiogram after the patient has been semisupine for 5 minutes (Section 5.4.4).

- Measure heart rate and blood pressure after the patient has been in a sitting position for 5 minutes. After the patient has been in a supine position for 5 minutes followed by sitting with legs dependent for 1 minute, measure orthostatic changes in heart rate and blood pressure.

- Perform the pulmonary function tests before and 30 minutes after administration of salbutamol and before dispensing the clinic dose of double-blind study medication (Section 5.4.5).

- Measure Residual Volume (RV) using body plethysmography (Section 5.4.6) **(at selected centres only)**

Patients who withdraw from the study during the visit should complete all scheduled visit assessments and a physical examination and haematology tests for CD4+/CD8+ lymphocyte ratio and serum C Reactive Protein (Section 5.3.13).

For patients who are continuing in the study:

- Contact RAMOS to obtain two study medication container numbers (Section 6.1). Locate the correct containers of study medication and dispense the next dose which the patient should take in the clinic with food. Give the assigned containers of study medication to the patient with instructions to allow at least 8 hours before taking the next dose. Remind the patient to take one tablet after breakfast and one tablet after the evening meal each day until the next scheduled visit.

- Check the patient's supply of salbutamol relief medication and issue a new salbutamol inhaler if necessary

- Issue the patient a new diary card with instructions to complete the card each morning.

- Review the procedure for reporting gastrointestinal adverse events with the patient.

Schedule Visit 10 at the same time of day in 56 (± 6) days time and remind the patient:

- to allow at least 8 hours before taking the next dose of study medication with food.

- **not** to take the study medication at least 8 hours before their next clinic visit.

- to refrain from using salbutamol or anticholinergic medication during the 4 hours immediately preceding 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, the salbutamol inhaler and spacer, and diary card with them at the next visit.

- to continue taking their anticholinergic medication, if prescribed, at a constant dose and salbutamol when needed to control symptoms.

5.3.10 Visit 10 (End of Week 36): Double-blind Treatment Phase

At this visit, the following assessments will be performed:

- Document if the patient has taken salbutamol or used anticholinergic medication during the 4 hours immediately preceding the visit or smoked during the 2 hours immediately preceding the visit.

- Record any changes or additions to the patient's concomitant medication in the CRF (Section 6.11.4).

- Document details of influenza vaccinations the patient may have had since the last visit.

- Document any changes in the patient's smoking status (Section 5.4.1).

- Determine if the patient has entered a Pulmonary Rehabilitation Program since the last visit.

- Determine the patient's compliance in taking study medication (Section 6.8). Emphasise the importance of compliance to patients whose compliance is <80% or >120%.

- Collect and review the patient's diary card and check that it has been completed correctly. Review the domiciliary PEF and use of relief medication (Section 5.4.7 Section 5.4.9) and record details in the CRF of all relief medication taken since the last visit.

- Record any adverse events which have occurred since the last visit on the Adverse Experiences page of the CRF and follow up, as appropriate (Section 8).

- Perform a COPD exacerbation assessment to determine if the patient has experienced any exacerbations during the period between Visits 9 and 10 and record details in the CRF (Section 8.1.2)

- Perform an assessment of resource utilisation for COPD since the patient's last visit and record details in the CRF. (Section 7.1 and Section 7.2).

- Collect blood and urine samples for routine haematology, biochemistry, (including beta-HCG for women of childbearing potential) and urinalysis (Section 5.4.8).

Greater than 4 hours after the patient's last salbutamol administration:

- Measure heart rate and blood pressure after the patient has been in a sitting position for 5 minutes. (Section 5.4.2).

- Perform the pulmonary function tests before and 30 minutes after administration of salbutamol and before dispensing the clinic dose of double-blind study medication (Section 5.4.5).

Patients who withdraw from the study during the visit should complete all scheduled visit assessments including the EQ-5D and SGRQ questionnaires, Investigator and Patient Global Assessment, a physical examination, orthostatic changes in blood pressure and heart rate, resting 12-lead ECG haematology tests for CD4+/CD8+ lymphocyte ratio and serum C Reactive Protein (Section 5.3.13).

For patients who are continuing in the study:

- Contact RAMOS to obtain two study medication container numbers (Section 6.1). Locate the correct containers of study medication and dispense the next dose which the patient should take in the clinic with food. Give the assigned containers of study medication to the patient with instructions to allow at least 8 hours before taking the next dose. Remind the patient to take one tablet after breakfast and one tablet after the evening meal each day until the next scheduled visit.

- Check the patient's supply of salbutamol relief medication and issue a new salbutamol inhaler if necessary

- Issue the patient a new diary card with instructions to complete the card each morning.

- Review the procedure for reporting gastrointestinal adverse events with the patient.

- Check consent of patient for additional faecal occult blood test at visit 11. (This test is an optional test. Patients not wishing to undertake this test do not need to withdraw)

- For patients who have consented to the additional faecal occult blood test issue a faecal occult blood kit and ask the patient to follow the instructions on the kit (Section 5.4.8). The faecal samples should be taken within 14 days of visit 11 either prior to the visit or immediately after the visit and returned to the investigator within 14 days for testing.

Schedule Visit 11 at the same time of day in 56 (± 6) days time and remind the patient:

- to allow at least 8 hours before taking the next dose of study medication with food.
- **not** to take the study medication at least 8 hours before their next clinic visit.
- to refrain from using salbutamol or anticholinergic medication during the 4 hours immediately preceding 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, the salbutamol inhaler and spacer, and diary card with them at the next visit.
- to continue taking their anticholinergic medication, if prescribed, at a constant dose and salbutamol when needed to control symptoms.

5.3.11 Visit 11 (End of Week 44): Double-blind Treatment Phase

At this visit, the following procedures will be completed:

- Document if the patient has taken salbutamol or used anticholinergic medication during the 4 hours immediately preceding the visit or smoked during the 2 hours immediately preceding the visit.
- Record any changes or additions to the patient's concomitant medication in the CRF (Section 6.11.4).
- Document details of influenza vaccinations the patient may have had since the last visit.
- Document any changes in the patient's smoking status (Section 5.4.1).
- Determine if the patient has entered a Pulmonary Rehabilitation Program since the last visit.
- Determine the patient's compliance in taking study medication (Section 6.8). Emphasise the importance of compliance to patients whose compliance is <80% or >120%.
- Collect and review the patient's diary card and check that it has been completed correctly. Review the domiciliary PEF and use of relief medication

(Section 5.4.7, Section 5.4.9) and record details in the CRF of all relief medication taken since the last visit.

- Record any adverse events which have occurred since the last visit on the Adverse Experiences page of the CRF and follow up, as appropriate (Section 8).

- Perform a COPD exacerbation assessment to determine if the patient has experienced any exacerbations during the period between Visits 10 and 11 and record details in the CRF (Section 8.1.2)

- Perform an assessment of resource utilisation for COPD since the patient's last visit and record details in the CRF. (Section 7.1 and Section 7.2).

- Collect blood and urine samples for routine haematology, biochemistry, (including beta-HCG for women of childbearing potential) and urinalysis (Section 5.4.8).

- For patients who have consented to an additional faecal occult test, review the faecal occult blood test and record results in CRF. If the test has not been conducted yet, please issue a test kit at this visit and instruct the patient to return it within 14 days for assessment.

- For patients who have consented to an additional faecal occult test review the results of the faecal occult blood test. If the test has not been conducted yet please issue a test kit at this visit an instruct the patient to return it within 14 days.

- ***Greater than 4 hours after the patient's last salbutamol administration:***

- Measure heart rate and blood pressure after the patient has been in a sitting position for 5 minutes. (Section 5.4.2).

- Perform the pulmonary function tests before and 30 minutes after administration of salbutamol and before dispensing the clinic dose of double-blind study medication (Section 5.4.5).

Patients who withdraw from the study during the visit should complete all scheduled visit assessments including the EQ-5D and SGRQ questionnaires, Investigator and Patient Global Assessment, a physical examination, orthostatic changes in blood pressure and heart rate, resting 12-lead ECG haematology tests for CD4+/CD8+ lymphocyte ratio and serum C Reactive Protein (Section 5.3.13).

For patients who are continuing in the study:

- Contact RAMOS to obtain two study medication container numbers (Section 6.1). Locate the correct containers of study medication and dispense the next dose which the patient should take in the clinic with food. Give the assigned containers of study medication to the patient with instructions to allow at least 8 hours before taking the next dose. Remind the patient to take one tablet after breakfast and one tablet after the evening meal each day until the next scheduled visit.

- Check the patient's supply of salbutamol relief medication and issue a new salbutamol inhaler if necessary

- Issue the patient a new diary card with instructions to complete the card each morning.

- Review the procedure for reporting gastrointestinal adverse events with the patient.

Schedule Visit 12 at the same time of day in 56 (± 6) days time and remind the patient:

- to allow at least 8 hours before taking the next dose of study medication with food.

- **not** to take the study medication at least 8 hours before their next clinic visit.

- to refrain from using salbutamol or anticholinergic medication during the 4 hours immediately preceding 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, the salbutamol inhaler and spacer, and diary card with them at the next visit.

- to continue taking their anticholinergic medication, if prescribed, at a constant dose and salbutamol when needed to control symptoms.

5.3.12 Visit 12 (End of Week 52): End of Double-blind Treatment Phase

- Document if the patient has taken salbutamol or used anticholinergic medication during the 4 hours immediately preceding the visit or smoked during the 2 hours immediately preceding the visit.
- Ask the patient to complete two health status questionnaires (EQ-5D and SGRQ) before performing all other assessments (Section 7.3, Appendix E and Appendix F).
- Record Investigator and Patient Global Assessments in the CRF (Section 5.4.10).
- Record any changes or additions to the patient's concomitant medication in the CRF (Section 6.11.4).
- Document details of influenza vaccinations the patient may have had since the last visit.
- Document any changes in the patient's smoking status (Section 5.4.1).
- Determine if the patient has entered a Pulmonary Rehabilitation Program since the last visit.
- Determine the patient's compliance in taking study medication (Section 6.8) and record in the CRF.
- Perform a physical examination, including a respiratory examination (Section 5.4.2).
- Collect and review the patient's diary card and check that it has been completed correctly. Review the domiciliary PEF and use of relief medication (Section 5.4.7 Section 5.4.9) and record details in the CRF of all relief medication taken since the last.
- Record any adverse events which have occurred since the last visit on the Adverse Experiences page of the CRF and follow up, as appropriate (Section 8).
- Perform a COPD exacerbation assessment to determine if the patient has experienced any exacerbations during the period between Visits 11 and 12 and record details in the CRF (Section 8.1.2)

- Perform an assessment of resource utilisation for COPD since the patient's last visit and record details in the CRF. (Section 7.1 and Section 7.2).

- Collect blood and urine samples for routine haematology, biochemistry, (including beta-HCG for women of childbearing potential) and urinalysis (Section 5.4.8).

Greater than 4 hours after the patient's last salbutamol administration:

- Perform a 12-lead electrocardiogram after the patient has been semisupine for 5 minutes (Section 5.4.4).

- Measure heart rate and blood pressure after the patient has been in a sitting position for 5 minutes. After the patient has been in a supine position for 5 minutes followed by sitting with legs dependent for 1 minute, measure orthostatic changes in heart rate and blood pressure (Section 5.4.2).

- Perform the pulmonary function tests before and 30 minutes after administration of salbutamol (Section 5.4.5).

- Measure Residual Volume (RV) using body plethysmography (Section 5.4.6) **(at selected centres only)**

- Ask the patient to return in 7 (± 3) days for a Safety Follow-Up Visit (Section 5.3.14). Patients may resume their previous COPD medications.

5.3.13 Early Withdrawal Assessments

Patients who withdraw from the study at a scheduled visit and who are willing to return for scheduled assessments should follow the procedure for patients withdrawing through to the safety follow up visit stage and then return for their next scheduled visit according to the original visit schedule. All further visits should be completed in the generic module for patients withdrawn from the study. Assessments will include Clinic FEV_1, exacerbation data, respiratory AEs and respiratory medications and GI AEs

Patients who withdraw from the study and who do not wish to return for further visits should complete all the assessments for that visit and the following: A physical examination, including a respiratory exam and orthostatic vital signs (Section 5.4.2), laboratory assessments including CD4+/CD8+ ratio and serum C Reactive Protein (Section 5.4.8), the EQ-5D and SGRQ questionnaires

(Sections 7.3), Investigator and Patient Global Assessments (Section 5.4.10), if not already included in the scheduled visit assessments.

Patients who withdraw from the study between scheduled clinic visits will be instructed to return to the clinic within 24 hours of stopping study medication for an Early Withdrawal Visit.

Early Withdrawal Visit

The following should be performed at an Early Withdrawal Visit:

- Document if the patient has taken salbutamol or used anticholinergic medication during the 4 hours immediately preceding the visit or smoked during the 2 hours immediately preceding the visit.
- Ask the patient to complete two health status questionnaires (EQ-5D and SGRQ) before performing all other assessments (Section 7.3, Appendix E and Appendix F).
- Record Investigator and Patient Global Assessments in the CRF (Section 5.4.10).
- Record any changes or additions to the patient's concomitant medication in the CRF (Section 6.11.4).
- Document details of influenza vaccinations the patient may have had since the last visit.
- Document any changes in the patient's smoking status (Section 5.4.1).
- Determine if the patient has entered a Pulmonary Rehabilitation Program since the last visit.
- Document the patient's compliance in taking study medication (Section 6.8).
- Perform a physical examination, including a respiratory examination (Section 5.4.2).
- Collect and review the patient's diary card. Review the domiciliary PEF and use of relief medication (Section 5.4.7 and 5.4.8 (P168) and Section 5.4.9) and record details in the CRF of all relief medication taken since the last visit.

- Record any adverse events which have occurred since the last visit on the Adverse Experiences page of the CRF and follow up, as appropriate (Section 8).

- Perform a COPD exacerbation assessment to determine if the patient has experienced any exacerbations since the last scheduled visit and record details in the CRF (Section 8.1.2)

- Perform an assessment of resource utilisation for COPD since the patient's last visit and record details in the CRF. (Section 7.1 and Section 7.2).

- Collect blood and urine samples for routine haematology, biochemistry, (including beta-HCG for women of childbearing potential) and urinalysis (Section 5.4.8).

Greater than 4 hours after the patient's last salbutamol administration:

- Perform a 12-lead electrocardiogram after the patient has been semisupine for 5 minutes (Section 5.4.4).

- Measure heart rate and blood pressure after the patient has been in a sitting position for 5 minutes. After the patient has been in a supine position for 5 minutes followed by sitting with legs dependent for 1 minute, measure orthostatic changes in heart rate and blood pressure.

- Perform the pulmonary function tests before and 30 minutes after administration of salbutamol (Section 5.4.5).

- Measure Residual Volume (RV) using body plethysmography (Section 5.4.6) **(at selected centres only)**

- Issue a faecal occult blood kit and ask the patient to follow the instructions on the kit and to return it at the next visit.

- If the patient does not want to continue with study visits, ask the patient to return in 7 (± 3) days for a Safety Follow-Up Visit. (Section 5.3.14). Patients may resume their previous COPD medications.

5.3.14 Safety Follow-up Visit

A Safety Follow-up visit is required for all patients including patients who complete Visit 12 and any patients who **withdraw** from double-blind therapy prior to completion of Visit 12 (either at a scheduled visit or between visits). This visit will occur 7 ± 3 days after the last visit or the Early Withdrawal Visit (Section 5.3.14). Patients will be asked to refrain from using salbutamol or anticholinergics (or other COPD medications) for 4 hours and from smoking for at least 2 hours immediately preceding the Follow-up Visit.

The following procedures will be performed at this visit:

- Document if the patient has taken salbutamol or used anticholinergic medication during the 4 hours immediately preceding the visit or smoked during the 2 hours immediately preceding the visit.
- Record any changes or additions to the patient's concomitant medication in the CRF (Section 6.11.4).
- Document details of influenza vaccinations the patient may have had since the last visit.
- Document any changes in the patient's smoking status (Section 5.4.1).
- Record any adverse events which have occurred since the last visit on the Adverse Experiences page of the CRF and follow up, as appropriate (Section 8).
- Perform a COPD exacerbation assessment to determine if the patient has experienced any exacerbations since the last scheduled visit and record details in the CRF (Section 8.1.2)
- Perform an assessment of resource utilisation for COPD since the patient's last visit and record details in the CRF. (Section 7.1 and Section 7.2).
- If abnormal physical examination findings were observed at the last visit, perform another physical examination, including a respiratory examination, at this visit.
- Perform a urine pregnancy test for women of child-bearing potential.
- If abnormal laboratory findings were observed at the last visit, obtain blood and urine samples for routine haematology and biochemistry and urinalysis.

Greater than 4 hours after the patient's last salbutamol administration:

- If abnormal findings were observed at the last visit perform a 12-lead electrocardiogram after the patient has been semisupine for 5 minutes.
- Measure blood pressure and heart rate after the patient has been sitting for 5 minutes (Section 5.4.2).
- Perform the pulmonary function tests before and 30 minutes after administration of salbutamol (Section 5.4.5).
- Complete the CRF Study Conclusion Record for the patient.

5.4 Clinical Observations and Procedures

5.4.1 Previous Medical History and Diagnosis

Visit 1

All relevant previous medical history will be documented at screening (Visit 1). Standard medical terminology will be used to record all current conditions by diagnosis together with significant past conditions, operations and therapeutic or diagnostic procedures. Pulmonary demography and history will also be recorded.

In addition, alcohol consumption and cigarette smoking history will be documented at Visit 1. Changes in cigarette smoking status will be recorded at all visits.

5.4.2 Physical & Respiratory Examination and Vital Signs

Physical/Respiratory Examination: Visits 1, 3 and 12; Early Withdrawal; Vital Signs: all Visits

The full physical examination (including respiratory examination) will consist of measurement of height and body weight (light clothes, no shoes) and full examination of major organ systems (Visit 1 only). At Visits 3, 12 and Safety Follow-up (if abnormal at the previous visit) or upon early withdrawal, the Investigator will answer the following question "Has there been a clinically significant worsening since the last assessment in the patient's physical condition?" Any changes should be documented as a Baseline Sign or Symptom at Visit 3 or an Adverse Event at Visit 12, Safety Follow-up or Early Withdrawal.

Greater than 4 hours after the patient's last salbutamol administration, vital signs (blood pressure and heart rate) will be measured at all visits after the patient has been sitting for 5 minutes.

At Visits 1, 3, 7, 9 and 12, Early Withdrawal and at visits associated with gastrointestinal adverse events, heart rate and blood pressure will be measured after the patient has been supine for 5 minutes and then after the patient sits up with legs dependent for 1 minute. If this measurement shows a decrease in systolic blood pressure of ≥20 mmHg or a decrease in diastolic blood pressure of ≥10 mmHg or an increase in heart rate of ≥20 beats/minute at Visits 1 or 3, the patient is not eligible to participate in the study.

At visits required within 24 hours of the occurrence of gastrointestinal adverse events, (Section 8.1.3) a structured assessment of these adverse events including a physical examination will be performed as detailed in Appendix G.

5.4.3 Chest Radiograph

Visit 1

To exclude the possibility of any abnormality that may mimic or co-exist with COPD (e.g., pneumothorax, bronchial carcinoma, active pulmonary TB) a postero-anterior (PA) chest radiograph (X-ray) should be performed at or within 12 weeks of Visit 1. The X-ray must be available to the Investigator by Visit 3 and patients should be excluded from the study as appropriate. Abnormal findings not consistent with the diagnosis of COPD should be documented in the CRF and followed-up as appropriate.

5.4.4 Electrocardiograph (ECG)

Visits 1, 3, 7, 9 and 12, Safety Follow-up, Early Withdrawal

Greater than 4 hours after the patient's last salbutamol administration, a 12-lead ECG will be performed at Visits 1, 3, 7, 9 and 12 and Safety Follow-up (if abnormal at the previous visit) or at 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 and details recorded in the CRF.

5.4.5 Pulmonary Function Tests

All Visits (except Visit 4)

Throughout the study, it is preferable that for any individual patient at each study visit, pulmonary function tests are administered by the same pulmonologist or trained pulmonary technician or nurse in order to ensure consistency of technique. The spirometry equipment provided by GlaxosmithKline (GSK) **must** be used for this study. All personnel administering pulmonary function tests must attend a training session prior to the start of the study. All PFTs will be performed in accordance with the spirometry manual provided to each site

Forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), peak expiratory flow rate (PEF), and forced expiratory flow at 25-75% of vital capacity (FEF_{25-75}) will be measured according to the BTPS (Body Temperature and Pressure Standard) convention using the spirometer provided by GSK, which is suitable for research purposes, calibrated and maintained to acceptable respiratory function laboratory standards. [14] Pulmonary function tests can be repeated up to 8 times to obtain three acceptable readings according to ATS guidelines. [14] For each set of three FEV_1 measurements, one FEV_1 must be within 10% of the highest.

Visits 1 and 2: Pulmonary function tests (PFTs) will be assessed at least 8 hours after the last dose of inhaled salbutamol or anticholinergic agent. Patients will also be asked to refrain from smoking in the 2 hours prior to PFTs.

Visits 3, 5, 6, 7, 8, 9, 10, 11 and 12: Pulmonary function tests (PFTs) will be assessed at least 4 hours after the last dose of inhaled salbutamol or anticholinergic agent. Patients will also be asked to refrain from smoking in the 2 hours prior to PFTs.

At all Visits (except Visit 2), PFTs will be performed before and 30 minutes after the administration of 400 mcg salbutamol via metered dose inhaler (MDI) with spacer. At Visit 2, PFTs will be performed before and 30 minutes after the administration of 80 mcg ipratropium via metered dose inhaler (MDI) with spacer. Patients will be provided with a spacer which they will be asked to bring to each visit.

Salbutamol and ipratropium reversibility will be calculated with the formulae below:

$$\text{Reversibility} = \frac{\text{Highest post-salbutamol FEV1 - Highest pre-salbutamol FEV1}}{\text{Highest pre-salbutamol FEV1}} \times 100$$

$$\text{Reversibility} = \frac{\text{Highest post-ipratropium FEV1 - Highest pre-ipratropium FEV1}}{\text{Highest pre-ipratropium FEV1}} \times 100$$

Percentage predicted FEV_1 will be calculated according to the]. EUROPEAN COMMUNITY FOR COAL AND STEEL [12

Note: Prior to randomisation at Visit 3, patients must demonstrate stability in pulmonary function. Clinic FEV_1 (absolute value) in the absence of salbutamol must not change (i.e., increase or decrease) by more than 20% between Visits 2 and 3. If the patient meets randomisation criteria, the first dose of double-blind study medication will be administered.

5.4.6 Residual Volume (Visits 3, 9 and 12 and Early Withdrawal - selected centres only)

At selected centres Residual Volume (RV) will be measured by body plethysmography at Baseline and Visits 9 and 12 (where RV = TLC – SVC (Total Lung Capacity - Slow Vital Capacity and Total Lung Capacity (TLC = TGV_{FRC}+IC). These tests will be conducted before and after administration of 400 mcg of salbutamol via MDI with a spacer.

Residual Volume is defined as the difference between the TLC and the maximum of the six collected SVC and FVC measurements.

$$RV_{Box} = TLC_{Box} - \max(|SVC|, |FVC|)$$

5.4.7 Domiciliary Peak Flow Measurement

The miniWright Peak Flow Meter will be used to measure the domiciliary peak expiratory flow (PEF)

Peak expiratory flow rates are to be measured each morning before any use of salbutamol or anticholinergic medication. PEF will be performed in triplicate, with the highest measurement then captured in the patient diary.

5.4.8 Laboratory Tests

Visits 1, 3, 5, 6, 7, 8, 9, 10, 11, 12, Safety Follow-up and Early Withdrawal

Approximately 20 ml of blood will be collected at each visit where blood is drawn for laboratory analyses. Patients who complete Visit 12 or who withdraw from the study will have blood and urine samples collected at the Safety Follow-up Visit, only if abnormalities were observed at the last visit. A urine pregnancy test will always be performed at the Safety 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 (including CD4/CD8 lymphocyte ratio at Visits 3, 12 and Early Withdrawal), platelet count and serum C Reactive Protein (at Visits 3, 12 and Early Withdrawal).

Clinical chemistry: Blood urea, creatinine, aspartate transaminase (ASAT/SGOT), alanine transaminase (ALAT/SGPT), gamma glutaryl-transferase (GGT), alkaline phosphatase (ALP), total protein, albumin, total bilirubin, sodium, potassium, chloride, glucose, uric acid.

Amylase will be measured at Visit 3 (Baseline) and for patients who report gastrointestinal symptoms which are of concern to them or interfere with daily activities (see Section 8.1.3).

Faeces: Faecal occult blood tests will be performed between Visits 1 and 3, immediately prior or post visit 11 (for those who consent for an additional test) and also after the final dose of double blind medication either at visit 12 or at the early withdrawal visit (three tests collected on consecutive bowel movements, if possible). The tests 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.

The test around visit 11 needs to be conducted within14 days of visit 11, either pre or post visit. Samples must be returned and tested within 14 days from the date of the first sample taken. Processing of test results outside this window should be avoided as this will reduce the sensitivity of the test.

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 8.1.3). 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 all visits except Visits 2 and 4 and Safety Follow-Up.
Urinary beta-HCG for women of child bearing potential at the Safety Follow-up Visit.

Additional laboratory tests will be performed where indicated for patients who report gastrointestinal adverse events which are of concern to them or interfere with their daily activities including eating or sleeping (see Section 8.1.3).

All laboratory testing for the study will be performed centrally by Quest Laboratories (Dorevitch laboratories in Australia and New Zealand). Samples will be sent by courier from each centre to Quest Laboratories (Dorevitch laboratories in Australia and New Zealand). The patient number, patient initials, protocol number, centre number, visit number and date will be recorded on a Requisition Form which will be sent with each sample to the central laboratory. Samples themselves will be labelled with the patient number, patient initials, the accompanying requisition number and the Investigator's account number. Full details for the preparation and shipment of samples will be provided by Quest (Dorevitch laboratories in Australia and New Zealand) to the Investigator before the start of the study. Pregnancy testing the Safety Follow-up Visit will be performed locally using kits provided by Quest (Dorevitch laboratories in Australia and New Zealand).

Reference ranges for all parameters will be obtained from the laboratory prior to starting the study and the tests and/or reference ranges 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 etiology should be identified and the sponsor notified. Clinically significant worsenings in laboratory findings must be recorded in the Baseline Signs and Symptoms or Adverse Events 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. If a positive faecal occult blood test is found between Visits 1 and 3, the patient should be withdrawn from the study. The test should be repeated and if also positive, the patient should be followed-up by the primary care physician or referred to a gastroenterologist as appropriate.

5.4.9 Diary Card

All Visits (except Visit 1 and Safety Follow-up)

A Diary Card will be issued at Visits 1 – 11. The patient will be asked to complete the diary each morning with details of the following:

- PEF measured prior to taking any study medication or salbutamol (highest of 3 readings recorded)

- Use of salbutamol during the previous 24 hours for symptomatic relief

- COPD symptoms experienced over the previous 24 hours (Cough, breathlessness, sputum production - volume, type (mucoid/purulent) and colour.

Variable	0	1	2	3	4
Breathlessness	Not breathless at rest or on exertion	Not breathless at rest, but breathless on moderate exertion (e.g. walking quickly)	Not breathless at rest, but breathless on mild exertion (e.g. walking on level ground)	Not breathless at rest, but breathless on minimal exertion (e.g. getting washed)	Breathless at rest
Cough	No cough	Mild cough (i.e. some, mostly morning)	Moderate cough (i.e. some morning and evening)	Severe cough	
Sputum production	None	Small amount of sputum	Moderate amount of sputum	Large amount of sputum	
Sputum colour	Colourless	White/grey	Light yellow/green	Dark yellow/green	

- Night-time awakenings
- Time missed from work/usual activities (noted as half or full days)
- Assistance of caregiver

5.4.10 Patient and Investigator Global Assessments

Visits 3, 9 and 12, Early Withdrawal

Patients will be asked, "How do you feel now in comparison with when you started to take study medication"? Investigators will be asked, "How do you assess the patient's COPD now in comparison to when they started to take study medication"? Both the patient and Investigator will respond according to the following:

- Very much improved
- Much improved
- Minimally improved
- No change
- Minimally worse

- Much worse
- Very much worse

6 Study Medication and Administration

6.1 Study Medication

Cilomilast will be provided as a yellow, round, convex tablet containing 15 mg of cilomilast (SB 207499). Matching placebo tablets will also be provided.

Metered Dose Inhalers (MDIs) of salbutamol (100 mcg/actuation, 200 actuation's per canister) will be provided for on-demand (prn) use during the study. A spacer will also be supplied to each patient at Visit 1. Patients may employ these for on-demand use if this is their customary inhalation method. Salbutamol is not considered study medication.

Double-blind study medication will be assigned to patients through GlaxoSmithKline's Registration and Medication Ordering System (RAMOS). Patients will be randomised (and stratified according to their smoking status at Baseline) in a 1:1 ratio to cilomilast 15 md bd or placebo . The investigator (or designee) must phone into RAMOS to register all patients at the time they are initially dispensed placebo run-in medication. Patients who are eligible to participate in the double-blind phase of the trial will be randomised to a treatment group through a call to RAMOS at Visit 3. During this call, RAMOS will confirm the patient's CRF number and provide two additional numbers: 1) a 6-digit container number which will identify the container of double-blind medication that should be assigned to the patient from the investigator's inventory; and 2) a 5-digit randomisation number which must be written in the patient's CRF. The container assigned during the randomisation call will contain sufficient double-blind study medication for the visit period. Although study medication will be stored at each site, the investigator (or designee) must phone into RAMOS to obtain a new study medication container number at each on-therapy visit (except Visit 12). All calls to RAMOS are confirmed with faxes which are sent to the investigator upon completion of each call. Detailed RAMOS user instructions and worksheets will be provided at study start. All RAMOS faxes and worksheets must be retained in the Investigator's study file.

6.2 Dosage and Administration

Patients who fulfil the entry criteria will enter a 4-week single-blind placebo run-in phase. During the run-in phase, patients will take one cilomilast-matched placebo tablet twice daily, in the morning immediately after breakfast and in the evening immediately after a meal. *Patients must not take their study medication for at least 8 hours prior to attending clinic visits. On the day of a clinic visit, the post assessment dose of study medication administered in the clinic will be administered with food.*

Patients who fulfil the Randomisation Criteria will enter a 52-week double-blind treatment phase. Patients will receive either cilomilast 15 mg or matching placebo BD. One tablet of study medication will be taken twice daily, in the morning immediately after breakfast and in the evening immediately after a meal. *Patients must not take study medication for at least 8 hours before attending clinic visits. On the day of the clinic visit, the post assessment clinic dose of study medication will be administered in the clinic with food.*

6.3 Blinding

All run-in medication will be blinded to the patient, and all medication for randomised patients will be blinded to both the Investigator and the patient. The blind will be maintained by GlaxoSmithKline who will maintain an updated copy of the master randomisation code.

Cilomilast 15 mg tablets and cilomilast-matched placebo tablets will be identical in appearance and the double-blind medication drug labels will identify only the six-digit container number. The patient's randomisation number will be provided during the randomisation call to RAMOS.

The randomisation code will not be disclosed to the Investigator or any personnel involved in the conduct of the study before the database is locked, unless in the case of an emergency.

Individual Code breaks will be provided to the Investigator and the participating local GlaxoSmithKline office. Each code-break will identify the container number and will include an unblinding panel which can be removed by scratching with a coin to reveal the container contents.

The medication code for a particular patient may only be broken in the event of a serious adverse event which the Investigator feels cannot be adequately treated

without knowing the identity of the study medication. Every effort must be made to contact the GSK Medical Monitor prior to breaking the code. If this is not possible and the situation is an emergency, the Investigator may break the code and contact the GSK Medical Monitor as soon as possible.

6.4 Packaging

For the single-blind placebo run-in phase, cilomilast-matched placebo tablets will be supplied in containers containing 70 tablets. One container of run-in medication (a 35-day supply) should be dispensed to eligible patients at Visit 1 and the same container should be re-dispensed at Visit 2.

Study medication for the 52-week double-blind treatment period will be presented in numbered containers. These containers will contain 70 of either cilomilast 15 mg or matching placebo tablets (a 35-day supply). Therefore, one container should be dispensed at each of Visits 3, 5 and 6 and two containers dispensed at each of Visits 7, 8, 9, 10 and 11. The container of tablets dispensed at Visit 3 will be re-dispensed at Visit 4. An overage of tablets is included in each container to allow for flexibility in the interval between visits.

6.5 Labelling and Preparation

Each container of study medication will be labelled with a two-panel label consisting of a fixed and a tear-off portion. The Investigator (or designate) will remove the tear-off portion of the label from the container at the time of dispensing and attach it to the appropriate page in the CRF. Labels on all containers will include the protocol number, container number (double-blind medication only), fill count, dosing directions, storage conditions, caution statements, and sponsor address. There will also be prompts for patient initials on the fixed portion of the label.

6.6 Storage

Prior to dispensing, all study medication will be kept safely locked, in a dry place at room temperature (20-25ºC or 68-77ºF) [USP].

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 will specify job 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 only be dispensed to patients in accordance with the protocol.
- Any unused products, including placebo, will be returned to GSK.

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 GSK. Any discrepancies must be accounted for. A certificate of return must be signed incorporating the assurance from the Investigator (or designate) that all unused investigational products have been returned. Supplies will, in the majority of cases, be returned to the local GSK site 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 the local GSK office. 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 Visits 2 through 12. Compliance will be calculated by using the formula below:

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

Compliance (%) will be entered into the CRF.

If a patient shows <80% or >120% compliance in taking study medication at any visit, the investigator should remind the patient of the importance of adhering to the study medication procedures.

6.9 Treatment of Study Medication Overdose

To date, there have been no cases of confirmed overdose with cilomilast. In the event of an overdose, general symptomatic and supportive measures should be initiated promptly and maintained for as long as necessary.

Any instance of a suspected or confirmed overdose must be fully documented as a Serious Adverse Event (Section 8.4.1) and communicated to the GSK Medical Monitor within 24 hours.

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. In case of occupational exposure, contact the Medical Monitor for the study.

6.11 Concomitant Medication/Treatment

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

6.11.1 Permitted Medications

The use of salbutamol 100 mcg/actuation, MDI with or without a spacer for use on an "as-needed" (prn) basis will be permitted throughout the study. Patients should use the inhaler and spacer (if customary) provided by GSK and not their own devices. The Investigator should issue a new inhaler every 4 weeks or sooner, if necessary.

The use of anticholinergic medication by MDI will be permitted during the study. Patients should continue to use their regular single-ingredient inhaler devices. Combined anticholinergic/beta$_2$-agonists formulations are not permitted (Section 6.11.2). The dose of the anticholinergic medication should remain stable from Visit 1 to Visit 12. The use of inhaled anticholinergic medication must be recorded in the concomitant medication section of the CRF.

Between Visits 1 and 12, patients should NOT use any additional bronchodilators that they possess at home. *If the patient experiences symptoms which do not respond adequately to rescue medication (e.g., salbutamol, two actuations every*

four hours), the patient must contact the Investigator. If a patient occasionally uses salbutamol at an interval of less than every 4 hours (not to exceed twice a day at the reduced interval), the patient may remain in the trial at the discretion of the Investigator.

Table 4 provides a list of permitted respiratory-related medications.

Note: This table is intended to provide examples of drugs commonly used by COPD subjects. It is not a complete list of medication classes or trade names.

Table 4 Examples of Permitted Medications

Medication Class	Selected Trade Names
Selected short-acting inhaled beta$_2$-agonists	Ventolin® **only**
Inhaled anticholinergic agents	Atrovent®
Nasal cromones	Rynacrom/Nasalcrom®
Nasal steroids	Beconase AQ®, Flixonase ®, Nasalide®, Nasacort®, Rhinocort®, Vancenase AQ®
Antibiotics	Augmentin®, Biaxin®, Ceclor®
Smoking cessation patches or gum	Nicoderm®, Nicotrol®, Habitrol®, Nicorette®

6.11.2 Prohibited Medications

Except in the short-term management of COPD exacerbations, the use of oral corticosteroids, combination short acting beta$_2$-agonists and anticholinergics, inhaled long-acting beta$_2$-agonists, inhaled short-acting beta$_2$-agonists, oral beta$_2$-agonists, nebulised beta$_2$-agonists, nebulised anticholinergics, inhaled cromolyn sodium or nedocromil, xanthines, leukotriene modifiers and mucolytics are not allowed between Visits 1 and 12. LTOT is also prohibited between Visits 1 and 12 unless subjects live at altitude.

Table 5 provides a list of prohibited medications along with Trade names.

Table 5 Prohibited Medications

Medication Class	Selected Trade Names
Inhaled corticosteroids	Azmacort®, Becotide®, Flixotide®, Pulmicort®, Syntaris®
Oral corticosteroids	prednisone, Medrol®, Decadron®, Sterapred®
Combination of inhaled short-acting beta$_2$-agonists & anticholinergics	Combivent® Duovent®
Selected short-acting inhaled beta$_2$-agonists	All **except** Ventolin®
Long-acting inhaled beta$_2$-agonists	Serevent® Foradil
Oral beta$_2$-agonists	Ventolin®, Volmax®, Bricanyl®
Nebulised beta$_2$-agonists	salbutamol, metraproterenol, Alupent®, Isuprel®, Ventolin®
Nebulised anticholinergics	Atrovent®
Inhaled cromolyn sodium	Intal®-
Inhaled nedocromil	Tilade®
Oral xanthines	Slo-Bid®, Theo-Dur®
Leukotriene modifiers	Accolate®, Singulair®
Long-term oxygen therapy (LTOT)*	n/a
Mucolytics (carbocysteine)	Mucodyne
* Several puffs of supplemental oxygen after exercise testing or when clinically indicated, at the investigator's discretion, would be acceptable. However, daily or prolonged use of supplemental oxygen is **not** permitted.	

Theophylline is not permitted at any time during the study.

6.11.3 Treatment of COPD Exacerbations

Only if clinically indicated, oral steroids or antibiotics may be administered for the short-term (<14 days) treatment of COPD exacerbations.

Patients who take any corticosteroids or are hospitalised for the treatment of COPD exacerbations during the run-in phase are not eligible to be randomised to the double-blind phase.

Refer to Section 8.1.2 for definitions of the level of COPD exacerbations.

6.11.4 Concomitant Medication

All concomitant medications taken during the study, *including* 'as needed' (prn) salbutamol, anticholinergic agents (at stable dose), must be recorded in the CRF along with the indication, dose, frequency and dates of administration. Any changes must be clearly recorded in the CRF.

7 Outcomes Research and Pharmacoeconomics

7.1 Outcomes Measurement and Analysis

Medical care utilisation data will be collected in association with COPD 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, beta$_2$-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 Economic Data Collection and Analysis

Patients will be asked to record in their diary card the amount of time missed from work or usual activities and if they required the assistance of a caregiver due to their COPD.

7.3 Health Status Analyses

EQ-5D (Appendix E***)***

Quality of life will be assessed with the EQ-5D at Baseline, Visits 9 and 12 and at Early Withdrawal in those countries where a validated translation is available.

The EQ-5D is a standardised, self-administered, generic instrument which produces a single index value of the patient's current health status ([15]). Subjects are asked to respond to five questions on different aspects of their health status that assess mobility, usual activities, self-care, pain and depression. Answers to each question are responded to on a three-point scale which indicates the level of impairment (no problem; some or moderate problem(s); unable, or extreme problem). This generates a unique description of the patients' health status which is valued between zero (representing death) and one (representing perfect health) according to the methodology developed by the authors ([16]).

As well as completing the five questions to generate a single health status index, patients are asked to rate their current health status using the visual analogue scale 'Thermometer'. The 'Thermometer' has endpoints of 100 (best imaginable health state) and 0 (worst imaginable health state). The subject rates their current health state by drawing a line from the box marked 'Your health state today' to the appropriate point on the 'Thermometer' scale. If subjects are visually impaired it is appropriate for the investigator to read aloud the instructions within the questionnaire and to record the responses on behalf of the patient.

St. George's Respiratory Questionnaire (Appendix F***)***

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 health status instrument. [13,17,18] 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 baseline). [19]

The SGRQ is a self-administered questionnaire designed to measure and quantify the impact of chronic respiratory disease on health status 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 F.

The SGRQ will be administered at Baseline (Visit 3) and at Visits 9 and 12. Any patient who withdraws from the study should complete the SGRQ at the time of withdrawal (Section 5.3.13).

8 Adverse Events

8.1 Eliciting and Documenting Adverse Events

It is the responsibility of the Investigator to detect and document all adverse events which occur during the study and which fulfil the definitions and criteria outlined in this protocol.

8.1.1 Adverse Event Definition

An adverse event (AE) is defined as:

"Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product"

An AE includes:

- An exacerbation, or an unexpected increase in frequency or intensity of a pre-existing condition (other than COPD), including intermittent or episodic conditions.
- Significant or unexpected worsening or exacerbation of COPD (see Section 8.1.2).
- A suspected drug interaction.
- An intercurrent illness.
- Any clinically significant laboratory abnormality.

An AE does not include:

- Anticipated day-to-day fluctuations of any pre-existing conditions, including the disease under study.
- Signs and symptoms of the disease under study that do not represent a significant worsening or exacerbation.
- Expected progression of the disease under investigation.

8.1.2 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 COPD exacerbation section in the CRF.

Exacerbations of COPD are categorised according to three levels of severity:

Level 1 (Mild-self treated): Acute worsening of COPD that is self-managed by the patient at home by increasing the dose of relief salbutamol medication by > 2 occassions/24 hour period on two or more consecutive days compared with their baseline (baseline = mean of last 10 days of run-in period) or use of other additional bronchodilator medication

Level 2 (Moderate- physician, investigator treated): Acute worsening of symptoms (cough, sputum production, breathlessness) requiring treatment with oral corticosteroids prescribed by a physician or primary care doctor, or as a result of hospital out-patient visit (including Emergency Room).

Exacerbations requiring oral corticosteroids will be treated with a standardised course of prednisolone or prednisone tablets 30mg/day for 10 days, or methylprednisolone tablets 24mg/day for 10 days.

Level 3 (Severe - attendance at hospital): Acute worsening of COPD that requires the patient to be admitted to hospital for treatment.

If appropriate, courses of antibiotics may be prescribed to treat an infection (Level 1, 2 or 3)

Subjects who take any corticosteroids for the treatment of a COPD exacerbation during the run-in phase or who are hospitalised are not eligible to be randomised to the double-blind phase of the study.

- **Note: Any exacerbation of COPD, regardless of level, that fulfils the SAE criteria must be recorded in the COPD SAE pages of the CRF.**

The number and severity of COPD exacerbations will be assessed by the investigator at each clinic visit, by reviewing the diary card entries as well as specific questioning. Details of all exacerbations will be recorded in the COPD Exacerbation Section in the CRF as follows: dates of onset and resolution; outcome, treatment and severity. In addition any information collected during the exacerbation should be recorded in the CRF (e.g. Symptoms: breathlessness, cough, chest pain, sputum (volume and purulence); associated URTI (nasal congestion, sore throat, runny nose); sleep disturbance; confusion/alertness-min case of pneumonia; oedema, ankle swelling; medications leading up to exacerbation; heart rate; respiratory rate; FEV_1; arterial blood gases/pulse oximetry; serum C Reactive Protein).

8.1.2.1 Resolution of Exacerbations

The time of resolution of an exacerbation will be determined by the investigator and/or subject. However, some guidance for distinguishing recurrence of a single exacerbation from distinct exacerbation episodes is provided as follows.

- Level 2 exacerbations treated with oral corticosteroids will be classified as separate exacerbations only if the courses of treatment are administered more than one week apart. A course of oral corticosteroids started within one week of finishing a previous course will be considered a continuation of the exacerbation.

- Likewise hospitalisation for an exacerbation within a week of completing a course of oral corticosteroids or initiation of a course oral corticosteroids within a week of discharge from hospital for an exacerbation will be considered a single continuous (Level 3) exacerbation.

Where a Level 1 exacerbation is immediately preceded or followed (within 1 week) by an exacerbation of any level, the investigator and/or subject will consider the possibility that this represents a continuation of the exacerbation.

8.1.3 Gastrointestinal Adverse Events

Adverse events related to the gastrointestinal tract will be closely monitored during this study and treated appropriately. 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 event(s) within 24 hours of occurrence. This assessment will include a structured history of the adverse event 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 if the patient reports melena during the randomised treatment phase of the study, the patient will be referred to a gastroenterologist for evaluation. For instances of gross bleeding or melena with or without GI AEs of concern, the patient should be instructed to call the Investigator within 24 hours and be instructed to begin testing stool for blood. The site investigator should examine the patient and refer the patient to a gastroenterologist for evaluation. Depending on the suspected site of bleeding an endoscopy will likely be required. If all faecal occult blood samples are negative and the patient is clinically well the patient should still be referred to gastroenterologist for evaluation. In this instance the gastroenterologist may decide to observe the patient rather than perform complete colonoscopy. 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 the first assessment, the Investigator should report these gastrointestinal adverse events to the GSK Medical Monitor.*

Assessments of faecal occult blood, complete blood count, and orthostatic changes in blood pressure will be completed until the gastrointestinal symptoms are resolved. Assessments will be performed by a qualified healthcare provider at the patient's home or at clinic visits. Any deterioration in the patients' condition since the previous assessment discovered by a healthcare provider will be reported to the Investigator by telephone immediately. 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 events are presented in Appendix G.

Note: All gastrointestinal adverse events of clinical concern (bloody or black stools, abdominal discomfort; such as, pain or cramps, diarrhoea or vomiting which causes them concern or interferes with their daily activities [including eating and sleeping]) must be recorded in the gastrointestinal adverse event section of the CRF. Any gastrointestinal adverse event, regardless of intensity, that fulfils the SAE criteria must be recorded in the gastrointestinal adverse event pages of the CRF.

8.1.4 Serious Adverse Event Definition

A serious AE must be reported to GSK within 24 hours (see Section 8.3.3)

A serious AE is any untoward medical occurrence which fulfils the definition for an AE (as defined in Section 8.1.1) AND in addition, is:

- Fatal
- Life threatening
- Disabling/incapacitating
- Results in hospitalisation or prolongs a hospital stay
- A congenital abnormality
- Any important medical occurrence which the Investigator regards as serious based on appropriate medical judgement

In addition, SB policy dictates that the following events must be notified within 24 hours and must be documented and reported as for serious AEs, on the Serious AE form:

- Cancer
- Overdose

  AND

- Pregnancy

To assist with the above definitions the following information is provided for clarification/ interpretation:

Life Threatening:

The patient was at immediate risk of death from the event. This term does not refer to an event which hypothetically might have caused death if it were more severe.

Disabling/Incapacitating:

The event results in a substantial and/or permanent disruption of the patient's ability to carry out normal life functions.

The Investigator must use clinical judgement in this assessment. The definition is not intended to include events which may be of relatively minor medical significance e.g. headache, nausea, influenza or accidental trauma such as sprained ankle which may temporarily prevent everyday life functions, unless a substantial disruption is recorded.

Hospitalisation:

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 received treatment that would not have been appropriate in the physician's office or in an out-patient setting.

A serious AE does **not** include hospitalisation for:

- Elective surgery or routine treatment/procedures related to a pre-existing condition that did not worsen. Instead, these must be recorded in the medical/surgical procedures section of the CRF.
- If anything untoward (i.e. complications) are reported during the procedure, these must be reported as an AE, either 'serious' or 'non-serious' according to the usual criteria.
- A routine clinical procedure as stipulated by the protocol.
- Non-medical reasons (i.e. social admissions, hospitalisations for social, convenience or respite care).

Cancer:

The patient must have developed a new cancer or recurrence. The expected progression of a pre-existing cancer (which is documented as pre-existing cancer in the CRF) is not a serious AE.

Overdose:

See Section 8.4 for reporting of overdose

Pregnancy:

See Section 8.7.1 for reporting of pregnancy

Other Medically Important Events:

Medical and scientific judgement should be exercised to ensure that other important medical events are promptly reported to GSK. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions or development of drug dependency.

8.2 Recording of Adverse Events

Any pre-existing conditions or signs and/or symptoms present in a patient prior to the start of the study (i.e. before informed consent) should be recorded on the Medical/Surgical History section within the CRF.

Any medical occurrences which occur after informed consent is obtained but prior to starting active or randomised treatment will be documented on the Baseline Signs & Symptoms section within the CRF.

All AEs occurring after administration of the first dose of double-blind study medication and on or before the final visit must be reported on the Adverse Event form in the CRF. All AEs must be recorded irrespective of whether they are considered drug related.

At each visit/assessment in the period defined above, AEs will be evaluated by the Investigator and recorded in the appropriate AE/serious AE section of the CRF.

Any AEs already documented 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 AE worsens in intensity/frequency then it should be recorded again as a worsening of the same event (i.e. NOT a new AE).

8.2.1 Soliciting of Adverse Events

As a consistent method of soliciting AEs, the patient should be asked 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, a diary will be provided in which the patient may record if they felt different since starting the study medication.

8.2.2 Evaluating the Adverse Event

8.2.2.1 Assessment of Intensity/Severity

The assessment of intensity/severity must be based on the Investigator's clinical judgement. Maximum intensity/severity should be assigned to one of the following categories:

Mild: An AE which is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.

Moderate: An AE which is sufficiently discomforting to interfere with normal everyday activities.

Severe: An AE which prevents normal everyday activities.

NB - An AE which is assessed as severe should not be confused with a serious AE. Refer to Section 8.1.4 for serious AE definition.

8.2.2.2 Assessment of Causality

Investigators are obligated to explain each AE and assess its relationship, if any, to study medication

The Investigator must use clinical judgement to determine the degree of certainty with which an AE is attributed to drug treatment. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors

and the temporal relationship of the event to study medication must be considered and investigated.

The Investigator may also consult the Investigator Brochure to consider his/her assessment in relation to the pharmacology of the drug, similar reactions with the class of drug and any existing literature.

Causality should be assessed using the following categories:

Not related: The AE is definitely not related to the 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 AE has not been demonstrated but there is a reasonable possibility that the event was caused by the drug.

Probable: There is a probable direct cause and effect relationship between the AE and the study drug.

8.3 Reporting and Recording of Serious Adverse Events

8.3.1 Regulatory Responsibility

GSK has a legal responsibility to notify both the local regulatory agencies, i.e. where the study is ongoing, and other regulatory agencies worldwide about the safety of a drug under investigation. Prompt notification (within 24 hours) of serious AEs by the Investigator to GSK is essential so that legal and ethical responsibilities related to patient safety are fulfilled (see 8.3.3).

8.3.2 Recording of Serious Adverse Events

All serious AEs that occur in the period defined in Section 8.2 must be recorded. This includes events occurring up to and including 30 days after the last dose of double-blind study medication.

All serious AEs will be recorded on the Serious AE form in the CRF.

Any serious AEs that occur after 30 days and which are brought to the attention of the Investigator need to be recorded and forwarded to GSK if assessed as possibly drug related.

Serious AEs which relate to pre-existing conditions and which occur prior to the start of the study (i.e. before informed consent) must be reported on the Medical/Surgical History forms and not as serious AEs.

Serious AEs that occur after informed consent is obtained but prior to starting active or randomised treatment will be documented on the Serious AE section within the CRF.

However, any serious AEs considered by the Investigator as related to study design, study conduct and/or study defined procedures must be recorded and reported to GSK to fulfil regulatory requirements. This includes any serious AEs which occur after informed consent has been obtained but prior to any study drug administration. In this case, the event must be recorded on the Serious AE form and reported in the same timescale as for other serious AEs.

8.3.3 Reporting of Serious Adverse Events to GlaxoSmithKline

All serious AEs will be reported to GSK **within 24 hours**. Facsimile transmission is always the preferred method of reporting (including non-working hours).

GSK study contact : [redacted]
GlaxoSmithKline
European Medical Affairs – Respiratory
Stockley Park West, Uxbridge, United Kingdom
Facsimile number : [redacted]
Telephone number :

Emergency 24 hour medical contact : [redacted]
Telephone number : [redacted]

Investigators must not wait to receive all information before notifying GSK of a serious AE on the Serious AE form.

The Serious AE form in the CRF must always be completed as fully as possible, signed by the Investigator and faxed to the GSK contact. Telephone reporting is not encouraged. It may be used for the initial notification but **does not replace the need for the Investigator to complete and sign the Serious AE form within 24 hours.**

As many details of the serious AE as possible must be reported. The Investigator must always provide an assessment of causality at the time of the initial report (see Section 8.2.2.2).

For each serious AE the following must always be sent to GSK in the initial report:

- Serious AE form (two pages)
- Demography
- Significant medical/surgical history and physical examination
- Study medication record
- Concomitant medication
- Form D (death form - if applicable)

8.3.4 Follow-up of Serious AEs

After the initial serious AE report the Investigator is required proactively to provide further information regarding the patient's condition.

Investigators must follow-up all patients with serious AEs until the event has subsided (or disappeared), the condition has stabilised, the event is otherwise explained, or the patient is lost to follow-up.

All follow-up information must be forwarded to the GSK contact (as specified in 8.3.3 above) **within 24 hours** of receipt.

To fulfil ethical and regulatory obligations, GSK may request additional follow-up information on any serious AE and the Investigator is obligated to assist. When requested by GSK, information from relevant hospital reports, pathology and autopsy reports must also be forwarded, if available.

Gastrointestinal adverse events (i.e., abdominal pain, cramps, discomfort, bloody stools, diarrhoea, black stools, or vomiting) will be followed up as described in Section 8.1.3.

8.4 Overdose

An overdose is defined as an excessive dose taken by a patient, either accidentally or intentionally, irrespective of whether it involves study medication or non-study medication. Overdose may be suspected or confirmed and may or may not be associated with clinical signs and symptoms.

It would definitely include, but not be limited to those events which based on the Investigators clinical judgement were considered to be of medical concern and/or require clinical observation and/or medical intervention.

As a guide, an overdose would include any dose greater than the highest daily dose included in the protocol or prescribing information (for marketed products).

Minor deviations to study drug administration (i.e. resulting from poor patient compliance) must be recorded in the study medication compliance section of the CRF and not as serious AEs).

8.4.1 Reporting of Overdose

For all overdoses the Serious AE form must be completed and reported within 24 hours as for any other serious AE (see Section 8.3.3). The documentation must include details of any associated signs/symptoms or if the overdose is asymptomatic this must be stated.

8.4.2 Further Information on Overdose

For further information of any known signs or symptoms of overdosage and appropriate treatment, together with details of any antidote, if known, refer to protocol/Investigator Brochure.

8.5 Treatment Failures

Re-emergence of underlying disease which has resulted from the possible ineffectiveness of study medication (treatment failure) does not need to be reported as an AE or serious AE unless the resulting event is more frequent than at baseline. Expected progression of the underlying disease does not need to be reported as a AE or serious AE unless the event is atypical in nature.

8.6 Post-study Events

A post-study event is any event that occurs outside the protocol defined period. This includes after completion of the study (i.e. beyond the post-treatment follow-up period/30 days) or following premature withdrawal.

All serious AEs (including deaths) if brought to the attention of the Investigator at any time post-study and considered by the Investigator to be possibly related to study medication, must be reported to GSK (see Section 8.3.3).

8.7 Pregnancy

Details of all pregnancies in patients that occur during the treatment and the follow-up period must be documented and reported to GSK. In addition any pregnancies brought to the attention of the Investigator after this period, and where it is known that study medication was taken at the time of conception, must also be reported.

Any pregnancies identified during the screening phase/prior to study medication administration do not need to be collected.

8.7.1 Reporting of Pregnancy

All pregnancies will be reported to GSK promptly. Although pregnancies are not generally serious AEs (and there is no serious criteria fulfilled) the Serious AE form must be completed and forwarded to the GSK contact specified in Section 8.3.3 within 24 hours. This will provide a record of the initial notification of the pregnancy.

8.7.2 Follow-up of Pregnancies

All pregnancies will require the completion of a pregnancy form which will be provided after initial notification on the Serious AE form. All pregnancies will be followed to term. A special form will be provided at the expected time of delivery. Any premature terminations, including elective abortions must be reported. The status of the mother and child must be forwarded to GSK after delivery.

8.7.3 Action Taken as a Result of Pregnancy

Patients who become pregnant during the study should discontinue the study immediately, unless the protocol states otherwise.

8.8 Unblinding Treatment Codes

Only in the event of a medical emergency that the Investigator feels cannot be adequately treated without knowing the identity of the study medication, may the treatment code be unblinded for a particular patient. Only if the situation is a medical emergency may the Investigator unblind the treatment code.

Wherever possible, the Investigator must make every effort to contact the GSK medical contact (see Section 8.3.3) prior to unblinding. **If this is not possible and**

the access to individual treatment codes is available (direct, or via a third party) at the investigational site the Investigator may unblind and inform the GSK medical contact as soon as possible thereafter.

The Investigator must complete a Serious AE form and forward it to the GSK contact designated in Section 8.3.3 within 24 hours.

8.9 Investigator Letters

Investigator letters are prepared according to SB policy and are forwarded to Investigators as necessary. The purpose of these letters is to communicate significant emerging safety issues and/or to fulfil specific regulatory requirements, regarding the drug under investigation.

An Investigator who receives an Investigator letter describing a serious AE or other specific safety information from GSK must file it with the Investigator Brochure and must notify the Ethics Committee, if appropriate, according to local requirements.

9 Subject Completion and Withdrawal

9.1 Definitions

Patients who have completed the assessments scheduled for Week 52 (Visit 12) will be defined as completing the study for the purposes of efficacy analyses.

Any patient who enters the study, (i.e., gives written informed consent) but does not, *for any reason* complete the study according to the definitions given above, will be considered as a withdrawal, whether or not they have received any study medication.

9.2 Procedures for Handling Withdrawals

Enrolment will continue until approximately 800 patients have been randomised. The double-blind medication assigned to withdrawn patient(s) will not be re-used. Patients who withdraw from the study will be asked to return for scheduled visits for essential assessments (FEV_1, exacerbations, respiratory AEs and respiratory medications and GI AEs) even after study medication has been discontinued.

Patients who terminate their participation in the study due to adverse events should be followed up as appropriate (Section 8.3.4) in order to determine the final outcome. Investigators should make every effort to encourage patients to remain in the study.

For all patients who withdraw or are withdrawn from the study **prior to** randomisation, pre-treatment early withdrawal assessments and procedures should be completed, including Baseline Signs and Symptoms, changes or additions to concomitant medication, vital signs and respiratory examination. Laboratory tests and an ECG should be performed if there were any abnormalities at the previous visit. Wherever possible, a follow-up visit should be scheduled.

For all patients who withdraw or are withdrawn from the study at a scheduled visit **after** randomisation, the assessments and procedures of the visit and any additional early withdrawal assessments and procedures (Section 5.3.13) should be completed. Patients who withdraw from the study between visits will be asked to return within 24 hours of stopping study medication for an Early Withdrawal Visit (Section 5.3.13).

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 Last Dose of study medication must be recorded in the CRF 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 event** (Section 8): 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 a lack of improvement in COPD symptoms. It does not include a deterioration in COPD or COPD exacerbation which must be regarded as an adverse event.
- **Protocol Deviation:** This includes lack of compliance (dosing, visit schedule, diary criteria).

- **Patient lost to follow-up**
- **Other:** Document reason in the CRF.

All adverse **event**s leading to withdrawal of a patient must be fully documented and followed-up as appropriate (Section 8). **To ensure that all withdrawals due to adverse events are correctly identified, "Adverse Event" should only be checked as the reason for withdrawal on the Study Conclusion page for those patients for whom an adverse event was considered to be the direct cause of the patient withdrawing from the study. This is particularly important when adverse events are ongoing at the time of withdrawal, but the reason for withdrawal is not related to the adverse events.**

10 Statistical Issues: Design and Analysis

The Biometrics Unit of GSK will perform all statistical analyses.

10.1 Objectives

The primary objective of the study is to assess the clinical efficacy of oral cilomilast 15 mg bd as maintenance treatment for patients with COPD. This will be demonstrated over a 52 week treatment period in subjects with COPD who are poorly reversible to bronchodilators by assessment of:

- Reduction in the risk of the occurrence of exacerbations of COPD for subjects treated with cilomilast 15 mg bd compared with placebo and
- Superior pulmonary function data (FEV_1) for subjects treated with cilomilast 15 mg bd compared with placebo

10.2 Hypotheses

The superiority of cilomilast to placebo will be demonstrated with respect to trough pre-bronchodilator FEV_1 and by comparing exacerbation incidences of moderate or severe COPD exacerbation.

The hypothesis of testing treatment difference in change from baseline in trough FEV_1 is two-tailed:

$$H_{01}: u_t = u_c \qquad H_{\alpha 1}: u_t \neq u_c,$$

where u_t and u_c are the means of change from baseline of trough FEV_1 averaged over all double-blind visits for the cilomilast group and placebo group, respectively.

The hypothesis of testing treatment difference of the exacerbation rates is also two-tailed:

$$H_{02}: R_1 = R_0 \qquad H_{\alpha 2}: R_1 \neq R_0,$$

where R_1 and R_0 are the moderate or severe COPD exacerbation incidences per patient year for cilomilast group and placebo group respectively.

10.3 Definition of Variables

10.3.1 Primary Efficacy Variable

- The mean change from baseline in trough pre-bronchodilator FEV_1 averaged over 52 weeks
- Moderate or severe COPD exacerbation incidence during the treatment period

10.3.2 Secondary Efficacy Variables

- The mean change from baseline in trough post-bronchodilator FEV_1 averaged over 52 weeks
- Time to first level 2 (moderate) or level 3 (severe) COPD exacerbation
- Time to first COPD exacerbation (all level)
- Exacerbation incidence for all levels of COPD exacerbations
- Quality of life as determined using the St Georges Respiratory Questionnaire (SGRQ)

10.3.3 Tertiary Efficacy Variables

- Pulmonary function parameters (Clinic FVC, clinic $FEV_{25-75,}$ morning PEF from Daily Diary Cards and clinic PEF).

- Residual Volumes (body box)
- Morning PEF from Daily Diary Cards
- Use of relief medication and percentage of days with no need for rescue medication (salbutamol)
- Duration of exacerbations
- Symptom scores and symptom free days (24 hour period)
- Number of nighttime awakenings
- Number and percent of withdrawals (NB as far as possible subjects discontinuing study medication should remain in the study for assessments for completion of the 12 month treatment period).
- Disease-specific quality of life: SGRQ subscales (symptoms, activity and impact)
- Generic Health Status (EQ-5D)
- Health Outcomes Endpoints: resource utilisation and indirect costs
- Time off work/normal activities due to COPD
- Global Subject Assessment
- Global Investigator Assessment
- Blood CD4+/CD8+ ratio
- Serum C Reactive Protein

10.4 Comparisons of Interest

10.4.1 Primary Comparisons of Interest

There are two primary comparisons of interest. The first is to compare the difference in change from baseline in pre-bronchodilator FEV_1 between the cilomilast group and the placebo treatment group (cilomilast – Placebo) averaged over all double-blind visits in the intent-to-treat population (see Section 10.7.1 for definition). The second is to compare the exacerbation incidences (moderate or

severe) during treatment period for cilomilast versus placebo. As statistical significance will be demonstrated for both primary endpoints, each of the primary comparisons will be performed at an alpha level of 0.05 without adjustment.

10.4.2 Other Comparisons of Interest

Time to first moderate or severe exacerbation during the treatment period will be compared between treatment groups, stratified for smokers/ex-smokers.

The exacerbation free curves will be compared between treatment groups, stratified for smokers/ex-smokers.

The incidence of all COPD exacerbations occurring during the treatment period will be compared between treatment groups, stratified for smokers/ex-smokers.

The difference in change from baseline in post-bronchodilator FEV_1 averaged over all double-blind visits will also be compared between the cilomilast group and the placebo treatment group (cilomilast – Placebo), stratified for smokers/ex-smokers.

Additional comparisons between treatment groups, stratified for smokers/ex-smokers, will be made for FEV_1 (both pre-bronchodilator and post-bronchodilator) at Weeks 4, 8, 12, 20, 28, 36, 44, 52 and endpoint in the double-blind period, where the endpoint is defined as the last on therapy evaluation.

10.5 Interim Analysis

No interim analysis is planned.

10.6 Target Sample Size

10.6.1 Sample Size Calculation

In order to obtain 550 evaluable patients, this study will randomise a total of 800 patients in a ratio of 1:1 for SB 207499 to placebo.

Sample size calculation for repeated measures analysis on FEV_1 is based a compound symmetric correlation structure across double-blind visits. A sample size of 550 will have a greater than 90% power to detect a difference of 50 ml in

FEV_1 assuming a standard deviation of 210 ml in the change from baseline, a correlation of 0.68 between visits and a significance level of 0.05.

Assuming a Poisson distribution for the number of COPD exacerbations (moderate and/or severe) during the treatment period and an exacerbation incidence of 0.8 per patient year for placebo group, a sample size of 550 will give greater than 90% power to detect a 30% reduction in exacerbation rate for cilomilast group compared with placebo group. The incidence of 0.8 per patient year is based on retrospective analysis of data from 091 extrapolated to one year.

The superiority of cilomilast to placebo with regard to COPD exacerbations (moderate and/or severe) will be further analysed by comparing exacerbation-free curves. Assuming 1) the censoring patterns for the observations are the same for the two independent treatment groups; 2) the exacerbation-free curves for the two treatment groups are $S_0(t)$ *and* $S_1(t)$ and $S_1(t) = [S_0(t)]^{\theta}$; 3) exacerbation-free rate for placebo group at one year is 42%, a sample size of 550 will give a greater than 90% power to detect a 15% difference (θ=0.65) in exacerbation-free rate for cilomilast group. The 42% exacerbation free rate is based on retrospective analysis of data from 091 extrapolated to one year.

10.6.2 Sample Size Sensitivity

The power of the repeated measure analysis is affected by assumed mean difference in FEV_1, the assumed standard deviation and the correlation structure across the visits in the double-blind period. The following table lists the statistical power at the stated sample size for mean treatment differences between 30 ml and 60 ml, standard deviations between 190 ml and 230 ml, and correlations between 0.60 and 0.80.

Sample size sensitivity (sample size=275/arm)

		Statistical Power			
Standard Deviation	**Correlation**	**Mean Difference (30ml)**	**Mean Difference (40ml)**	**Mean Difference (50ml)**	**Mean Difference (60ml)**
190	0.60	63%	86%	97%	99%
190	0.70	58%	82%	95%	99%
190	0.80	53%	78%	92%	98%
210	0.60	55%	79%	93%	99%
210	0.70	50%	74%	90%	97%
210	0.80	45%	69%	87%	96%
230	0.60	47%	72%	89%	97%
230	0.70	43%	66%	84%	95%
230	0.80	39%	61%	80%	92%

10.6.3 Sample Size Re-Estimation

There is no planned sample size re-estimation for this study.

10.7 Methods of Analysis

10.7.1 Populations of Interest

The intent-to-treat (ITT) population for the analysis of FEV_1 will include all patients who have received at least one dose of double-blind medication and for whom a baseline and, at least, one on-therapy FEV_1 assessment is available. An on-therapy assessment is defined as any evaluation performed after the first dose and within one day after the last dose of study medication in the 52-week double-blind period. A similar ITT definition will apply to all other continuous efficacy variables.

The per-protocol population will include all patients who are in the intent-to-treat population and do not significantly violate the protocol.

Analyses for the per-protocol population will be restricted to FEV_1 and exacerbation rate for Level 2 and 3 exacerbations.

Analysis for number of COPD exacerbations during treatment period as well as time to the first COPD exacerbation will include all randomised patients.

FEV_1 and COPD exacerbations will also be analysed by patients' smoking status.

10.7.2 Statistical Methods

Efficacy Analysis

Descriptive statistics of all demographic and baseline characteristics will be tabulated for completers, withdrawals and all randomised patients.

All linear models to assess treatment effects for efficacy measures will be performed using SAS PROC MIXED®.

The primary assessment of treatment differences for mean change from baseline in FEV_1 (pre-bronchodilator) averaged over 52 weeks will be based on a repeated measure model with fixed effects for treatment, centre and time. Time will be treated as a nominal variable in the analysis. A compound symmetric correlation structure will be used. Least squares means along with 95% confidence intervals will be calculated for each treatment group. Least squares means and 95% confidence intervals will also be calculated for the treatment difference. Differences between treatment groups will be assessed using t-tests on the least squares means.

Above repeated measure model will also be used for analysing FVC, FEF_{25-75} and post-bronchodilator FEV_1.

The incidence of a moderate or severe COPD exacerbations occurring during the treatment period will be analysed using a maximum likelihood based analysis, assuming a Poisson distribution, with time on treatment as an offset variable. The mean rate per year will be presented for each treatment.

A log-rank test will be performed using SAS PROC LIFETEST® to compare the exacerbation-free curves of a moderate or severe COPD exacerbation between cilomilast treatment group and placebo treatment group.

The exacerbation-free rate at 52 weeks, and associated 95% confidence intervals, will be estimated for each treatment group using the Kaplan-Meier product limit.

Additionally, a Cox Proportional Hazards Model will be used to assess covariates influencing time to first exacerbation. Covariates will include treatment, gender, age, smoking status at screening and percent-predicted FEV_1.

Similar analysis will be performed for all exacerbation.

The impact of treatment-by-centre interaction and covariates (age, sex, disease severity and smoking status) will be explored for the primary analyses of the primary endpoints. If evidence of a qualitative treatment-by-centre interaction is found, exploratory analyses will be undertaken to further describe the interaction, and results will be presented by centre. Interaction terms will be tested at a significance level of 0.10.

Normality assumption of trough FEV_1 and the assumption of $S_1(t) = [S_0(t)]^{\theta}$ for the two exacerbation-free curves will be also explored through graphical examinations.

Number of healthcare resource utilisations during the treatment period will be analysed using a poisson regression model.

All continuous efficacy variables will also be analysed using the ANOVA model with fixed effects treatment, centre at all double-blind visits as well as endpoint. All categorical variables will be tabulated using contingency table. Treatment-by-centre interaction terms and normality will not be assessed for these endpoints.

Safety Analysis

Evaluation of safety data will include all randomised patients and will be based on comparisons of patient experience by assigned medication regimen.

Adverse events will be tabulated by relationship to study medication, severity, time of initial onset, and action taken.

Contingency tables will be provided to evaluate the number of patients with clinical laboratory results, vital signs and ECGs of concern.

11 Administrative Matters

To comply with Good Clinical Practice Guidelines, important administrative obligations relating to Investigator responsibilities, monitoring, archiving data, audits, confidentiality and publications must be fulfilled, as provided in Appendix B.

References

1. Global Initiative for Obstructive Lung Disease (GOLD) Workshop Report. WHO/NHLBI, 2000

2. THOM TJ. 1989. International comparisons in COPD mortality. *American Review Respiratory Diseases,* **140,** 27 - 34.

3. MURRAY CJL, LOPEZ AD. 1997. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. *Lancet,* **349,** 1498.

4. JONES PW, QUIRK FH, BAVEYSTOCK CM.. 1991. The St George's Respiratory Questionnaire. *Respiratory Medicine,* **85 (supp B),** 25 - 31.

5. SEEMUNGAL TA, DONALDSON GC, PAUL EA, BESTALL JC, JEFFRIES DJ, WEDZICHA JA.. 1998. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Resp Crit Care Med,* **157,** 1418-22.

6. CONNORS AF JR, DAWSON NV, THOMAS C, HARRELL FEJR, DESBIENS N, FULKERSON WJ. 1996. Outcomes following acute exacerbation of severe chronic obstructive lung disease. The SUPPORT investigators (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments. *Am J Resp Crit Care Med,* **154,** 959-67.

7. WEINBERGER M, ODDONE EZ, HENDERSON WG. 1996. Does primary care reduce hospital readmissions? Veterans Affairs Cooperative Study Group on Primary Care and Hospital Readmissions. *N Engl J Med,* **334,** 1441-7

8. DOLL R, PETO R, WHEATLEY K, GRAY R, SUTHERLAND I. 1994. Mortality in relation to smoking: 40 years observations on male British doctors. *British Medical Journal,* **309,** 901-10.

9. FLETCHER CM, PETO R.. 1977. The natural history of chronic airflow obstruction.. *British Medical Journal,* **1,** 1645-8.

10. TORPHY TJ, UNDEM BJ. 1991. Phospodiesterase inhibitors:new opportunities for the treatment of asthma.. *Thorax,* **46,** 512-523.

11. SB 207499 Investigator Brochure. Fifth Edition (September 2000).

12. EUROPEAN COMMUNITY FOR COAL AND STEEL. 1983. Standardisation of Lung Function Tests. *Bull Europ Physiopath Resp,* **Suppl 5,**

13. JONES PW. 1991. Measurement of Quality of Life in Chronic Obstructive Lung Disease. *Eur Resp Rev,* **1(5),** 445-453.

14. AMERICAN THORACIC SOCIETY. 1995. Standardisation of spirometry. *Am J Crit Care Med,* **152,** 1107-1136.

15. THE EUROQOL GROUP. 1990. EuroQol - a new facility for the measurement of health-related quality of life.. *Health Policy,* **16,** 199-208.

16. The EuroQol Group: EuroQol EQ-5D user guide

17. JONES PW, ET AL. 1992. A self-complete measure for chronic airflow limitation, the St. George's Respiratory Questionnaire. *Am Rev Respir Dis,* **145,** 1321-1327.

18. JONES PW. 1997. Changes in quality of life in COPD patients treated with salmeterol. *Am J Respir Crit Care Med,* **155,** 1283-1289.

19. JONES PW. 1995. Issues concerning health-related Quality of Life in COPD. *Chest,* **107,** 187S-193S.

Appendices

Appendix A Declaration of Helsinki

October 1996
WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Recommendations guiding physicians in biomedical research involving human patients
Adopted by the 18th World Medical Assembly Helsinki, Finland, June 1964 and amended by the
29th World Medical Assembly Tokyo, Japan, October 1975
35th World Medical Assembly Venice, Italy, October 1983
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 patients must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the etiology 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 patients.

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 to 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 patients. 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 patients 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 patients 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 patients should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human patient must always rest with a medically qualified person and never rest on the patient of the research, even though the patient has given his or her consent.

4. Biomedical research involving human patients cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the patient.

5. Every biomedical research project involving human patients should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the patient or to others. Concern for the interests of the patient must always prevail over the interests of science and society.

6. The right of the research patient to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the patient and to minimise the impact of the study on the patient's physical and mental integrity and on the personality of the patient.

7. Physicians should abstain from engaging in research projects involving human patients 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 patient 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 patient'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 patient 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 patient is a minor, permission from the responsible relative replaces that of the patient 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 PATIENTS (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 patients should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness. 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.

3. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the patient.

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 patients or facilities away from the study at hand.

To submit an up-to-date curriculum vitae and other credentials (e.g., medical license number in the United States) 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 GSK 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 patients following approval as appropriate by the Ethical Review Committee or Institutional Review Board.

III. Sponsor's Termination Of Study

GSK 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 GSK.

CRFs (and patient diary cards, if applicable), will be supplied by GSK for recording all data. It is the responsibility of the Investigator or co-Investigator to ensure that CRFs (and patient diary cards) are legible and completely filled in with a black ink ball-point pen. Enter the patient's identification (2-3 alphabetic letters representing the patient's initials or first 2-3 letters of patient's first or last name), the patient identification (PID) if not already pre-printed, and the visit date on the CRF page headers 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 patient 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 5 days. Similarly, when a patient 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 5 days. This also applies to forms for potential study participants who were not randomised to a treatment group.

As soon as the patient 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 event page(s) as well as the Study Conclusion Record page of the CRF to confirm that they have reviewed the data and that the data are completed and accurate. If sections of a CRF are to be brought into GSK prior to study conclusion, a section conclusion signature is required.

An original (top copy) CRF must be submitted for all patients who have undergone protocol specific procedures, whether or not the patient completed the study.

While completed CRFs will be reviewed by an GSK professional monitor at the study site, 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 study monitor.

V. Monitoring By GlaxoSmithKline (i.e., the Sponsor)

Monitoring visits by a professional representative of the sponsor will be scheduled to take place before entry of the first patient, during the study at appropriate intervals and after the last patient is completed.

These visits are for the purpose of confirming that GSK-sponsored studies are being conducted in compliance with the relevant Good Clinical Practice regulations/guidelines, 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 patient records and CRFs as well as drug disposition records in an easily retrievable form until disposal has been agreed in writing with GSK. The Investigator must have a 'key' linking the patient's identification code (i.e., treatment number) to the patient'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.

GSK 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.

VII. Audits

For the purpose of compliance with Good Clinical Practice and Regulatory Agency Guidelines, it may be necessary for GSK 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 GSK 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.

GSK has a substantial investment in clinical studies. Having the highest quality data and studies are essential aspects of drug development. GSK has a Regulatory Compliance staff who audit investigational sites. Regulatory Compliance assesses the quality of data with regard to accuracy, adequacy and consistency. In addition, Regulatory Compliance assures that GSK sponsored-studies are in accordance with the relevant Good Clinical Practices regulations/guidelines.

To accomplish these functions, Regulatory Compliance selects investigational sites to audit. These audits usually take 1 to 2 days. The GSK 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 GSK audit, therefore, helps prepare an Investigator for a possible regulatory agency inspection, as well as assuring GSK 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
- ERC approval
- Test article accountability
- Approved study protocol and amendments
- Informed consent of patients (written or witnessed oral consent)
- Medical records supportive of CRF data
- Reports to the ERC and the sponsor
- Record retention

GSK will gladly assist Investigators prepare for an inspection.

VIII. Confidentiality And Publication

You agree that all information communicated to you by GSK is the exclusive property of GSK and you will ensure that the same shall be kept strictly confidential by you or any other person connected with the work and shall not be disclosed by you or such person to any third party without the prior written consent of GSK. You shall communicate the results of the work promptly to GSK.

We agree that you 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 us provided that, if we shall so request, you will delay publication for a maximum of six months to enable us to protect our 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 GSK Medical Monitor prior to submission. GSK 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 GlaxoSmithKline.

In drafting this section, additional stipulations can be included in accordance with local custom and practice but the above aspects must also be retained.

Appendix C Sample Informed Consents

INVESTIGATOR:

CLINICAL STUDY TITLE:	A Randomised, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy, Safety and Tolerability of Oral Cilomilast (15 mg bd) When Given as Maintenance Treatment for 12 Months to Subjects with Chronic Obstructive Pulmonary Disease (COPD)
PROTOCOL NO:	SB 207499/157
SPONSOR:	GlaxoSmithKline ("The Company")
DATA CONTROLLER:	GlaxoSmithKline

Description/Purpose of the Study

You have Chronic Obstructive Pulmonary Disease (COPD) which is known to cause the symptoms or problems that you have when breathing. COPD includes chronic bronchitis and emphysema. As a patient with COPD, you are being invited to take part in this medical research study sponsored by GlaxoSmithKline (GSK) to investigate the safety and effectiveness of cilomilast. Cilomilast is an investigational drug. This means that it has **not** been approved for sale by the U.S. Food and Drug Administration (FDA) or other country governments, but it may be tested in research studies like this one.

Cilomilast is an experimental drug that blocks the action of substances in the body called phosphodiesterases. There is evidence from scientific studies to suggest that phosphodiesterases may be involved in producing some of the symptoms of COPD. If the effects of phosphodiesterases in the lungs can be blocked by cilomilast, the breathing problems which occur in patients with COPD may be improved.

If you qualify and agree to participate in this study, you will be involved in the study for about 57 weeks. During the study, you will be assigned, by chance (similar to the toss of a coin), to one of two different treatment groups:

Treatment Group 1: 15 mg of cilomilast
Treatment Group 2: Placebo (inactive tablets)

Although in every way they look like the active cilomilast tablets, placebo tablets are inactive and have no effect on the treatment of COPD. There is a 50% chance that you will receive the active medication and a 50% chance that you will receive the inactive tablets. Neither you nor the doctor will know if you are taking the experimental drug or the inactive placebo. However, in the event of an emergency, the identity of the tablets can rapidly be determined.

Whichever kind of tablets you are given, it will be called "study medication". You will take one tablet of "study medication" two times a day (in the morning and in the evening) with a glass of water immediately after a meal. It is very important that you **take the study medication immediately after meals** as directed by the doctor.

At some point during the study, all participants will receive placebo. Not knowing which treatment you are receiving is necessary to ensure objective observations by the doctor.

Throughout the study, you will be given salbutamol inhalers to take home with you. Salbutamol inhalers (like Ventolin®) are already available to treat the problems you have breathing. If you take anticholinergics you will be able to continue using them at stable doses. You must agree not to take any other COPD medications except as instructed by the study doctor after you enter the study.

Study medication must be taken only by the person for whom it was prescribed. It must be kept out of the reach of children or persons with limited capacity to read or understand.

A total of approximately 800 patients at up-to100 centres in Europe and Australia/New Zealand will take part in this study.

You will be expected to visit the doctor's office at least 13 times at approximately the same time of day. You will be asked **not** to use inhaled beta$_2$-agonists (Ventolin® inhaler) or anticholinergic agents (Atrovent® inhaler) for **4 hours** before the visit. Also, you may **not** smoke for 2 **hours** before each visit. Smoking and using inhalers will affect the lung function (breathing) tests which will be done at every visit.

At the first visit, the study doctor or a member of the study staff will ask you questions about your past health (illnesses or injuries). On following visits, you will be asked how you have felt since the last visit.

A chest X-ray may be performed at the first visit because your doctor needs to check that your symptoms are due to COPD and not caused by any other illness related to your lungs. If a recent (within the previous 12 weeks) chest X-ray film is available for your doctor to review, it may not be necessary to have a repeat chest X-ray.

A complete physical examination, (including height and weight measurements at Visit 1), will be done 3 (and possibly 4) times. Your blood pressure and heart rate will be measured at every visit. At Visits 1, 3, 7, 9 and 12 your blood pressure will be measured while you are lying down and while you are sitting. At each visit (except one), lung function ("breathing" or "blowing") tests will be performed, and you will be asked how short of breath you feel during usual activities. You will also be asked about your COPD symptoms and health status through questionnaires at 3 visits.

At each visit (except one) you will have small wires pasted to your body at several places to record an electrocardiogram (ECG). This will measure the electrical activity of your heart.

To test for bleeding in your gastrointestinal system, you will be asked to collect specimens of your faecal matter (stools) using test kits provided between Visits 1 and 3 and if you withdraw early from the study (three tests collected on consecutive bowel movements, if possible). The tests are to be performed according to the instructions provided with the 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.

Approximately 20 ml (2 teaspoons) of blood will be taken through a needle from a vein for laboratory tests at 10 (and possibly 11) visits. If you are a female who can become pregnant, a pregnancy test will also be done. Urine samples for

pregnancy testing will be obtained at one visit. Urine samples for laboratory tests will be obtained at 10 and (possibly 11 visits).

You will be given a supply of salbutamol, a miniWright Peak Flow Meter and a diary. You will be required to measure peak flow in triplicate each morning and to record the highest of these measurements in your diary. You will also use the diary to record the number of uses of salbutamol that you use each day. You will be asked to use the diary to record any symptoms of COPD you may have. The information in the diary is very important and you will need to bring it with you to each visit.

The protocol has been reviewed and accepted by an independent ethics review committee.

The study doctor and/or institution is being paid to conduct this study.

Risks Associated with the Study

Drug Side Effects

As with any investigational new drug, there is the possibility that some patients may experience unanticipated adverse effects from cilomilast.

In animal studies, the administration of cilomilast to rats and mice has been linked to the development of serious blood vessel abnormalities in the heart and intestinal tract. No such disease has been seen in other animals that received cilomilast.

In previous research with cilomilast, more than 4000 people have participated in cilomilast studies. Overall, the most common side effects seen in these patients were nausea and headache. Other adverse effects relating to the gastrointestinal tract, such as diarrhoea, vomiting, and abdominal pain have also been noted in humans taking cilomilast. In the interest of your safety, GSK is researching these gastrointestinal complaints. If you experience black or bloody stools, abdominal discomfort, such as pain or cramps, diarrhoea, 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 a small stool sample at home to be

returned to the clinic for analysis. The study 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 decides that the problem is resolved.

To date, no studies have been performed to show how cilomilast interacts with over-the-counter medications. Therefore, it is important that you tell you study doctor about **all** medicines (both prescription and over-the-counter) that you are taking.

There may be a risk of allergy to the drug used in this study. Signs of allergic reaction may include redness, itching, rash, inflammation, or (in rare cases) difficulty breathing and lightheadedness. Severe allergic reactions may result in death.

Irregular heart rhythms and congestive heart failure have occurred in several patients receiving cilomilast. The relationship between these side effects and cilomilast or the study plan is uncertain, because the side effects have been seen in study patients receiving placebo as well as in patients receiving cilomilast.

The drug in this study may involve other risks or side effects that are not known at this time.

You will be told of any changes in the way the study will be performed and of any new medical risks which come to the attention of the Investigator during the course of the study that could affect your willingness to continue in the study.

Risks of Study Procedures

Certain procedures, including some lung function (breathing) tests, chest X-ray, heart rate and blood pressure monitoring, form part of the clinical study. These tests would normally be carried out by a doctor in a routine examination of your condition and present practically no risk to you. However, some patients have experienced lightheadedness from breathing tests.

Risks associated with drawing blood with a needle and syringe are pain, bruising at the site of the needle stick, lightheadedness, fainting and infection. During the

entire study, less than 3/4 cup of blood will be removed from each patient. Your body will quickly make up for this small loss.

Other Risks

Your condition may not improve or may worsen while participating in this study.

Benefits Associated With the Study

There is no guarantee that you will benefit by participating in this study. However, you and other patients in the future may benefit from this medical research. Such benefits include the possibility that your condition may improve and that this study may help develop a new therapy for you and others with COPD.

Office visits, procedures (tests) related to the study and study medication will be provided at no charge to you.

Alternative Therapy

Other therapies are available to treat COPD. These treatments include theophylline (Theo-Dur®, Slo-Bid®), inhaled/oral steroids (Azmacort®, Vanceril®), long-acting inhaled beta-agonists (Serevent®) and leukotriene modifiers (Zyflo®, Accolate®, Singulair®).

If you have questions about the other therapies, ask the study doctor for additional information. He or she can explain the risks and benefits of these alternative treatments. You do not have to participate in this study to receive treatment for your condition.

Risks if You Become Pregnant

Some drugs can interact with oral birth control pills in such a way that protection provided by "the pill" against pregnancy is reduced. While it is unlikely, the possibility of a decrease in birth control protection while taking cilomilast cannot be ruled out at this time.

In order to evaluate the potential risk of giving cilomilast to women of childbearing potential if pregnancy should occur while taking cilomilast, studies were completed in pregnant animals. Cilomilast has been given to pregnant rats

and rabbits, and there were no adverse findings to suggest that if pregnancy did occur during the duration of clinical studies with cilomilast, there would be a risk to the development of the unborn child.

While results from animal studies are important and may be relevant to what might happen in humans, the effects of cilomilast on the growth and development of an unborn baby are not known at this time. Birth defects, including physical deformities, mental retardation, premature birth or other problems are known risks of some drugs.

Because effects of cilomilast on the unborn baby are not known at this time, you will not be allowed to enter this study if you are pregnant. Woman who are nursing will also not be allowed to enter this study.

If you take part in this study and there is any chance you could become pregnant, you must use one of the allowed birth control methods while in the study. Allowed birth control options include oral birth control pills, Norplant®, Depo-Provera®, an IUD, a condom with spermicide or a diaphragm with spermicide. Women of childbearing potential must use one of these methods for at least 1 month prior to Visit 1 and must continue using the same birth control method during the study and for 30 days after discontinuing study medication. The study doctor can also suggest where you can get more information and advice.

Even when you use one of the allowed birth control methods, there is a small risk you could become pregnant anyway. Because of this, you will be tested during the study to see if you have become pregnant. These tests **do not prevent** you from becoming pregnant and will only determine if you are pregnant a week or two **after** you are already pregnant. Even if you stop taking cilomilast as soon as your pregnancy is discovered, you cannot be sure that your baby has suffered no harm. If you think that you are pregnant or are concerned that you may have become pregnant, you should tell the study doctor immediately. If you become pregnant during the study, the study doctor will help to make sure you get proper advice and that you and your unborn baby get proper care while you are pregnant.

If you become pregnant during the study, you will be withdrawn from the study. If you become pregnant within a month of completing the study, you should tell the study doctor as soon as possible.

Confidentiality and Source Document Review

You understand and consent to the following:

It will be necessary for representatives of GlaxoSmithKline or possibly drug or health regulatory agencies to access your medical records. Your participation in the study will be treated as confidential, that is, any personally identifiable information will be held and processed under secure conditions at GlaxoSmithKline (or an agent of GlaxoSmithKline) with access limited to appropriate GlaxoSmithKline staff or other authorised agents having a requirement to maintain the confidentiality of the information. You will not be referred to by name in any report of the study. Your identity will not be disclosed to any person, except for the purposes described above and in the event of a medical emergency or if required by law.

Your personal data will be processed electronically to determine the outcome of this study, and to provide it to drug or health regulatory agencies. Your data may be transferred to other countries for these purposes.

GlaxoSmithKline complies with internal procedures to protect personal information even in countries whose data privacy laws are less strict than those of this country. The data may also be used for other medical research purposes.

You may be entitled under law to access your personal data and to have any justifiable corrections made. If you wish to do so, you should request this from the doctor conducting the study.

Right to Ask Questions and/or Withdraw from the Study

You have the right to ask any questions concerning the potential and/or known hazards of this study at any time. You will be informed of any significant new information relating to your safety that may affect your decision to remain in this study.

If you have any questions concerning this study, please call:

Investigator: _____ Telephone: _____

This study has been reviewed by an Ethics Committee (ERC) which operates independently of the Sponsor and the Investigator (study doctor). ERCs are primarily concerned with protecting the safety and rights of people who volunteer to participate as investigational research subjects.

Compensation (Medical/Financial) to be provided

If you become ill or injured as a result of participation in this clinical study, medical treatment will be provided and the reasonable costs of such treatment will be paid by "the Company." If you have any questions concerning the availability of medical care or if you think you have experienced a research-related illness or injury, contact:

Name: Investigator: _____ Telephone: _____

Costs

To help with the time and travel expenses, you will be reimbursed for any costs incurred as a participant in this study.

Voluntary Participation

Your participation in this study is voluntary. You may decide not to participate and you have the right to withdraw from the study at any time, without any penalty or loss of benefits to which you are otherwise entitled. If you decide to withdraw from the study, your routine medical care will not be affected in any way. You should obtain evaluation and treatment for your COPD after withdrawing from or completing the study.

You may be withdrawn from the study at any time without your consent, by the study doctor or the Sponsor, if it is believed to be in your best interest, if you do not follow directions, or for administrative reasons.

If you leave the study early, you must return all unused study medication. You will be asked questions about your experience with the study drug. You may also be asked to co-operate in having usual visit assessments and any laboratory tests and physical examinations the study doctor considers necessary.

Consent

I, (Full name – printed) _____ , have read and understand all the preceding information describing this study and all my questions have been answered to my satisfaction. I voluntarily consent to participate in the study and for my family physician to be advised of my participation in this study.

Signature of Patient _____ Date: DD/MMM/YY
(Parent/Legal Representative) (to be inserted by patient/representative)

Name of Investigator _____
(or person who conducted the informed consent)

Signature of Investigator _____ Date: DD/MMM/YY
(or person who conducted the informed consent)

Position: _____

Sample Informed Consent Statement for additional faecal occult blood test

This consent and information sheet is designed as an addendum to the main study consent form.

At some point prior to study visit 11 you will be asked to undertake an additional faecal occult blood test. This test is entirely voluntary. If you decide not to provide a sample, you do not need to give any reasons, and your medical care will not be affected in any way. A decision not to provide a sample will **not** prevent you from continuing in the study.

This test will involve taking two pea sized samples from your stools on three consecutive occasions. This will cause no additional risk to you.

The test should be performed according to the instructions provided with the kit. 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.

You will either be given the test kit at study visit 10 for return at study visit 11 or you will be given the sample at study visit 11 for return within 14 days. It is important that the samples are processed within 14 days of taking them.

The test will show if you have any bleeding within you gastrointestinal tract, the results of this will help us to assess the safety of the drug we are researching. The reason why we need an extra test is to provide additional data to assess the safety of the drug. We already have two such tests within the study but feel that more data will help us to demonstrate the safety of this drug. There is currently no signal from the clinical studies we have undertaken that suggests that the study drug will increase the incidence of gastrointestinal bleeding.

The results of the test will be recorded as part of the study results and as such will be treated with the same strict data protection policies as the rest of the trial data.

There is no payment for this procedure but you will be reimbursed for any reasonable additional expenses that you incur directly related to providing this sample.

If you have any concerns or questions about this procedure please contact your study doctor

Consent

I, (Full name – printed) _____, have read and understand all the preceding information describing this procedure and all my questions have been answered to my satisfaction. I voluntarily consent to providing stool samples for an additional faecal occult blood test as part of the clinical study protocol number 207499/157.

Signature of Patient _____ Date: DD/MMM/YY
(Parent/Legal Representative) (to be inserted by patient/representative)

Name of Investigator _____
(or person who conducted the informed consent)

Signature of Investigator _____ Date: DD/MMM/YY
(or person who conducted the informed consent)

Position: _____

Appendix D Prediction Equations

Predicted FEV_1 (litres):

Females

$FEV_1 = 0.0395*H - 0.025*A – 2.6$

Males

$FEV_1 = 0.0430*H - 0.029*A - 2.49$

Where H = height in cm
A = age in years

Reference

EUROPEAN COMMUNITY FOR COAL AND STEEL. 1983. Standardisation of Lung Function Tests. *Bull Europ Physiopath Resp,* **Suppl 5,**

Predicted Residual Volume

%Predicted RV is calculated from the Body Plethysmography measurement of residual volume (RV_{Box}) which is itself calculated using a maximum of the latest six collected post-salbutamol SVC and FVC measurements.

$$\%\text{Predicted RV} = [RV_{Box}/ \text{Predicted RV}] \times 100$$

Prediction equations for RV are defined as:

Females

$RV = 1.81H + 0.016A – 2.00$

Males

$RV = 1.31H + 0.022A – 1.23$

where H = height in m
A = age in years

Reference

Quanjer PH, *et al.* 1993. Lung volumes and forced ventilatory flows. Report working party, standardisation of lung function tests, European community for steel and coal :Official statement of the European Respiratory society. *Eur. Resp. J*. 6 (16). 5-40.

Note: The above equations should be used for calculation of predicted FEV_1, and RV wherever possible. If the source of predicted FEV_1 or RV is different for any participating centre, this should be documented by both GlaxoSmithKline and the Investigator.

Appendix E The EQ-5D Questionnaire

Background

EQ-5D is a standardised instrument for use as a measure of health outcome. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for heath status that can be used in the clinical and economic evaluation of healthcare as well as population heath surveys. EQ-5D has been specially designed to complement other quality of life measures such as the SF-36, NHP, SIP or disease-specific measures.

The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. This decision results in a one-digit number expressing the level selected for that dimension. The digits for five dimensions can be combined in a five-digit number describing the respondent's health state. It should be noted that the numerals 1-3 have no arithmetic properties and should not be used as a cardinal score.

A respondent may sometimes find that the number of levels is too limited. For example, for the mobility question, a respondent in a wheelchair is not 'confined to bed', but he/she may find 'some problems in walking about' appears to under-estimate their level of difficulty. If an administrator is present he/she should stress the instruction: 'please indicate which statements *best* describe your own health state today'. It is the respondent's personal evaluation that is required and on no account should a prompt be given.

Specific Tips for Self-Administration

The EQ-5D is a very simple questionnaire and therefore quite easy for patients to complete on their own. Patients should be handed the questionnaire by the clinic nurse or the study co-ordinator for completion. The patient should return the questionnaire to this person afterwards.

Patients should be provided with a quiet place in which to complete the questionnaire. Noisy waiting rooms and clinics tend to be distracting.

Patients should be on their own when they complete the questionnaire. Friends and relatives should wait in a separate room. You want the patient's responses, not a family consensus!

When the patient has completed the questionnaire, the co-ordinator should review it to ensure that all questions have been answered.

A copy of the questionnaire to be used in this study is provided on the following pages.

EQ-5D


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

Appendix F The St. George's Respiratory Questionnaire

Background

The St. George's Respiratory Questionnaire (SGRQ) is an index designed to measure and quantify health-related health status in patients with chronic airflow limitation. It has been shown to correlate well with established measures of symptom level, disease activity and disability.

The first part ("Symptoms") evaluates symptomatology, 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 activities that cause breathlessness or are limited because of breathlessness. The "Impacts" section covers a range of factors 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.

Administering the SGRQ

The SGRQ will be administered prior to all other scheduled procedures at Baseline (Visit 3), Week 28 (Visit 9) and Week 52 (Visit 12). In addition, any patient who withdraws from the study for any reason should also complete the questionnaire.

Like the EQ-5D, the test is to be self-administered in a quiet room in the clinic away from friends, relatives and other patients. The patient must not be allowed to complete the questionnaire at home.

Patients should be handed the questionnaire by the clinic nurse or the study co-ordinator for completion. Ask the patient to complete it as honestly as possible and emphasise that there are no right or wrong answers; only the answer that best applies to them. Explain that they must answer every question and that a clinic nurse or study co-ordinator will be available to give advice if necessary.

Handling questions from patients

Answers to some possible questions are provided in the "Guide to Completing the SGRQ" section following the questionnaire. The study co-ordinator should review these guidelines before seeing patients to prepare for their questions.

If the patient asks for help answering a question, the study co-ordinator must not give them a direct answer. The goal of a health status questionnaire is to get an understanding of how patients view their own illnesses. It is advised to redirect the question to the patient.

Questions may be read to patients who have difficulty reading, but responses must be theirs alone.

Completing the SGRQ

When the patient has completed the questionnaire, the co-ordinator should review it to ensure that all questions have been answered. If any question is blank, double-check with the patient without being critical.

If the study co-ordinator sees an answer that seems incorrect (e.g., the patient marks that he coughs a few days a month and it is documented that he coughs more often) do not question its accuracy. By questioning a patient's answer, the co-ordinator is basically telling the patient that he/she is wrong and the patient may change the original answer even though he/she feels it was correct.

A copy of the SGRQ as well as a Guide to Completing the SGRQ is provided on the following pages.

Reference

1. JONES PW, ET AL. 1992. A self-complete measure for chronic airflow limitation, the St. George's Respiratory Questionnaire. *Am Rev Respir Dis*, **145**, 1321-1327.

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.

St. George's Respiratory Questionnaire. Reproduced and used with permission from PW Jones. U.S. version adapted and modified with permission by Judith Barr, Sc.D., Northeastern Univ., Boston, MA.

Appendix G Gastrointestinal Adverse Event Monitoring

Introduction

At Visit 1, patients will be instructed to contact the Investigator as soon as possible if they experience gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhoea, vomiting) which cause the patient concern or interfere with usual activity (including eating and sleeping) at any time during the study. The Investigator will assess these adverse events within 24 hours of occurrence.

Such patients will be followed daily until resolution of these adverse events. The Investigator should report these gastrointestinal adverse events to the GSK Medical Monitor within 24 hours of the assessment. In some cases, the Investigator may delegate the daily follow-up assessments to a visiting nurse or other qualified healthcare provider. Any deterioration in the patient's condition discovered at a follow-up assessment that is performed by a healthcare provider other than the Investigator must be reported to the Investigator by telephone immediately. All results of follow-up assessments performed by a healthcare provider other than the Investigator must be submitted to the Investigator by the end of the working day on which the assessment was performed.

In the interest of patient safety and providing consistent data relating to all of these gastrointestinal adverse events, a specific format will be followed for history, physical examination, laboratory assessment, and pharmacokinetic assessment of these patients. The format is outlined below and supplied in the CRF. Suggestions for additional diagnostic tests or procedures are also outlined below, however, the clinical judgement of the Investigator is paramount in decisions relating to diagnosis and treatment. The assessment of the gastrointestinal symptom should be made in the context of the population studied, considering advanced age, other risk factors, and the possibility of concurrent disease. Alarm features include orthostatic changes in heart rate or blood pressure, evidence of anaemia or gastrointestinal bleeding, vomiting, unexplained weight loss, dysphagia, an abdominal mass or lymphadenopathy or peritoneal signs.

First assessment (Within 24-Hours)

This assessment will be performed on all patients who report gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhoea, vomiting) which cause the patient concern or interfere with usual activity (including sleeping or eating). The assessment must include a history, physical examination and laboratory assessment, as outlined below. Patients who experience a gastrointestinal adverse experience of concern **and** have a positive faecal occult blood test or melena during the randomised treatment phase of the study must be referred to a gastroenterologist for a colonoscopy. Additional diagnostic tests may be performed, at the discretion of the Investigator.

History:

The Investigator will elicit the history of the symptom with attention to the following features:

Time of onset of gastrointestinal symptom

Time of last dose of study medication

Quality of the pain (for example)
- Sharp
- Dull
- Boring

Spatial characteristics
- Location in the abdomen
- Location to which it radiates

Pain radiates?
- Yes, location
- No

Stool assessment and appearance

Physical Examination:

The Investigator will perform a complete physical examination of the patient, with emphasis on the abdomen. Results of the physical examination will be recorded as follows:

- 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 (may use self sample kit or rectal examination)
- Complete blood count with differential
- Urinalysis
- Amylase
- Electrolytes
- Blood glucose
- Liver function tests

Follow-up and Notification

All gastrointestinal adverse events (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhoea, vomiting) which cause the patient concern or interfere with usual activity (including eating and sleeping) will be reported to the GlaxoSmithKline Medical Monitor within 24 hours of initial assessment. Further investigation and review will be arranged as clinically appropriate at the Investigator's discretion. All events should be followed to resolution.

Additional Testing

Referral to a gastroenterologist is mandatory if the patient has a gastrointestinal adverse experience of concern **and** a positive faecal occult blood test or melena during the randomised treatment phase of the study. 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 event 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.

Daily Follow-up Assessments

Patients who report gastrointestinal adverse events that cause them concern or interfere with usual activity will be assessed as appropriate at the Investigator's discretion. All events should be followed to resolution. Patients can return to the clinic for these evaluations or the Investigator may designate a qualified healthcare provider to perform follow-up assessments. These assessments should include an interim physical examination and interim laboratory assessment.

Physical Examination:

Physical examination will be performed as outlined below:

- Assessment of general appearance to assess for signs such as jaundice.
- Heart rate and blood pressure (supine followed by sitting with legs dependent) to assess orthostatic changes.

Laboratory Testing:

- Complete blood count.
- Faecal occult blood test (self sample kit).

PROTOCOL AMENDMENT APPROVAL FORM
(Phase II– Core Phase IV and US Local Phase IV)

Study Drug: 207499 Protocol Number: 157

Protocol Approval Date: 26 (D D) MAR (M M M) 03 (Y Y)

Title: **A Randomised, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy, Safety and Tolerability of Oral Cilomilast (15 mg bd) When Given as Maintenance Treatment for 12 Months to Subjects with Chronic Obstructive Pulmonary Disease (COPD).**

Amendment Number:.....three..... (attach proposed amendment/rationale)

Agreed by:

Co-ordinating Author: [redacted]

[redacted] ..... 27 MAR 03
Signature

.....

Clinical Project Director: [redacted]

[redacted] 03 Apr 03
Signature

Approved by*:

VP/Director CDMA [redacted]

[redacted] 01 004 03
(signature) D D M M M Y Y

Director/VP Biometrics [redacted]

..... / / /
(signature) D D M M M Y Y

RETURN PROTOCOL AND ANY COMMENTS TO

[redacted]..... by 31 MAR 03
D D M M M Y Y

Form sent to: [redacted] and [redacted]

PROTOCOL AMENDMENT APPROVAL FORM
(Phase II– Core Phase IV and US Local Phase IV)

Study Drug: 207499 Protocol Number: 157

Protocol Approval Date: 26 (DD) MAR (MMM) 03 (YY)

Title: **A Randomised, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy, Safety and Tolerability of Oral Cilomilast (15 mg bd) When Given as Maintenance Treatment for 12 Months to Subjects with Chronic Obstructive Pulmonary Disease (COPD).**

Amendment Number:.....three.....(attach proposed amendment/rationale)

Agreed by:

Co-ordinating Author: [redacted] ..... Signature DD MMM YY

.....

Clinical Project Director: [redacted] ..... Signature DD MMM YY

Approved by*:

VP/Director CDMA [redacted] ..... (signature) DD MMM YY

Director/VP Biometrics [redacted] [redacted] (signature) 27 MAR 03

RETURN PROTOCOL AND ANY COMMENTS TO

[redacted] ..... by 31 MAR 03

Form sent to: [redacted] and [redacted]

Division:	World Wide Development	**Document Number:**	UC2003/00001/00
Document Type:	Reporting and Analysis Plan	**Study Identifier:**	SB-207499/157
Site of Issue:	Upper Providence		
Classification:	Level 2	**Issue Date:**	9 March 04

Title:

Reporting and Analysis Plan for SB-207499/157 A Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy, Safety and Tolerability of Oral Cilomilast (15 mg BID) When Given as Maintenance Treatment for 12 Months to Subjects with Chronic Obstructive Pulmonary Disease (COPD)

Abstract: (For Internal Use Only)

A Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy, Safety and Tolerability of Oral Cilomilast (15 mg BID) When Given as Maintenance Treatment for 12 Months to Subjects with Chronic Obstructive Pulmonary Disease (COPD)

Authors: [redacted] Ph.D., [redacted] Ph.D., [redacted] Ph.D., [redacted] Ph.D.

Compound Numbers/Keywords (if applicable): SB-207499/157

Distribution:

CONFIDENTIAL UC2003/00001/00
SB-207499/157

Approval Page

Study Identifier: SB-207499/157

Study Title: Reporting and Analysis Plan for SB-207499/157 A Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy, Safety and Tolerability of Oral Cilomilast (15 mg BID) When Given as Maintenance Treatment for 12 Months to Subjects with Chronic Obstructive Pulmonary Disease (COPD)

Document/Version Number: UC2003/00001/00

Date of Issue: 9 March 2004

E-mail Approval.

Approver(s):	**Signature:**	**Date:**
Type Name Type Approver's Title and Functional Area		

Title:

Reporting and Analysis Plan for SB-207499/157 A Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy, Safety and Tolerability of Oral Cilomilast (15 mg BID) When Given as Maintenance Treatment for 12 Months to Subjects with Chronic Obstructive Pulmonary Disease (COPD)

UC2003/00001/00

Author(s): [redacted] Ph.D., [redacted] Ph.D., [redacted] Ph.D., [redacted] Ph.D.

Document/Version Number: UC2003/00001/00

Date of Issue: 9 March 2004

Copyright 2003 the GlaxoSmithKline group of companies. All rights reserved.
Unauthorised copying or use of this information is prohibited.

TABLE OF CONTENTS

PAGE

1. INTRODUCTION....4

2. STUDY OBJECTIVES AND ENDPOINTS....4
2.1. Study Objective....4
2.2. Study Endpoints....4
2.2.1. Primary Endpoints....4
2.2.2. Secondary Endpoints....5
2.2.3. Tertiary Endpoints....5
2.3. Hypotheses....6

3. STUDY DESIGN....6

4. PLANNED ANALYSES....6
4.1. Interim Analyses....6
4.2. Meta-Analysis....6

5. SAMPLE SIZE CONSIDERATIONS....7
5.1. Sample Size Sensitivity....7
5.2. Sample Size Re-estimation....8

6. ANALYSIS POPULATIONS....8
6.1. Randomised Population....8
6.2. Intent-to-treat (ITT) Population....8
6.3. Per-protocol (PP) Population....8
6.4. Protocol Violations....9
6.4.1. Violations of Eligibility Criteria....9
6.4.2. Visit Specific Protocol Violations....10
6.4.3. Conduct of Study Deviations....10

7. COMPARISONS OF INTEREST....10
7.1. Primary Comparisons of Interest....10
7.2. Other Comparisons of Interest....11

8. GENERAL CONSIDERATIONS FOR DATA ANALYSES....11
8.1. Pooling of Centers for Efficacy Analysis....11
8.2. Multiplicity....11
8.3. Sub-populations of Interest....11

9. DATA HANDLING CONVENTIONS....12
9.1. Missing Data....12
9.2. Derived Data....13
9.2.1. Baseline and Endpoint....13
9.2.1.1. Baseline....13
9.2.1.2. Endpoint....13
9.2.2. Duplicate or repeated observations....13
9.2.3. Study Medication Record....13
9.2.3.1. Date of First Dose in the Double-blind Period....13
9.2.3.2. Date of Last Dose in the Double-blind Period....14

9.2.3.3. Exposure to Double-blind Study Medication 14
9.2.4. Compliance 14
9.2.4.1. Number of Tablets Consumed 14
9.2.4.2. Number of Days Between Visits 14
9.2.4.3. Visit Level Compliance 14
9.2.4.4. Overall Compliance 14
9.2.5. Visit Dates 14
9.2.6. Last Study Day 15
9.2.7. Prior, Concomitant and Post-therapy Medications 15
9.2.7.1. Prior Medications 15
9.2.7.2. Concomitant Medications 15
9.2.7.3. Post-therapy Medications 15
9.2.8. Pulmonary Function Tests (PFTs) 15
9.2.9. COPD Exacerbation 15
9.2.10. Saint George's Respiratory Questions (SGRQ) 16
9.2.10.1. Treatment of Missing Values on SGRQ 16
9.2.10.2. Multiple Responses on SGRQ 16
9.2.11. EQ-5D and Indirect Cost 16
9.2.11.1. EQ-5D 16
9.2.11.2. Indirect Cost 18
9.2.12. Patient and Physician's global Assessments 18
9.2.13. Diary Data 18
9.2.14. Adverse Events 18
9.2.14.1. Baseline Signs and Symptoms 18
9.2.14.2. On-therapy Adverse Events 19
9.2.14.3. Post-therapy Adverse Event 19
9.2.14.4. Adverse Event Leading to Withdrawal 19
9.2.14.5. Adverse Event with Missing Onset Date 19
9.2.15. Electrocardiographs (ECGs) / Clinical Laboratories / Sitting Vital Signs / Orthostatic Vital Signs 19
9.2.15.1. On-therapy assessments 19
9.2.15.2. Worst-case On-therapy Assessments 19
9.2.15.3. New-onset ECG Finding 19
9.2.15.4. Calculation of Orthostatic Changes 20
9.2.16. Values of Clinical Concern 20

10. STATISTICAL ANALYSIS 22
10.1. Patient Disposition, Baseline Characteristics and Demography 22
10.2. Efficacy analysis 23
10.2.1. Analysis of Primary Efficacy Variables 23
10.2.1.1. Primary Analysis of FEV_1 23
10.2.1.2. Primary Analysis of Exacerbation Rate 23
10.2.1.3. Sensitivity Analysis to Access Impact on Primary Analysis 24
10.2.2. Analysis of Secondary Efficacy Variables 24
10.2.3. Analysis of Tertiary Efficacy Variables 25
10.2.4. Pharmacoeconomic Analysis 25
10.3. Safety Analysis 25
10.3.1. Adverse Experience 25
10.3.2. Clinical Laboratories 26
10.3.3. Vital Signs 26
10.3.4. Electrocardiographs 26

1. INTRODUCTION

Study 157 is a pivotal Phase III study to assess the efficacy and safety of cilomilast versus placebo over a year timeframe as maintenance treatment in patients with COPD. This is a double-blind, placebo controlled, randomized, parallel group study requiring a maximum of 13 visits over a 57-week period. A 4-week single-blind placebo run-in period will be followed by 52 weeks of treatment with double-blind study medication. A safety follow-up visit will be conducted 7 ± 3 days after the last dose of study medication. Patients are encouraged to come for their regular visits even if they have stopped their study medication.

Patients eligible to enter the double-blind period must meet the randomisation criteria as defined in the protocol. Qualified patients will be randomized in a 1:1 ratio to receive either cilomilast 15 mg or matching placebo tablets twice daily. Assignment to study drug will be stratified according to smoking status at baseline prior to randomization for 'current smokers' and 'ex-smokers'.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objective

The primary objective of the study is to demonstrate the clinical efficacy of oral cilomilast (15 mg bd) versus placebo by assessment of reduction in risk of the occurrence of COPD exacerbation and improvement in pulmonary function (FEV_1) over a 52 week treatment period.

The secondary objective of the study is to further define the clinical safety and tolerability of cilomilast 15 mg bd versus placebo by assessment of adverse events and laboratory measurements over a 52 week period in subjects with COPD.

2.2. Study Endpoints

2.2.1. Primary Endpoints

The co-primary variables in this study are the change from baseline in trough pre-bronchodilator FEV_1 averaged over 52 weeks and the incidence rate of level 2 (moderate) and level 3 (severe) COPD exacerbations during the treatment period, where level 2 and level 3 exacerbation are defined as:

Level 2 (Moderate- physician, investigator treated): Acute worsening of symptoms (cough, sputum production, breathlessness) requiring treatment with oral corticosteroids prescribed by a physician or primary care doctor, or as a result of hospital out-patient visit (including Emergency Room).

CONFIDENTIAL UC2003/00001/00
SB-207499/157

Level 3 (Severe - attendance at hospital): Acute worsening of COPD that requires the patient to be admitted to hospital for treatment.

2.2.2. Secondary Endpoints

There are five secondary endpoints in this study:

- Mean change from baseline in trough post-bronchodilator FEV_1 averaged over 52 weeks
- Time to first level 2 (moderate) or level 3 (severe) COPD exacerbation
- Time to first COPD exacerbation (all levels)
- Incidence rate of exacerbation for all levels of COPD exacerbations
- Quality of life as determined using the St. George's Respiratory Questionnaire (SGRQ)

2.2.3. Tertiary Endpoints

The following tertiary endpoints are being collected:

- Pulmonary function parameters (clinic FVC, clinic PEF, clinic FEV_{25-75}).
- Residual volumes (body box)
- Morning PEF from daily diary cards
- Use of relief medication and percentage of days with no need for rescue medication (salbutamol)
- Duration of exacerbations
- Symptom scores and symptom free days from daily dairy cards (24 hour period)
- Number of nighttime awakenings
- Number and percent of withdrawals (NB as far as possible subjects discontinuing study medication should remain in the study for assessments for completion of the 12 month treatment period).
- Disease-specific quality of life: SGRQ subscales (symptoms, activity and impact)
- Generic health status (EQ-5D)
- Health outcomes endpoints: resource utilisation and indirect costs
- Time off work/normal activities due to COPD
- Global subject assessment
- Global investigator assessment
- Blood CD4+/CD8+ ratio
- Serum C reactive protein

2.3. Hypotheses

The primary hypothesis of this study is to demonstrate the superiority of cilomilast to placebo with respect to trough pre-bronchodilator FEV_1 and incidence rate of moderate or severe COPD exacerbations.

The hypothesis of testing treatment difference in change from baseline in trough FEV_1 is two-tailed: $H_{o1} : \mu_t = \mu_c$ versus $H_{a1} : \mu_t \neq \mu_c$, where μ_t and μ_c are the means of change from baseline of trough FEV_1 averaged over all double-blind visits for the cilomilast group and placebo group respectively.

The hypothesis of testing treatment difference of the exacerbation rates is also two-tailed: $H_{o2} : R_t = R_c$ versus $H_{a2} : R_t \neq R_c$, where R_t and R_c are the moderate or severe COPD exacerbation incidence rates per patient year for cilomilast group and placebo group respectively.

3. STUDY DESIGN

This phase III study is a double-blind, placebo controlled, randomised, parallel group study requiring a maximum of 13 visits over a 57-week period. Subjects meeting the Visit 1 inclusion criteria are entered into a 4 week single-blind placebo run-in period to collect baseline data. During the study subjects are permitted to take ipratropium bromide (constant dose) and salbutamol (prn) for the treatment of COPD. At the end of this 4 week period, subjects complying with inclusion/exclusion criteria will be eligible for continuation into the double-blind phase of the study for 52 weeks.

Subjects will be randomly allocated to either cilomilast 15mg bd or placebo bd. Study medication will be administered immediately after breakfast and evening meal. Assignment to study drug will be stratified according to smoking status at Baseline (prior to randomisation) for 'current smokers' and 'ex-smokers'. Randomisation schedule was generated in blocks using a GSK Coding Memo System and the GlaxoSmithKline Registration and Medication Ordering System (GSK RAMOS).

4. PLANNED ANALYSES

Data will be unblinded and database will be frozen after quality of the data has ~~been~~ met GSK standard.

4.1. Interim Analyses

There is no planned interim analysis for this study.

4.2. Meta-Analysis

There is no planned Meta-analysis for this study.

CONFIDENTIAL UC2003/00001/00
SB-207499/157

5. SAMPLE SIZE CONSIDERATIONS

Sample size calculation is based on a repeated measures analysis assuming a compound symmetric correlation structure across double-blind visits. The method for determining sample size in repeated measures analysis is identical to that provided by Frison and Pocock[1].

In order to obtain 550 evaluable patients, this study will randomise a minimum of 800 patients in a ratio of 1:1 for cilomilast to placebo. Power analyses performed for FEV_1 with the stated sample size indicate that there will be greater than 90% power to detect a clinically relevant difference of 50 ml in FEV_1 assuming a standard deviation of 210 ml in the change from baseline, a correlation of 0.68 between visits and a significance level of 0.05.

Assuming a Poisson distribution for the number of COPD exacerbations (moderate and/or severe) during the treatment period and an exacerbation incidence of 0.8 per patient year for placebo group, a sample size of 550 will give greater than 90% power to detect a 30% reduction in exacerbation rate for cilomilast group compared with placebo group. The incidence of 0.8 per patient year is based on retrospective analysis of data from Study 091 extrapolated to one year.

The superiority of cilomilast to placebo with regard to COPD exacerbations (moderate and/or severe) will be further analysed by comparing exacerbation-free curves. Assuming 1) the censoring patterns for the observations are the same for the two independent treatment groups; 2) the exacerbation-free curves for the two treatment groups are $S_0(t)$ and $S_1(t)$, and $S_1(t) = [S_0(t)]^{\theta}$; 3) exacerbation-free rate for placebo group at one year is 42%, a sample size of 550 will give a greater than 90% power to detect a 15% difference (θ=0.65) in exacerbation-free rate for cilomilast group. The 42% exacerbation free rate is based on retrospective analysis of data from Study 091 extrapolated to one year.

5.1. Sample Size Sensitivity

The power of the repeated measures analysis is affected by assumed mean difference in FEV_1, the assumed standard deviation of change from baseline and the correlation structure across the visits in double-blind period. The following tables list the statistical power at the stated sample size for mean treatment differences between 30 ml and 60 ml, standard deviations between 190 ml and 230 ml, and correlations between 0.60 and 0.80.

[1] Frison L, Pocock SJ. 1992. Repeated Measures Analysis in Clinical Trials: Analysis Using Mean Summary Statistics and Its Implications for Design. Statistics in Medicine, 11, 1685-1704.

Table 1 Sample Size Sensitivity (sample size = 275/arm)

		Statistical Power			
Standard Deviation	Correlation	Mean Difference (30ml)	Mean Difference (40ml)	Mean Difference (50ml)	Mean Difference (60ml)
190	0.60	63%	86%	97%	99%
190	0.70	58%	82%	95%	99%
190	0.80	53%	78%	92%	98%
210	0.60	55%	79%	93%	99%
210	0.70	50%	74%	90%	97%
210	0.80	45%	69%	87%	96%
230	0.60	47%	72%	89%	97%
230	0.70	43%	66%	84%	95%
230	0.80	39%	61%	80%	92%

5.2. Sample Size Re-estimation

There is no planned sample size re-estimation for this study.

6. ANALYSIS POPULATIONS

6.1. Randomised Population

This population consists of all patients who have a randomisation id number assigned and are confirmed to receive at least one dose of double-blind study medication. All safety variables will be analyzed for this population.

6.2. Intent-to-treat (ITT) Population

The intent-to-treat population for the primary analysis of FEV_1 will include all patients who have received at least one dose of double-blind medication and for whom a baseline and at least one on-therapy FEV_1 assessment are available. An on-therapy assessment is defined as any evaluation performed after the first dose and within one day after the last dose of study medication in the 52-week double blind period.

Analysis of number of COPD exacerbations during treatment period as well as time to the first COPD exacerbation will include all randomised patients.

6.3. Per-protocol (PP) Population

The per-protocol population will include all patients who are in the intent-to-treat population and do not significantly violate the protocol. Analyses for the per-protocol population will be restricted to FEV_1 and exacerbation rate for Level 2 and 3 exacerbations.

6.4. Protocol Violations

6.4.1. Violations of Eligibility Criteria

For these violations all primary endpoint data are excluded from the per-protocol analysis.

- Patients who have previously taken cilomilast
- Pre- salbutamol FEV_1/FVC ratio > 0.7 at Visit 1
- Increase in FEV_1 of >15% absolute (pre Protocol amendment 2) and > 10% of predicted normal (post protocol amendment 2) and/or > 200 ml following salbutamol at Visit 1
- Post- salbutamol FEV_1 <30% or >70% of predicted value at Visit 1
- Participation in a pulmonary rehabilitation program (PRP) within 4 weeks prior to Visit 1
- Greater than a 20% change in pre- salbutamol clinic FEV_1 between Visits 2 and 3 Excluded Medication Protocol Violations

Unless stated otherwise any primary endpoint data collected after the initiation of an excluded medication is excluded from per-protocol analysis.

- Concomitant oral or IV xanthine use within 2 weeks prior to Visit 3
- Concomitant oral or inhaled long-acting beta-2 agonist use within 2 weeks prior to Visit 3
- Concomitant inhaled short acting beta-2 agonist use other than salbutamol within 2 weeks prior to Visit 3
- Concomitant leukotriene modifiers use within 2 weeks prior to Visit 3
- Concomitant combined beta-2 agonist/ipratropium use within 2 weeks prior to Visit 3
- Concomitant long term oxygen therapy use within 2 weeks prior to Visit 3
- Concomitant oral and/or inhaled corticosteroid (ICS/OCS) within 2 weeks prior to Visit 3
- Nebulized or oral salbutamol or nebulized anticholinergics within 2 weeks prior to Visit 3
- Concomitant antibiotic use for COPD exacerbation within 2 weeks prior to Visit 3
- Concomitant use of nedocromil (bronchodilator and anti-inflammatory properties) within 2 weeks prior to Visit 3
- Anticholinergic use that is discontinued within 2 weeks prior to Visit 3
- Anticholinergics initiated after Visit 1

CONFIDENTIAL UC2003/00001/00
SB-207499/157

- Exclusionary medication use for the indication of COPD exacerbation for more than six weeks total exposure during the double-blind period (all data subsequent to six weeks exposure will be excluded)

6.4.2. Visit Specific Protocol Violations

For these violations, primary efficacy data collected at the visit is excluded from the per-protocol analysis.

- Study medication compliance <80% or >120% during active, on-therapy dosing
- Salbutamol/albuterol and/or anticholinergic medication within 4 hours of pulmonary function testing
- Entered a PRP during the study (Exclude all data collected subsequent to entry)
- Use of study medication within 7 hours of first (trough) PFT

6.4.3. Conduct of Study Deviations

For these deviations, no data is excluded from the per-protocol analysis.

- Age <40 or >80 years
- Cigarette smoking history <10 pack years
- Study medication compliance <80% or >120% during placebo run-in period (recorded at Visit 2 and Visit 3)
- Level 2 or level 3 exacerbation of COPD within 6 weeks prior to visit 3
- Emergency room visit for treatment of COPD within 2 weeks prior to visit 1
- Exclusionary medication used more than 2 weeks for COPD exacerbation (does not include patients exceeding 6 weeks total exposure as described above)
- Exclusionary medication used for less than 2 weeks for indication other than COPD exacerbation
- Smoking within 2 hours of pulmonary function testing (at visit 3 or later)

7. COMPARISONS OF INTEREST

7.1. Primary Comparisons of Interest

There are two primary comparisons of interest. The first is to compare the difference in change from baseline in pre-bronchodilator FEV_1 between the cilomilast group and the placebo treatment group (cilomilast – placebo) averaged over all double-blind visits in the intent-to-treat population. The second is to compare the exacerbation rates (moderate or severe) during treatment period for cilomilast verses placebo. As statistical significance will be demonstrated for both primary endpoints, each of the primary comparisons will be performed at an alpha level of 0.05 without adjustment.

CONFIDENTIAL UC2003/00001/00
SB-207499/157

7.2. Other Comparisons of Interest

Time to first level 2 or levele 3 exacerbation during the treatment period will be compared between treatment groups, stratified for smokers/ex-smokers.

The exacerbation free curves will be compared between treatment groups, stratified for smokers/ex-smokers.

The incidence of all COPD exacerbations occurring during the treatment period will be compared between treatment groups, stratified for smokers/ex-smokers.

The difference in change from baseline in post-bronchodilator FEV_1 averaged over all double-blind visits will also be compared between the cilomilast group and the placebo treatment group (cilomilast – placebo), stratified for smokers/ex-smokers.

Additional comparisons between treatment groups, stratified for smokers/ex-smokers, will be made for FEV_1 (both pre-bronchodilator and post-bronchodilator) at Weeks 4, 8, 12, 20, 28, 36, 44, 52 and endpoint in the double-blind period, where the endpoint is defined as the last on therapy evaluation.

8. GENERAL CONSIDERATIONS FOR DATA ANALYSES

8.1. Pooling of Centers for Efficacy Analysis

Centers will be grouped by country.

8.2. Multiplicity

As both FEV_1 and exacerbation incidence are required to be positive in this study no multiplicity adjustment will be performed. The modified Bonferroni procedure of Hochberg[2] will be used to adjust for secondary endpoints. The procedure will use the p-values from the five secondary endpoints.

8.3. Sub-populations of Interest

For each of the co-primary endpoints, the following sub-populations of interest will be examined:

- Sex – [Males, Females]
- Percent Predicted FEV_1 – [<35% (severe), 35% to <50% (moderate), ≥50% (mild)]
- Smoking Status – There will be two sets of categories for smoking status.

[2] Hochberg Y. 1988. A sharper Bonferroni procedure for multiple tests of significance. Biometrika, 75, 800-802.

CONFIDENTIAL UC2003/00001/00
SB-207499/157

1. Three categories [Non-smoker throughout, Smoker throughout, Smoker changed to non-smoker during the study and vice versa]
2. Two categories [Non-smoker at baseline, Smoker at baseline]

In case there are discrepancies between the true smoking status recorded in CRF and one from RAMOS system, effort should be made to make sure the CRF is correct. The one recorded in the CRF will be used for analysis. If the number of discrepancies is large, analysis will be performed both ways for FEV_1 and exacerbation.

- Non-reversible patients – [patients with an absolute volume increase ≤200 ml regardless of their FEV_1 reversibility assessment or an absolute volume increase ≥200 ml with FEV_1 reversibility assessment ≤15% or after the administration of salbutamol 400 mcg via MDI at Visit 1 (Screening), complement of the above]

9. DATA HANDLING CONVENTIONS

9.1. Missing Data

Missing data arising from patients sporadically missing visits or assessments at visits will be assumed missing completely at random. No attempts will be made to assess the impact of missing data arising by this mechanism. Several analyses will be performed to assess the impact of missing data arising from patients withdrawing early from the study. In this regard withdrawals and completers will be characterized both demographically and with regard to baseline disease characteristics.

Analyses will also be performed to identify the pattern of dropouts and their impact on the assessment of FEV_1. The pattern of response will be displayed graphically over time for completers and for early withdrawals. A graphical display of response over time will also be displayed where the worst possible scores prior to withdrawal are imputed for patients who withdraw due to insufficient therapeutic effects for both treatment groups.

In addition, for patients who stop their study medication and continue to come to the scheduled visits, graphical display of response over time (from baseline to the last visit, regardless of scheduled or not) will be displayed to assess the withdrawal effects. Repeated measure analysis and ANOVA used for primary analysis will be used for all patients (regardless of withdrawal) and all visits (regardless of after withdrawal or not).

If evidence of informative censoring is observed then a pattern mixture model will be used to estimate the treatment effect[3].

Exacerbation data after withdrawal will be combined with on therapy data to analyze the level 2 and 3 exacerbation rate.

---

[3] LITTLE R.J.A., 1994. A Class of Pattern-Mixture Models for Normal Incomplete Data, Biometrika 81, 471-483.

CONFIDENTIAL UC2003/00001/00
SB-207499/157

9.2. Derived Data

9.2.1. Baseline and Endpoint

9.2.1.1. Baseline

In general the last non-missing evaluation prior to the first dose is defined as baseline. However there are some exceptions to this. For all efficacy variables except exacerbation, and SGRQ and EQ-5D, observations within 10 minutes post first dose are considered for baseline. For exacerbation there is no 10-minute window and for SGRQ and EQ-5D baseline is defined as the observation at baseline (Visit 3).

For ECG and vital signs, evaluations occurring within fifteen minutes post first dose of double-blind study medication will be considered for baseline.

For laboratory evaluations, only date is compared. Laboratory samples collected in association with Gastro-intestinal Adverse Events (GI AEs) of concern on the date of the randomisation visit or prior to the date of the randomisation visit will not be considered for baseline.

For Orthostatic Vital Sign Change, as date and time are not available, all measurements collected on or prior to Visit 3 will be considered for baseline.

9.2.1.2. Endpoint

Endpoint will be defined as the last non-missing on-therapy assessment collected for a patient regardless of the type of visit the assessment was collected at. For SGRQ, Endpoint will be defined as the assessment at the last on therapy visit no matter it is prior or post the last dose.

9.2.2. Duplicate or repeated observations

In cases where multiple observations are available or tests are repeated for a particular visit, the latest evaluation will be used in the analysis. If a latest evaluation can not reasonably be determined based on date and/or time then the average of the multiple evaluations will be taken.

9.2.3. Study Medication Record

9.2.3.1. Date of First Dose in the Double-blind Period

Date of first dose will be the earlier of the date provided in the study medication record and the date provided for the in-clinic dose at Visit 3.

9.2.3.2. Date of Last Dose in the Double-blind Period

Date of the last dose will be the later of the date provided in the study medication record, the date and time of the in-clinic dose at Visit 12 and the date provided on the study conclusion page of the case report form (CRF).

9.2.3.3. Exposure to Double-blind Study Medication

This will be calculated according to the following:

(date of last dose in the double-blind period) – (date of first dose in the double-blind period) + 1

Randomised patients whose date of first dose in the double-blind period is not available but is confirmed to have received a dose of double-blind study medication will have an assumed exposure of one day. Relative Day

(date of assessment/event) – (date of first dose) + 1

Note: for assessments and events occurring prior to the date of first dose of double-blind study medication, "1" will not be added when calculating the relative day.

9.2.4. Compliance

9.2.4.1. Number of Tablets Consumed

n(tablets dispensed) – n(tablets returned) – n(tablets lost)

9.2.4.2. Number of Days Between Visits

(date of current visit) – (date of previous visit)

9.2.4.3. Visit Level Compliance

$$\frac{100 * (\text{number of tablets consumed at a visit})}{2 * (\text{number of days between visits})}$$

9.2.4.4. Overall Compliance

$$\frac{100 * \sum(\text{number of tablets consumed at a visit})}{2 * \sum(\text{number of days between visits})}$$

9.2.5. Visit Dates

The date for each visit will be defined as the date the patient presented to the clinic. If this date is not available, the date that standard vital signs were recorded will be used.

9.2.6. Last Study Day

The last visit day regardless of withdrawal.

9.2.7. Prior, Concomitant and Post-therapy Medications

9.2.7.1. Prior Medications

Any medication used prior to the date of the first dose including those which continued beyond the date of first dose of double-blind study medication.

9.2.7.2. Concomitant Medications

Any medication initiated post the date of the first dose of double-blind study medication and prior to the last dose of double-blind study medication. Medications initiated prior to the date of the first dose of double-blind study medication and continued on or after the date of the first dose of double-blind study medication will also be considered concomitant.

9.2.7.3. Post-therapy Medications

Any medication initiated on or after the date of last dose of double-blind study medication. This does not include medications continuing from the double-blind period.

9.2.8. Pulmonary Function Tests (PFTs)

The flow loop with the highest FEV_1 value from a technically acceptable loop will be used as the best flow loop. Values of FVC, PEF and FEF_{25}-FEF_{75} will all be taken from the investigator determined best loop.

9.2.9. COPD Exacerbation

Only those exacerbations with an onset date on or after the first dose of double-blind study medication will be used in the analysis. For those exacerbations with an onset date on the date of first dose of double-blind study medication the onset time will be compared to the dosing time to determine if the event is on-therapy. If an onset time is not available the event will be classified as on-therapy. There are two types of censor in this study, censored by the end of double blind medication (no later than one day after the last dose of double-blind study medication) and by the last study day (defined in 9.2.7). A censored patient for an event will be defined as any patient for whom the event is not observed during the time period of interest. For patients who are censored, the time to event is defined as the total number of days of exposure to double-blind study medication or the number of days in study (visit clinic) depending on censor type used.

For the purpose of calculating the duration of an exacerbation with missing resolution date, duration will be defaulted to the difference of the onset day and last study day if the difference is less than two weeks. Otherwise the duration is defaulted to two weeks..

Duration of exacerbation on therapy is the number of days of exacerbation during the on therapy period.

9.2.10. Saint George's Respiratory Questions (SGRQ)

The SGRQ contains 76 weighted items grouped into three components, categorised as Symptoms, Activity and Impacts. Each component score will be calculated by summation of the weighted values within each category, dividing by the maximum possible score for that category and multiplying by 100. The total score will be calculated by aggregating the weighted scores from all 76 items and dividing by the maximum possible score for the SGRQ and multiplying by 100. This calculation is outlined in the developer's guide.

9.2.10.1. Treatment of Missing Values on SGRQ

If any questions in part 1 of the questionnaire (Symptoms Domain) are missed, then they will be treated as having a negative response (i.e. 0). Up to 20% of questions may be missed in part 2 of the questionnaire (Activity and Impacts domain). If more than 20% of questions are missing from a domain, then the domain total will be set to missing. This equates to no more than 3 missed questions for the activity domain and no more than 6 missed questions for the impact domain. If there are more than 10 missed items in the whole of part 2 of the questionnaire, then the total score will be set to missing. It is possible to have a domain total present with the total score missing.

Provided that fewer than 20% of questions are missing, they will be dealt with by using the denominator which is made up of the maximum possible weights for the non-missing questions.

9.2.10.2. Multiple Responses on SGRQ

If multiple responses are available for a particular item, the average weight for that item will used in the analysis.

9.2.11. EQ-5D and Indirect Cost

9.2.11.1. EQ-5D

EQ-5D (EuroQoL) has been designed as an international, generic instrument for describing and quantifying health related quality of life. Data collected in this study consists of 5 dimensions (mobility, self care, unusual activity, pain/discomfort, and anxiety/depression) and a thermometer score. Each dimension has three levels, level 0 (no problem), level 1 (some or moderate problems) and level 2 (unable or extreme problems) with scores 0 ,1 and 2 respectively. Each level of five dimensions contributed a component of a five digit number and the five digit number corresponds to a score. The score is missing if one of the five dimentions is missing. There are total 243 health states defined.

Valuations for the 243 health states defined by the EuroQoL classification have calculated using a regression model.The following formula and worked example indicate how these coefficients are to be used so as to compute the estimated values for each state.

Table 2 Calculating EuroQoL state valuations

EuroQoL dimension	Level 1 Coefficient	Level 2 Coefficient
Mobility	0.069	0.314
Self-care	0.104	0.214
Usual activity	0.036	0.094
Pain / discomfort	0.123	0.386
Anxiety / depression	0.071	0.236
	Constant = 0.081	N3 = 0.269

The arithmetic needed to recover the estimated value for any health state from this table of decrements is given by

1- sum(level(where level>0)*coefficient)-constant*[at least one level 1]-N3*[at least one level 2]

Where [] is an indicator function with value 0 or 1.

A worked example: taking health state 0 0 1 1 2 for mobility, self care, unusual activity, pain/discomfort, and anxiety/depression

Full health (0 0 0 0 0) = 1.0

Constant term for level 1 (for any dysfunctional state)(subtract 0.081)

Mobility.. level 0(subtract 0)

Self-care.. level 0(subtract 0)

Usual activity.. level 1 (subtract 0.036)

Pain / discomfort.. level 1 (subtract 0.123)

Anxiety / depression.. level 2 (subtract 0.236)

Level 2 occurs within at least 1 dimension(subtract N3 parameter 0.269)

Hence the estimated value for state 0 0 1 1 2 is given by

1.0 - 0.081 - 0.036 - 0.123 - 0.236 - 0.269 = **.255**

9.2.11.2. Indirect Cost

Indirect costs were collected as time missed from work or usual activities due to COPD exacerbation problems and caregiver assistance. Time missed from work or usual activities will be recorded as days and time receiving caregiver assistance will be recorded as average weekly hours.

9.2.12. Patient and Physician's global Assessments

Two new categories will be created, improvement and no improvement, as defined below,

Improvement = Very much improved, Much improved, Minimally improved

No improvement = No change, Minimally worse, Much worse,Very much worse

9.2.13. Diary Data

Several measures of efficacy will be derived from patient diary data. All diary symptom assessments will be recorded in the evening and based on observations over the course of the day. The Summary Symptom Score will be calculated as the sum of cough, breathlessness, sputum production - volumeand colour. If any of the four components are missing the Summary Symptom Score will also be set to missing.

The percentage of days symptom free is defined as the number of days during which the patient recorded no symptoms with respect to cough, sputum and breathlessness. A symptom free day equates to a Summary Symptom Score of 0. Percent of symptom-free days will be calculated as 100 times the number of days symptom free divided by the total number days for which complete symptom data is available. Complete symptom data for a specific day is defined as a non-missing summary symptom score.

Baseline for the diary measures will be defined as the average of all available data in the 14 days prior to Visit 3. The average over the 14 days immediately prior to the visit will be calculated for each patient and used as the representative score for that visit. Patients who have less than 10 days of diary data for a given visit will be excluded from the analysis for that visit. For percentage of symptom-free days the score used for analysis will be based on the percentage as calculated using all available days during the interval. Analyses will also be performed on the percent of days symptom-free during the entire double-blind period.

9.2.14. Adverse Events

9.2.14.1. Baseline Signs and Symptoms

Any event with an onset date prior to the initial dose of double-blind study medication.

9.2.14.2. On-therapy Adverse Events

Any event with an onset date on or after the date of first dose of double-blind study medication and prior to two days after the last dose of double-blind study medication. For events occurring on the date of initial dose of double-blind study medication, the time of dosing will be compared to the time of onset to determine if the event should be categorized into the on-therapy or run-in period. If an onset time is not available the event will be classified as on-therapy.

9.2.14.3. Post-therapy Adverse Event

A post-therapy adverse experience is defined as any event with an onset date at least two days after the last dose of study medication

9.2.14.4. Adverse Event Leading to Withdrawal

An adverse event leading to withdrawal is one where the "withdrawn" field in CRF is checked as "Yes".

9.2.14.5. Adverse Event with Missing Onset Date

Adverse events with a missing onset date will be assumed to onset on Day 1 of the double-blind period.

9.2.15. Electrocardiographs (ECGs) / Clinical Laboratories / Sitting Vital Signs / Orthostatic Vital Signs

9.2.15.1. On-therapy assessments

Any assessments performed after the first dose of double-blind study medication and no later than one day after the last dose of double-blind study medication. Visit 3 labs associated with GI AEs of concern will also be considered on-therapy.

9.2.15.2. Worst-case On-therapy Assessments

This is defined as the result with the highest concern level observed during the double-blind treatment period. Patients who are beyond the normal range in both the high and low direction during the double-blind period will be presented in both categories.

9.2.15.3. New-onset ECG Finding

An on-therapy finding that was not observed during the pre-therapy period (any of Visits 1, 2 or the Visit 3 assessments).

9.2.15.4. Calculation of Orthostatic Changes

The orthostatic change for a given vital sign measurement will be calculated as the difference between the measurement taken with legs dependent and the measurement taken in the supine position:

$$\text{Orthostatic Change} = \text{measurement}_{\text{dependent}} - \text{measurement}_{\text{supine}}$$

9.2.16. Values of Clinical Concern

This would be useful as fasting is optional.

Table 3 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 ULN - 1.2 x ULN]	> 1.2 x ULN
Hematocrit	<0.8 x LLN	[0.8 x LLN – 1 x LLN)	(1 x ULN - 1.2 x ULN]	> 1.2 x ULN
WBC	≤3.0 x 103/mm3	(3.0 x 103/mm3 – 1 x LLN)	(1 x ULN - 20.0 x $10^3/mm^3$)	≥ 20.0 x $10^3/mm^3$
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	not defined	not defined	(1 x ULN - 2 x ULN]	> 2 x ULN
Platelet Count	<100 x 109/L	[100 x 109/L – 1 x LLN)	(1 x ULN - 500 x 10^9/L]	> 500 x 10^9/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 ULN - 2.5 x ULN]	> 2.5 x ULN
Total Bilirubin	not defined	not defined	(1 x ULN - 1.5 x ULN]	> 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 ULN - 1.5 x ULN]	> 1.5 x ULN
BUN (SI Units)	not defined	not defined	(1 x ULN - 17.85 mmol/L]	> 17.85 mmol/L
BUN (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)	≤130 mmol/L	(130 mmol/L – 1 x LLN)	(ULN - 150 mmol/L)	≥ 150 mmol/L
Sodium (non-SI Units)	≤130 mEq/L	(130 mEq/L – 1 x LLN)	(ULN - 150 mEq/L)	≥ 150 mEq/L
Potassium (SI Units)	≤3.0 mmol/L	(3.0 mmol/L – 1 x LLN)	(ULN - 5.5 mmol/L)	≥ 5.5 mmol/L
Potassium (non-SI Units)	≤3.0 mEq/L	(3.0 mEq/L – 1 x LLN)	(ULN - 5.5 mEq/L)	≥ 5.5 mEq/L
Glucose (fasting / non-fasting)	<2.0 mmol/L	[2.0 mmol/L – 1 x LLN)	(ULN - 8.0 mmol/L]	> 8.0 mmol/L
Glucose (non-fasting)	<2.0 mmol/L	[2.0 mmol/L – 1 x LLN)	(ULN - 8.0 mmol/L]	> 8.0 mmol/L
Need Phil's input				
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 (y, [x – y) = value (x and < y, (x – y) = value > x and < y

Table 4 Vital Sign Values 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 ≥ 20 mm Hg
Orthostatic Change in Diastolic BP	not defined	not defined	not defined	decrease ≥ 10 mm Hg
Orthostatic Change in Heart Rate	not defined	not defined	not defined	increase of ≥ 10 bpm

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

Table 5 Electrocardiographic Values of Interest and Potential Clinical Concern

Parameter	Low Concern	Low	High	High Concern
QRS interval	not defined	not defined	120 – 199	≥ 200 msec
PR interval	not defined	not defined	200 – 249	≥ 250 msec
Atrial rate	(<50 bpm and 2 bpm lower than nadir from baseline) or (<45 bpm)	(45–<50 bpm and not less than 2 bpm nadir from baseline) or (50-55 bpm)	100 – 120 bpm	> 120 bpm
Ventricular rate	(<50 bpm and 2 bpm lower than nadir from baseline) or (<45 bpm)	(45–<50 bpm and not less than 2 bpm nadir from baseline) or (50-55 bpm)	430 – 450 msec (borderline, male); 450 – 470 msec (borderline, female)	> 450 msec (prolonged, male); >470 msec (prolonged, female)
QTc change from baseline	not defined		increase 30 – 60 msec	increase > 60 msec
QRS axis				Change from baseline by >±30 degrees, normal QRS axis at baseline (-30 to +90 degrees), and QRS interval at baseline <120msec

Need information from [redacted] to decide whether we need T-wave QT corrected by Bazett's formula.

10. STATISTICAL ANALYSIS

10.1. Patient Disposition, Baseline Characteristics and Demography

The distribution of time to withdrawal will be estimated using the Kaplan-Meier product limit estimate. Baseline and demographic characteristics will be summarized using frequencies and percents as well as descriptive statistics. No hypothesis testing will be

CONFIDENTIAL UC2003/00001/00
SB-207499/157

performed for treatment differences in patient baseline characteristics, demography or patient disposition.

Concomitant and prior medications, post-therapy medications and concomitant medications given for COPD exacerbations will be coded to generic terms using the GSK Drug dictionary. The number and percentage of patients will be summarized according to generic terms.

Patient compliance will be calculated at each visit. The number of patients below 80% and above 120% will be presented. Descriptive statistics will also be presented.

Changes in smoking status will be evaluated through a two-by-two contingency table classifying patients by their smoking status at baseline versus their status at a given visit.

10.2. Efficacy analysis

10.2.1. Analysis of Primary Efficacy Variables

All linear models to assess treatment effects for efficacy measures will be performed using SAS procedure MIXED. Centers within countries will be combined and used in the models.

10.2.1.1. Primary Analysis of FEV_1

The primary assessment of treatment differences for mean change from baseline in FEV_1 (pre-bronchodilator) averaged over 52 weeks will be based on a repeated measures model with fixed effects of treatment, time and country[4]. Time will be treated as a nominal variable in the analysis. A compound symmetric correlation structure will be used. Least squares means along with 95% confidence intervals will be calculated for each treatment group. Least squares means and 95% confidence intervals will also be calculated for the treatment difference. Differences between treatment groups will be assessed using t-tests on the least squares means.

10.2.1.2. Primary Analysis of Exacerbation Rate

The rate of a moderate or severe (level 2 or 3) COPD exacerbations occurring during the treatment period will be analyzed using a maximum likelihood based analysis, assuming a Poisson distribution, with total duration on treatment as an offset variable. The mean rate per patient year will be presented for each treatment.

[4] Jennrich RI and Schlucter. 1986. Unbalanced repeated measures models with structured covariance matrices. Biometrics, 42, 805-820.

10.2.1.3. Sensitivity Analysis to Access Impact on Primary Analysis

Sensitivity analyses will be performed for FEV_1 to evaluate the impact of treatment-by-time interaction, normality of the underlying data and covariance structure of the underlying data on the inference drawn from the above repeated model. Sensitivity analyses will also be performed for FEV_1 and exacerbation to evaluate the impacts of treatment-by-center interaction and covariates (age, sex, disease severity and smoking status),

Treatment by Time Interaction

Treatment-by-time interaction will be tested at a significance level of 0.10. The model for testing this interaction will have all effects specified in the primary model with the addition of the interaction term. If evidence for a treatment-by-time interaction is observed then a repeated measures analysis will be performed to estimate differences in the rate of change in FEV_1 between the two treatment groups. This model will include all effects described for the primary model as well as a treatment-by-time interaction term. Time will be treated as a continuous variable in this model. In addition, if the interaction occurs at the beginning of the study, the above repeated measure analysis will be performed on the latter visits.

Normality of Underlying Data

The normality assumption of trough FEV_1 will be explored through graphical examination of the residuals. The marginal residuals from each timepoint in the repeated measures analysis will be plotted in a normal probability plot.

Treatment by Country Interaction

The impact of treatment-by-country interaction will be explored for the primary analyses of the primary endpoints, FEV_1 and exacerbation If evidence of a qualitative treatment-by-country interaction is found, exploratory analyses will be undertaken to further describe the interaction and results will be presented by country. Treatment-by-country interaction will be tested at a significance level of 0.10.

10.2.2. Analysis of Secondary Efficacy Variables

Post-bronchodilator FEV_1 will be analyzed using the repeated measures model described above for pre-bronchodilator FEV_1. In addition to the repeated measures analysis, both pre-bronchodilator and post-bronchodilator FEV_1 will also be analyzed using an ANOVA model with fixed effects of treatment and country at each double-blind visit as well as at endpoint.

Time to the first moderate or severe COPD exacerbation (exacerbation-free curves) will be estimated using Kaplan-Meier product limit method. The exacerbation-free rate at 52 weeks, and associated 95% confidence intervals, will be estimated for each treatment group. A log-rank test will be performed using SAS PROC LIFETEST® to compare the two curves between cilomilast and placebo groups.

Same analyses will be performed for all level exacerbation.

Exacerbation will also be presented by exacerbation level.

Total score of SGRQ will be analyzed using an ANOVA model with fixed effects of treatment and country at each double-blind visit as well as at endpoint.

Treatment-by-country interaction terms and distribution assumptions will not be assessed for these endpoints.

10.2.3. Analysis of Tertiary Efficacy Variables

Change from baseline in FVC, PEF (clinic only) and FEF_{25-75} will be analyzed using the repeated measures model described above. All continuous variables (except ones mentioned below) will also be analyzed using an ANOVA model with fixed effects for treatment and country at each double-blind visit as well as at endpoint (based on change from baseline).

Use of relief medication, percentage of days with no need for rescue medication (salbutamol), number of nighttime awakenings and duration of exacerbation will be tabulated using descriptive statistics and analyzed using Wilcoxon rank sum test. All patients should be included in the analysis with 0 or 100% as valid values, for example, patient without exacerbation will have 0 duration.

Global subject assessment and global investigator assessment will be tabulated using contingency tables and improvement versus no improvement will be tested using chi square test.

10.2.4. Pharmacoeconomic Analysis

SGRQ sub scores, EQ-5D dimension score and thermometer score, and indirect cost will be analyzed the same way as the total SGRQ score (ANOVA).

Number of healthcare resource utilizations during the treatment period will be analyzed using a poisson regression model.

Mean days missed and assistance needed , mean days in study and their ratio will be displayed.

10.3. Safety Analysis

10.3.1. Adverse Experience

All adverse experiences in the double-blind period will be presented for both treatment groups by body system, severity level (mild, moderate and severe), time of initial onset and action taken. Time to onset will be assessed for AEs using a life-table analysis. This will be done for AEs with a 5% or greater incidence in the cilomilast group. In addition, the cumulative incidence of nausea, abdominal pain, diarrhea and vomiting by time will

be estimated using the Kaplan-Meier product limit estimate. This methodology will also be used to assess cumulative incidence of GI AEs of concern and DI AE body system. No formal statistical hypothesis testing will be performed for adverse experiences.

10.3.2. Clinical Laboratories

Descriptive statistics for blood chemistry and hematology by visit/week and treatment group will be provided. Transitions from baseline in blood chemistry and hematology parameters will be presented. The number and percent of patients with a concern will be presented by baseline concern category. A summary over the entire double-blind period will be performed using the "worst-case" for each patient. A summary will also be performed at endpoint for each patient. Endpoint will be defined as the last on-therapy evaluation. Fecal occult blood measurements will be summarized for all patients and separately for the population of patients with GI AEs of concern. The number and percentage of patients with positive results will be presented.

10.3.3. Vital Signs

Vital signs heart rate, systolic blood pressure and diastolic blood pressure will be summarized similarly as for clinical laboratory variables.

Orthostatic vital signs will be summarized as above for all patients and separately for the population of patients with GI AEs of concern.

10.3.4. Electrocardiographs

ECG variables atrial rate, ventricular rate, PR interval, QRS interval and aixs, uncorrected QT interval and corrected QT interval using Bazett formular (QTc) will be summarized the same as for clinical laboratory variables with the addition that new-onset ECG findings based on cardiologist interpretation of the tracings will be presented by SNOMED terminology.

Protocol	Centre Number	Patient Number
207499/157		[redacted]

CONFIDENTIAL

SmithKline Beecham
Pharmaceuticals

PROTOCOL 207499/157

GENERIC MODULE FOR PATIENTS WITHDRAWN FROM STUDY MEDICATION WHO ARE WILLING TO RETURN FOR ESSENTIAL ASSESSMENTS.

A RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL GROUP STUDY TO EVALUATE THE EFFICACY, SAFETY AND TOLERABILITY OF ORAL CILOMILAST (15 MG BID) WHEN GIVEN AS MAINTENANCE TREATMENT FOR 12 MONTHS TO SUBJECTS 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 and centre number on all pages 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 | *= 1st January 2001*
Day Month Year

TIME

Unless specified otherwise, please use the 24 hour clock

e.g. | 1 5 | 3 0 | *= 3.30 p.m*
24hr:min

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*

SCHEDULE OF ASSESSMENTS

Visit	1	2	3	4	5	6	7	8	9	10	11	12		13
	Screen		Base-line									End of DB	Early With-drawal	Follow -up
Time relative to baseline (weeks)[1]	-4	-2	0	+2	+4	+8	+12	+20	+28	+36	+44	+52		+53
Signed written informed consent	x													
Medical & surgical history	x													
Pulmonary symptoms	x													
Postero-anterior chest X-ray[2]	x													
Medication history including influenza vaccination[3]	x													
Health Status Assessments: SGRQ and EQ-5D			x						x			x	x	
Patient global assessment			x						x			x	x	
Investigator global assessment			x						x			x	x	
Physical examination [4]	x		x									x	x	x[5]
Smoking status	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Exacerbation assessment	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Resource utilisation				x	x	x	x	x	x	x	x	x	x	x
Diary Card Review		x	x	x	x	x	x	x	x	x	x	x	x	
Baseline signs and symptoms [6]	x	x	x											
Adverse experiences [6]				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
Study medication compliance		x	x	x	x	x	x	x	x	x	x	x	x	
Resting 12-lead ECG	x		x				x		x			x	x	x[5]
Vital signs (BP, HR)[7]	x[7]	x	x[7]	x	x	x	x[7]	x	x[7]	x	x	x[7]	x[7]	x
PFTs pre and post salbutamol: Pre-dose [8]	x		x		x	x	x	x	x	x	x	x	x	x
PFTs: salbutamol reversibility [9]	x		x											
PFTs: ipratropium reversibility		x												
Residual Volume (body box) pre-/ post-salbutamol Selected sites only			x						x			x	x	
Laboratory tests	x		x[10]		x	x	x	x	x	x	x	x[10]	x[10]	x[5]
Faecal occult blood test [11]	x	x										x	x	
Dispense single-blind med	x[12]	x[13]												
Dispense double-blind med			x[14]	x[13]	x[15]	x[15]	x[15]	x[15]	x[15]	x[15]	x[15]			
Study conclusion record														x[16]

1 All visit dates must be scheduled at the visit interval listed here using the Baseline visit as Day 0.
2 Chest X-ray to be taken at entry to the run-in period or in the 3 months prior to entry to the run-in period
3 Details of 'flu vaccinations will be recorded at every visit
4 Includes respiratory examination.
5 Only if abnormalities are present at Visit 12/Early Withdrawal.
6 Does not include COPD exacerbations
7 Orthostatic vital signs to be measured at Visits 1, 3, 7, 9, and 12
8 Includes FEV_1, FVC, FEF_{25-75} and PEF measured by spirometry by the same study personnel at each visit before dose of study medication is taken.
9 Includes FEV_1, FVC, FEF_{25-75} and PEF measured by spirometry by the same study personnel at each visit 30 minutes after administration of 400 mcg of salbutamol via MDI with or without a spacer, and before dose of study medication is taken.
10 Includes Blood CD4+/CD8+ ratio and serum C Reactive Protein
11 In addition to the usual laboratory tests, three faecal occult blood tests will be performed between Visits 1 and 3, at the end of the treatment period and at Early Withdrawal
12 Register the patient with RAMOS.
13 The container of study medication issued at the previous visit will be re-issued at this visit
14 Call RAMOS to randomise the patient and to obtain study medication assignment and container number.
15 Call RAMOS to obtain study medication container number(s)
16 Or earlier if the subject withdraws from the study prior to Visit 12.

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			
207499/157					

2 0 7 4 9 9 1 5 7

EASS

Please do not split modules

Module EASS : Generic module for patients withdrawn from study medication who are willing to return for essential assessments, Adverse Experiences, Concomitant Medications, Medical Procedures, COPD Exacerbations, Resource Utilisation

Please enter visit :

CRF Pages **EA1 - EA22**

Unprocessed Forms : **Within this module the following occur which will generate attachments that need to be brought in-house.**

None

FOR OFFICE USE ONLY Module Comments:

Sent to Data Mngt	Review Complete Date: User:	First Entry Complete Date: User:
Second Entry Complete Date: User:	Validation Complete Date: User:	**Clintrial PID:**

00000

SmithKline Beecham
Pharmaceuticals

Protocol	**Centre Number**	**Patient Number**		**Visit Date** Day Month Year	**Visit**
207499/157		[redacted]			

GENERIC MODULE FOR PATIENTS WITHDRAWN FROM STUDY MEDICATION WHO ARE WILLING TO RETURN FOR ESSENTIAL ASSESSMENTS.

PRESENTATION TO CLINIC

Note: ***Patients must wait for 4 hours after beta$_2$-agonist and / or anticholinergic administration before the pulmonary function tests are performed.***

Did the patient take a dose of beta$_2$ agonist in the past 24 hours?

☐ No

☐ Yes → Record date and time of the patient's last dose of beta$_2$ agonist: Day Month Yr 24hr:min

Did the patient take a dose of anticholinergic in the past 24 hours?

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: Day Month Yr 24hr:min

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes → Date and time of patient's last cigarette Day Month Yr 24hr:min

SMOKING STATUS

Does the patient currently smoke?

☐ No

☐ Yes → If 'Yes' please record the average number of cigarettes per day :

00000

SmithKline Beecham
Pharmaceuticals

Page	**EA2**

Protocol		**Patient Number**			**Visit**
207499/157		[redacted]			

RESOLUTION OF COPD EXACERBATIONS

Have any COPD Exacerbations resolved since the last visit?

☐ No

☐ Yes ⟶ *If 'Yes', please record details in the COPD Exacerbation section at the back of this module.*

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes ⟶ *If 'Yes' please record details in the COPD Exacerbation section at the back of this module.*

Level 1 (Mild-self treated): Acute worsening of COPD that is self-managed by the patient at home by increasing the dose of relief salbutamol medication by > 2 occasions/24 hour period on two or more consecutive days compared with their baseline (baseline = mean of last 10 days of run-in period) or use of other additional bronchodilator medication

Level 2 (Moderate- physician, investigator treated): Acute worsening of symptoms (cough, sputum production, breathlessness) requiring treatment with oral corticosteroids prescribed by a physician or primary care doctor, or as a result of hospital out-patient visit (including Emergency Room).

Exacerbations requiring oral corticosteroids will be treated with a standardised course of prednisolone or prednisone tablets 30mg/day for 10 days, or methylprednisolone tablets 24mg/day for 10 days.

Level 3 (Severe - attendance at hospital): Acute worsening of COPD that requires the patient to be admitted to hospital for treatment.

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, including an increase in usual COPD medications, must be recorded in the COPD Medications or Procedures pages.

00000

SmithKline Beecham
Pharmaceuticals

Page	**EA3**

Protocol **207499/157**		**Patient Number** [redacted]			**Visit**

RESOURCE UTILISATION

If the patient has received any COPD exacerbation-related medical care since the last visit, record details on the Resource Utilisation pages of the COPD Exacerbation section at the back of this module.

DIARY CARD REVIEW

Review the diary card in the presence of the patient. Question any increased symptoms for possible COPD exacerbations. Place diary in the plastic wallet at the back of this module and re-issue another diary card.

ADVERSE EXPERIENCES (RESPIRATORY AND GASTROINTESTINAL ONLY)

If there have been any gastrointestinal or respiratory 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 (RESPIRATORY AND GASTROINTESTINAL ONLY)

If there has been any change in the patient's concomitant medication for a gastrointestinal or respiratory indication (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.

00000

SmithKline Beecham
Pharmaceuticals

Protocol **207499/157**		**Patient Number** [redacted]			**Visit** ☐☐

INVESTIGATOR INSTRUCTIONS

The following procedures (Pulmonary Function Tests) must be performed greater than 4 hours after the patient's last salbutamol administration.

PRE-SALBUTAMOL PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed at least 4 hours after the last dose of inhaled beta$_2$-agonist or anticholinergic agent.

Measure the patient's pulmonary function up to eight times to obtain three acceptable readings using the spirometer provided by SB. ***(Note: Please follow instructions in the Spirometry Manual).*** *For each set of three FEV_1 measurements, one FEV_1 must be within 10% of the highest. Please record the results of the effort with the highest FEV_1 below.*

Measurement	Time	FEV_1 (L)	FVC (L)	FEF_{25-75} (L/sec)	PEF (L/min)
1	☐☐ 24hr:min	☐.☐☐	☐.☐☐	☐.☐☐	☐☐☐

Place the spirometry reports in the plasic wallet at the back of this module.

POST-SALBUTAMOL PULMONARY FUNCTION TESTS

Provide the patient with a salbutamol MDI and spacer. Administer 400 mcg (4 puffs) of salbutamol via MDI with a spacer. Remind the patient to use this inhaler (with or without the spacer), rather than any salbutamol inhaler they may have at home, for "as required" rescue-medication use during the study.

Record the time of salbutamol inhalation ☐☐ 24hr:min

Wait 30 minutes

Measure the patient's pulmonary function up to eight times to obtain three acceptable readings using the spirometer provided by SB. ***(Note: Please follow instructions in the Spirometry Manual).*** *For each set of three FEV_1 measurements, one FEV_1 must be within 10% of the highest. Please record the results of the effort with the highest FEV_1 below.*

Measurement	Time	FEV_1 (L)	FVC (L)	FEF_{25-75} (L/sec)	PEF (L/min)
1	☐☐ 24hr:min	☐.☐☐	☐.☐☐	☐.☐☐	☐☐☐

Place spirometry reports in the plastic wallets at the back of this module.

00000

SmithKline Beecham
Pharmaceuticals

Page	**EA5**

Protocol **207499/157**		**Patient Number** [redacted]			**Visit**

INSTRUCTIONS TO THE INVESTIGATOR

*If the patient is **not** willing to return for further essential assessment visits, please collect all diary cards and study salbutamol inhalers at this last visit.*

(tick if done)

*If the patient **is** willing to return for further essential assessment visits, please:* ☑

- *Issue the patient a new diary card and remind the patient to complete the card each morning.* ☐
- ***Remind the patient:***
  - i *to refrain from using salbutamol or anticholinergic agents during the **4 hours** immediately preceding the next visit.* ☐
  - ii *to refrain from smoking for **2 hours** immediately preceding the visit.* ☐
  - iii *to bring the study salbutamol inhaler and spacer, and the diary card.* ☐
  - iv *to continue to take the anticholinergic medication, if prescribed, at a constant dose, and salbutamol when needed to control symptoms.* ☐
  - v *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 occurrence.* ☐

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 study procedures should be reported as a serious event

IF AN 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

g_ae_instr_01

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			Adverse Experiences
207499/157		[redacted]			

ADVERSE EXPERIENCES *(RESPIRATORY AND GASTROINTESTINAL ONLY)(Non-serious)*

g_ae_01

*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 last visit?" 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).

☐ Please mark this box if no adverse experiences occurred since the last module

Adverse Experience *(please print clearly)*		
For SB		
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 SAE section and follow instructions given there***	[1] ☐ Resolved [2] ☐ Ongoing [3] ☐ Died	[1] ☐ Resolved [2] ☐ Ongoing [3] ☐ Died
Experience Course	[1] ☐ Intermittent → No. of episodes ☐ [2] ☐ Constant	[1] ☐ Intermittent → No. of episodes ☐ [2] ☐ Constant
Intensity (maximum)	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Action Taken with Respect to Investigational Drug	[1] ☐ None [2] ☐ Dose reduced [3] ☐ Dose increased [4] ☐ Drug interrupted/restarted [5] ☐ Drug stopped	[1] ☐ None [2] ☐ Dose reduced [3] ☐ Dose increased [4] ☐ Drug interrupted/restarted [5] ☐ Drug stopped
Relationship to Investigational Drug	[1] ☐ Not related [2] ☐ Unlikely [3] ☐ Suspected (reasonable possibility) [4] ☐ Probable	[1] ☐ Not related [2] ☐ Unlikely [3] ☐ Suspected (reasonable possibility) [4] ☐ Probable
Corrective Therapy *If 'Yes', record details in the Concomitant Medication section and/ or Medical Procedures section if appropriate*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No

SmithKline Beecham Pharmaceuticals

Protocol	Centre Number	Patient Number			Adverse Experiences
207499/157		[redacted]			

ADVERSE EXPERIENCES *(RESPIRATORY AND GASTROINTESTINAL ONLY)(Non-serious) - Continued*

*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 last visit?" 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

g_ae_01

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).

Adverse Experience *(please print clearly)*		
For SB		
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 SAE section and follow instructions given there***	[1] Resolved [2] Ongoing [3] Died	[1] Resolved [2] Ongoing [3] Died
Experience Course	[1] Intermittent → No. of episodes [2] Constant	[1] Intermittent → No. of episodes [2] Constant
Intensity (maximum)	[1] Mild [2] Moderate [3] Severe	[1] Mild [2] Moderate [3] Severe
Action Taken with Respect to Investigational Drug	[1] None [2] Dose reduced [3] Dose increased [4] Drug interrupted/restarted [5] Drug stopped	[1] None [2] Dose reduced [3] Dose increased [4] Drug interrupted/restarted [5] Drug stopped
Relationship to Investigational Drug	[1] Not related [2] Unlikely [3] Suspected (reasonable possibility) [4] Probable	[1] Not related [2] Unlikely [3] Suspected (reasonable possibility) [4] Probable
Corrective Therapy *If 'Yes', record details in the Concomitant Medication section and/ or Medical Procedures section if appropriate*	Yes No	Yes No
Was patient withdrawn due to this specific AE?	Yes No	Yes No

SmithKline Beecham Pharmaceuticals

Protocol	Centre Number	Patient Number			Adverse Experiences
207499/157		[redacted]			

ADVERSE EXPERIENCES *(RESPIRATORY AND GASTROINTESTINAL ONLY)(Non-serious) - Continued*

*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 last visit?" 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

g_ae_01

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).

Adverse Experience *(please print clearly)*		
For SB		
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 SAE section and follow instructions given there***	[1] Resolved [2] Ongoing [3] Died	[1] Resolved [2] Ongoing [3] Died
Experience Course	[1] Intermittent → No. of episodes [2] Constant	[1] Intermittent → No. of episodes [2] Constant
Intensity (maximum)	[1] Mild [2] Moderate [3] Severe	[1] Mild [2] Moderate [3] Severe
Action Taken with Respect to Investigational Drug	[1] None [2] Dose reduced [3] Dose increased [4] Drug interrupted/restarted [5] Drug stopped	[1] None [2] Dose reduced [3] Dose increased [4] Drug interrupted/restarted [5] Drug stopped
Relationship to Investigational Drug	[1] Not related [2] Unlikely [3] Suspected (reasonable possibility) [4] Probable	[1] Not related [2] Unlikely [3] Suspected (reasonable possibility) [4] Probable
Corrective Therapy *If 'Yes', record details in the Concomitant Medication section and/ or Medical Procedures section if appropriate*	Yes No	Yes No
Was patient withdrawn due to this specific AE?	Yes No	Yes No

00000

SmithKline Beecham
Pharmaceuticals

Protocol	**Centre Number**	**Patient Number**			**Concomitant Medication**
207499/157		[redacted]			

CONCOMITANT MEDICATION *(RESPIRATORY AND GASTROINTESTINAL ONLY)*

Record any changes in concomitant medication taken since the last 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. At the patient's final study visit, record the end date for prn study rescue medication (salbutamol) use, using the date the study inhaler was returned.

☐ No concomitant medication changes since the last module

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded in the Adverse Experiences 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** (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	
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							

** For Route, see general instructions for acceptable abbreviations.*

g_conmed_01

SmithKline Beecham
Pharmaceuticals

Protocol	**Centre Number**	**Patient Number**			**Concomitant Medication**
207499/157		[redacted]			

CONCOMITANT MEDICATION *(RESPIRATORY AND GASTROINTESTINAL ONLY)(Cont.)*

Record any changes in concomitant medication taken since the last 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. At the patient's final study visit, record the end date for prn study rescue medication (salbutamol) use, using the date the study inhaler was returned.

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	
For SB							
For SB							
For SB							
For SB							
For SB							
For SB							
For SB							
For SB							
For SB							

** For Route, see general instructions for acceptable abbreviations.*

g_conmed_01

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			Medical Procedures
207499/157		[redacted]			

MEDICAL PROCEDURES

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*

All indications for procedures should be recorded on the Baseline Signs and Symptoms Form.

Procedure	Indication	Procedure Start Date Day Mth Yr	Procedure End Date Day Mth Yr
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			COPD Exacerbations (AE)
207499/157		[redacted]			

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 last 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***

Has the patient suffered any COPD Exacerbations since the last module ?

☐ No

☐ Yes → *If 'Yes', please complete page below*

Adverse Event	COPD EXACERBATION
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, STOP: delete details of this exacerbation and go to SAE COPD Exacerbation pages.***	[1] ☐ Resolved [2] ☐ Ongoing [3] ☐ Died
Event Course	[1] ☐ Intermittent → No. of episodes ☐ [2] ☐ Constant
Intensity (maximum) *See definitions page for Adverse Experiences form.*	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Action Taken with Respect to Investigational Drug	[1] ☐ None [2] ☐ Dose reduced [3] ☐ Dose increased [4] ☐ Drug interrupted/restarted [5] ☐ Drug stopped
Relationship to Investigational Drug	[1] ☐ Not related [2] ☐ Unlikely [3] ☐ Suspected (reasonable possibility) [4] ☐ Probable
Corrective Therapy *If 'Yes', record details on the COPD Medications or Procedures page*	☐ Yes ☐ No
Was patient withdrawn due to this specific event?	☐ Yes ☐ No

DEFINITIONS OF LEVELS OF EXACERBATION OF COPD

Level 1 (Mild-self treated): Acute worsening of COPD that is self-managed by the patient at home by increasing the dose of relief salbutamol medication by > 2 occasions/24 hour period on two or more consecutive days compared with their baseline (baseline = mean of last 10 days of run-in period) or use of other additional bronchodilator medication

Level 2 (Moderate- physician, investigator treated): Acute worsening of symptoms (cough, sputum production, breathlessness) requiring treatment with oral corticosteroids prescribed by a physician or primary care doctor, or as a result of hospital out-patient visit (including Emergency Room).

Exacerbations requiring oral corticosteroids will be treated with a standardised course of prednisolone or prednisone tablets 30mg/day for 10 days, or methylprednisolone tablets 24mg/day for 10 days.

Level 3 (Severe - attendance at hospital): Acute worsening of COPD that requires the patient to be admitted to hospital for treatment.

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			COPD Exacerbations (AE)
207499/157		[redacted]			

FURTHER DETAILS OF COPD EXACERBATIONS

COPD exacerbation onset date : Day Month Yr

Level of exacerbation (see definitions on facing page):

[1] ☐ Level 1
[2] ☐ Level 2
[3] ☐ Level 3

Pumonary function test result (FEV_1) (if done):

☐.☐☐ L

Did the patient suffer from any of the following during the exacerbation:

[1] ☐ Chest pain
[2] ☐ Upper Respiratory Tract Infection
[3] ☐ Confusion
[4] ☐ Change in alertness
[5] ☐ Pneumonia
[6] ☐ Oedema
[7] ☐ Ankle swelling

ARTERIAL BLOOD GASES (only for COPD exacerbations)

Where feasible, an arterial blood gas sample is to be taken for analysis

COPD exacerbation onset date : Day Month Yr

PO_2 (mmHg)	**PCO_2** (mmHg)	**pH**	**Resting SaO_2** (%)
☐☐☐	☐☐	☐.☐☐	☐☐☐

RESOURCE UTILISATION

Please complete the Resource Utilisation pages for this exacerbation.

SmithKline Beecham Pharmaceuticals

Protocol	Centre Number	Patient Number			COPD Exacerbations (AE)
207499/157		[redacted]			

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 last 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 Event	COPD EXACERBATION
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, STOP: delete details of this exacerbation and go to SAE COPD Exacerbation pages.***	[1] ☐ Resolved [2] ☐ Ongoing [3] ☐ Died
Event Course	[1] ☐ Intermittent → No. of episodes ☐ [2] ☐ Constant
Intensity (maximum) *See definitions page for Adverse Experiences form.*	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Action Taken with Respect to Investigational Drug	[1] ☐ None [2] ☐ Dose reduced [3] ☐ Dose increased [4] ☐ Drug interrupted/restarted [5] ☐ Drug stopped
Relationship to Investigational Drug	[1] ☐ Not related [2] ☐ Unlikely [3] ☐ Suspected (reasonable possibility) [4] ☐ Probable
Corrective Therapy *If 'Yes', record details on the COPD Medications or Procedures page*	☐ Yes ☐ No
Was patient withdrawn due to this specific event?	☐ Yes ☐ No

DEFINITIONS OF LEVELS OF EXACERBATION OF COPD

Level 1 (Mild-self treated): Acute worsening of COPD that is self-managed by the patient at home by increasing the dose of relief salbutamol medication by > 2 occasions/24 hour period on two or more consecutive days compared with their baseline (baseline = mean of last 10 days of run-in period) or use of other additional bronchodilator medication

Level 2 (Moderate- physician, investigator treated): Acute worsening of symptoms (cough, sputum production, breathlessness) requiring treatment with oral corticosteroids prescribed by a physician or primary care doctor, or as a result of hospital out-patient visit (including Emergency Room).

Exacerbations requiring oral corticosteroids will be treated with a standardised course of prednisolone or prednisone tablets 30mg/day for 10 days, or methylprednisolone tablets 24mg/day for 10 days.

Level 3 (Severe - attendance at hospital): Acute worsening of COPD that requires the patient to be admitted to hospital for treatment.

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			COPD Exacerbations (AE)
207499/157		[redacted]			

FURTHER DETAILS OF COPD EXACERBATIONS

COPD exacerbation onset date : ☐☐ ☐☐☐ ☐☐ Day Month Yr

Level of exacerbation (see definitions on facing page):

[1] ☐ Level 1
[2] ☐ Level 2
[3] ☐ Level 3

Pumonary function test result (FEV_1) (if done):

☐.☐☐ L

Did the patient suffer from any of the following during the exacerbation:

[1] ☐ Chest pain
[2] ☐ Upper Respiratory Tract Infection
[3] ☐ Confusion
[4] ☐ Change in alertness
[5] ☐ Pneumonia
[6] ☐ Oedema
[7] ☐ Ankle swelling

ARTERIAL BLOOD GASES (only for COPD exacerbations)

Where feasible, an arterial blood gas sample is to be taken for analysis

COPD exacerbation onset date : ☐☐ ☐☐☐ ☐☐ Day Month Yr

PO_2 (mmHg)	**PCO_2** (mmHg)	**pH**	**Resting SaO_2** (%)
☐☐☐	☐☐	☐.☐☐	☐☐☐

RESOURCE UTILISATION

Please complete the Resource Utilisation pages for this exacerbation.

SmithKline Beecham Pharmaceuticals

Protocol	Centre Number	Patient Number		SB Receipt Date (Day Month Year)	COPD Exacerbations (SAE)
207499/157		[redacted]			

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation

Person Reporting SAE _____ *(Please print clearly)*

AEGIS Number _____ . _____

Serious Adverse Experience	**COPD Exacerbation**
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*	[1] ☐ Resolved [2] ☐ Ongoing [3] ☐ Died
Experience Course	[1] ☐ Intermittent → No. of episodes ☐ [2] ☐ Constant
Intensity *(maximum)*	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Action Taken with Respect to Investigational Drug	[1] ☐ None [2] ☐ Dose reduced [3] ☐ Dose increased [4] ☐ Drug interrupted/ restarted [5] ☐ Drug stopped
Relationship to Investigational Drug	[1] ☐ Not related [2] ☐ Unlikely [3] ☐ Suspected (reasonable possibility) [4] ☐ Probable
Corrective Therapy *If 'Yes', record details in the COPD Concomitant Medication section*	☐ Yes ☐ No
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No

→ *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

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 _____

00000

SmithKline Beecham
Pharmaceuticals

Protocol	**Centre Number**	**Patient Number**		**SB Receipt Date** Day Month Year	**COPD Exacerbations (SAE)**
207499/157		[redacted]			

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation

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 Number (please do NOT enter the container number): ☐☐☐☐☐

Investigator's Signature: _____ Date ☐☐ ☐☐☐ ☐☐☐☐
(confirming that the above data are accurate and complete) Day Month Year

Please PRINT Name _____

SB Medical Monitor's Signature: _____ Date ☐☐ ☐☐☐ ☐☐☐☐
Day Month Year

Please PRINT Name _____

DEFINITIONS OF LEVELS OF EXACERBATION OF COPD

Level 1 (Mild-self treated): Acute worsening of COPD that is self-managed by the patient at home by increasing the dose of relief salbutamol medication by > 2 occasions/24 hour period on two or more consecutive days compared with their baseline (baseline = mean of last 10 days of run-in period) or use of other additional bronchodilator medication

Level 2 (Moderate- physician, investigator treated): Acute worsening of symptoms (cough, sputum production, breathlessness) requiring treatment with oral corticosteroids prescribed by a physician or primary care doctor, or as a result of hospital out-patient visit (including Emergency Room).

Exacerbations requiring oral corticosteroids will be treated with a standardised course of prednisolone or prednisone tablets 30mg/day for 10 days, or methylprednisolone tablets 24mg/day for 10 days.

Level 3 (Severe - attendance at hospital): Acute worsening of COPD that requires the patient to be admitted to hospital for treatment.

00000

SmithKline Beecham
Pharmaceuticals

Protocol	**Centre Number**	**Patient Number**		**SB Receipt Date** Day Month Year	**COPD Exacerbations (SAE)**
207499/157		[redacted]			

FURTHER DETAILS OF SERIOUS COPD EXACERBATIONS

COPD exacerbation onset date : Day Month Yr

Level of exacerbation (see definitions on facing page):

[1] ☐ Level 1
[2] ☐ Level 2
[3] ☐ Level 3

Pumonary function test result (FEV_1) (if done):

☐.☐☐ L

Did the patient suffer from any of the following during the exacerbation:

[1] ☐ Chest pain
[2] ☐ Upper Respiratory Tract Infection
[3] ☐ Confusion
[4] ☐ Change in alertness
[5] ☐ Pneumonia
[6] ☐ Oedema
[7] ☐ Ankle swelling

ARTERIAL BLOOD GASES (only for serious COPD exacerbations)

Where feasible, an arterial blood gas sample is to be taken for analysis

COPD exacerbation onset date : Day Month Yr

PO_2 (mmHg)	**PCO_2** (mmHg)	**pH**	**Resting SaO_2** (%)
☐☐☐	☐☐	☐.☐☐	☐☐☐

RESOURCE UTILISATION

Please complete the Resource Utilisation pages for this exacerbation.

00000

SmithKline Beecham
Pharmaceuticals

Protocol	**Centre Number**	**Patient Number**			**COPD Exacerbations (ConMed)**
207499/157		[redacted]			

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)	**Freq.** (eg bd, prn)	**Route***	**Medical Illness/ Diag.**	**Start Date** *(be as precise as possible)* Day Mth Yr	**End Date** *(or if Continuing mark box)* Day Mth Yr	☐	COPD Exacerbation Onset Date
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								

** For Route, see General Instructions for acceptable abbreviations.*

SmithKline Beecham
Pharmaceuticals

Protocol	**Centre Number**	**Patient Number**			**COPD Exacerbations (ConMed)**
207499/157		[redacted]			

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** Day Mth Yr	**Procedure End Date** Day Mth Yr	COPD Exacerbation Onset Date
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				

SmithKline Beecham
Pharmaceuticals

Protocol	**Centre Number**	**Patient Number**			**Resource Utilisation For COPD Exacerbations**
207499/157		[redacted]			

RESOURCE UTILISATION FOR COPD EXACERBATIONS

Has the patient had any medical care for COPD Exacerbations that have occurred since the previous module?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below*

Has the patient had any **Physician contact** (COPD care excluding scheduled protocol visits) since the previous module?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below*

Date of Contact Day Mth Yr	Telephone	Home Visit		Office/ Practice	Out-patients	Reason for contact	COPD Exacerbation Onset Date Day Mth Yr
		Day	Night				

Has the patient had any **Emergency Room (ER)/Urgent Care Visits/Procedures (i.e., lung surgery)** since the previous module?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below*

Date of Contact Day Mth Yr	**Reason for contact**	**Patient Admitted from ER?**		COPD Exacerbation Onset Date Day Mth Yr
		Yes	**No**	

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			Resource Utilisation For COPD Exacerbations
207499/157		[redacted]			

RESOURCE UTILISATION FOR COPD EXACERBATIONS - (cont)

Has the patient had any **Hospitalisations** since the previous module?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below* ***(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	COPD Exacerbation Onset Date Day Mth Yr

Has the patient had any **Intensive Care Unit (ICU) stays** ***(did the patient stay in the ICU during any of the above hospitalisations?)*** since the previous module?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below*

Date Admitted to ICU Day Mth Yr	Date Discharged from ICU Day Mth Yr	Reason for ICU Admission	COPD Exacerbation Onset Date Day Mth Yr

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			
207499/157					

2 0 7 4 9 9 1 5 7

SAEEA

Please do not split modules

Module : **Serious Adverse Experiences**

CRF Pages **EA23 -EA24**

Unprocessed Forms : **Within this module the following occur which will generate attachments that need to be brought in-house.**

None

FOR OFFICE USE ONLY Module Comments:

Sent to Data Mngt	Review Complete Date: User:	First Entry Complete Date: User:
Second Entry Complete Date: User:	Validation Complete Date: User:	**Clintrial PID:**

REPORTING SERIOUS ADVERSE EXPERIENCES (SAE)

INSTRUCTIONS

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

g_sae_instr_01

00000

SmithKline Beecham
Pharmaceuticals

Protocol	**Centre Number**	**Patient Number**		**SB Receipt Date** Day Month Year	**Serious Adverse Experiences**
207499/157		[redacted]			

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
[1] ☐ Resolved
[2] ☐ Ongoing
[3] ☐ Died

Experience Course
[1] ☐ Intermittent — No. of episodes ☐
[2] ☐ Constant

Intensity *(maximum)*
[1] ☐ Mild
[2] ☐ Moderate
[3] ☐ Severe

Action Taken with Respect to Investigational Drug
[1] ☐ None
[2] ☐ Dose reduced
[3] ☐ Dose increased
[4] ☐ Drug interrupted restarted
[5] ☐ 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
[1] ☐ Not related
[2] ☐ Unlikely
[3] ☐ Suspected (reasonable possibility)
[4] ☐ 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

g_sae_01

00000

SmithKline Beecham Pharmaceuticals

Protocol	Centre Number	Patient Number		SB Receipt Date (Day Month Year)	Serious Adverse Experiences
207499/157		[redacted]			

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 Number (please do NOT enter the container number): ☐☐☐☐☐

Investigator's Signature: _____ Date ☐☐ ☐☐ ☐☐☐☐
(confirming that the above data are accurate and complete) Day Month Year

Please PRINT Name _____

SB Medical Monitor's Signature: _____ Date ☐☐ ☐☐ ☐☐☐☐

Please PRINT Name _____ Day Month Year

g_sae_01

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number		Investigator
207499/157		[redacted]		_ _

CRF TRACKING/REVIEW FORM (TRF) (EA BOOK)

Please submit COMPLETE modules only. Do not submit whole blank modules.

☐ Screening Failure (archive only)

- *Mark the **Unused** box for all remaining modules that will **not** be completed and sent in-house*
- *Ensure the Missing Pages field is completed if pages are missing from modules*
- *Ensure the Patient Numbers entered match the information on the CRF*
- *Complete one TRF per batch of modules to be sent in-house*
- *Ensure all sections of the TRF are legible*

Module	Module Description	Page Range	Modules		Missing pages (if applicable)
			Sent to DM	Unused	
EASS	EA Visit, AE, CM, MP, COPD, RU Visit ☐☐	EA1 - EA22	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
PFTEA	Essential Assess. PFT printout	n/a	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
SAEEA	Serious Adverse Experiences	EA23 - EA24	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
FORMD	Form D	n/a	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _

If multiple modules are submitted together, please ensure they are sorted according to the order above

Site Monitor's Name _ *(Print clearly)*

Site Monitor's Signature _ **Date Submitted** ☐☐ ☐☐☐ ☐☐
Day Month Yr

g_trf_01

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number		Investigator
207499/157		[redacted]		_____

CRF TRACKING/REVIEW FORM (TRF) (EA BOOK)

Site Monitor's comments (eg. protocol violations or deviations)

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

Site Monitor's Name _____ *(Print clearly)*

Site Monitor's Signature _____ **Date Submitted** Day Month Yr

g_trf_01

SmithKline Beecham
Pharmaceuticals

Protocol **207499/157**		**Patient Number** [redacted]			**Visit 1 Screening**

CASE REPORT FORM VERSION CHECK

Was the patient randomised to this study under Protocol Amendment 2 (Approved 14-Aug-02)?

☐ No

☐ Yes

DEMOGRAPHY

Date of Birth ☐☐ ☐☐ ☐☐☐☐ (Day Month Year)

Race

[1] ☐ White

[2] ☐ Black

[3] ☐ Oriental

[4] ☐ Other → *specify:* _ _ _ _ _ _ _ _ _ _ _ _ _ _ _

Gender

[M] ☐ Male

[F] ☐ Female

g_demog_01

Protocol		Patient Number			Visit 1 Screening
207499/157		[redacted]			

POST-SALBUTAMOL PULMONARY FUNCTION TESTS

Provide the patient with a salbutamol MDI and spacer. Administer 400 mcg (4 puffs) of salbutamol via MDI with a spacer. Remind the patient to use this inhaler (with or without the spacer), rather than any salbutamol inhaler they may have at home, for "as required" rescue-medication use during the study. ***Record the start date for this prn salbutamol use in the Prior and Concomitant medication section.***

Record the time of salbutamol inhalation ☐☐ 24hr:min

Wait 30 minutes

Measure the patient's pulmonary function up to eight times to obtain three acceptable readings using the spirometer provided by SB. ***(Note: Please follow instructions in the Spirometry Manual).*** *For each set of three FEV_1 measurements, one FEV_1 must be within 10% of the highest. Please record the results of the effort with the highest FEV_1 below.*

Measurement	Time	FEV_1 (L)	FVC (L)	FEF_{25-75} (L/sec)	PEF (L/min)
1	☐☐ 24hr:min	☐.☐☐	☐.☐☐	☐.☐☐	☐☐☐

Reversibility = $\frac{\text{Highest post-salbutamol } FEV_1 - \text{Highest pre-salbutamol } FEV_1}{\text{Predicted normal } FEV_1} \times 100$

☐☐ (% reversibility to salbutamol)

Does the patient have an increase in FEV_1 of ≤ 10% relative to predicted normal and/or ≤ 200ml after administration of salbutamol?

☐ No → *If 'No' please withdraw the patient and* ***complete the Study Continuation / Withdrawal page*** *at the back of this book.*

☐ Yes

Is the patient's post-salbutamol FEV_1 30% to 70% (inclusive) of predicted normal for height, age and gender?

☐ No → *If 'No' please withdraw the patient and* ***complete the Study Continuation / Withdrawal page*** *at the back of this book.*

☐ Yes

Place spirometry reports in the plastic wallets at the back of this book.

SmithKline Beecham
Pharmaceuticals

Protocol 207499/157		Patient Number [redacted]			Visit 1 Screening

INCLUSION CRITERIA

Complete the following inclusion criteria.

	Yes	No
1. Male or female adults between 40 and 80 years of age (inclusive). ***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®) for at least 1 month prior to Visit 1 (Screening) and should continue using the same contraceptive measure during the study.*	☐	☐
2. Subjects with a clinical diagnosis of COPD, as defined by GOLD guidelines. (A diagnosis of COPD should be considered in any patient who has symptoms of cough, sputum production, or dyspnoea, and/or a history of exposure to risk factors for the disease. The diagnosis is confirmed by spirometry. The presence of a post-bronchodilator FEV_1 < 80% of the predicted value in combination with an FEV_1/FVC <70% confirms the presence of airflow limitation that is not fully reversible).	☐	☐
3. Subjects with a smoking history of ≥ 10 pack years (1 pack year = 20 cigarettes smoked per day for 1 year or equivalent). Ex-smokers are eligible to enter the study provided they have at least 10 pack years smoking history.	☐	☐
4. Subjects with a pre-bronchodilator FEV_1 to FVC ratio (FEV_1:FVC) ≤ 0.7 at Visit 1.	☐	☐
5A. Subjects with poor reversibility of airways obstruction, defined by an increase of ≤ 10% in FEV_1 relative to predicted normal or ≤ 200ml (or both) after the administration of salbutamol 400mg via MDI at Visit 1 (Screening).	☐	☐
6. Subjects with a post-salbutamol FEV_1 of ≥ 30% and ≤ 70% of predicted normal for height, age and gender at Visit 1.	☐	☐
7. Subjects who are willing and able to complete a Daily Record Card (DRC) and use a peak expiratory flow meter satisfactorily.	☐	☐
8. Subjects who give their signed and dated written informed consent to participate.	☐	☐
9. Subjects who, in the opinion of the Investigator, are not at risk of severe or life-threatening exacerbations of COPD and will be able to stop all COPD medications apart from short-acting anti-cholinergics and salbutamol from Visit 1.	☐	☐

Do not admit the patient to this study if any "NO" box has been marked.

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 1

	(tick if done)
• *If the patient is not continuing in the study, please **complete the Study Continuation/ Withdrawal page** at the back of this book.*	
• *If the patient is continuing in the study, please:*	☑
• *Issue the patient with a diary card and remind the patient to complete the diary card each morning and to bring the diary card with them to the next visit.*	☐
• *Demonstrate how to measure peak flow using the miniWright Peak Flow Meter. Issue the patient a miniWright peak flow meter with instructions to measure peak flow each morning and to record details in the diary card.*	☐
• *Issue the patient with the faecal occult blood test kit. Instruct the patient to follow the Patient Instructions provided with the kit. In particular, patients are not to collect samples during or until 3 days after a menstrual period or while they have bleeding hemorrhoids or blood in the urine. In addition, patients are not to take aspirin or other non-steroidal anti-inflammatory drugs for 7 days prior to and during the test period, and they are 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. Samples should be collected as specified and returned by the next visit if possible.*	☐
• *Ask the patient to return for the next visit in 14 + / - 3 days at the same time of day.*	☐
• ***Remind the patient:***	
i *__not__ to take their dose of study medication for at least 8 hours prior to their next study visit appointment.*	☐
ii *to refrain from using salbutamol or anticholinergic agents during the **8 hours** immediately preceding the next visit.*	☐
iii *to refrain from smoking for **2 hours** immediately preceding the visit.*	☐
iv *to bring any remaining study medication or study medication containers, the study salbutamol inhaler and spacer, and the diary card, with them to the next visit.*	☐
v *to continue to take the anticholinergic medication, if prescribed, at a constant dose, and salbutamol when needed to control symptoms.*	☐
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 occurrence.*	☐

Protocol		Patient Number			Visit 2 Single-blind Run-in Week -2
207499/157		[redacted]			

PRE-IPRATROPIUM PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed at least 8 hours after the last dose of inhaled beta$_2$-agonists or anticholinergic agent.

Measure the patient's pulmonary function up to eight times to obtain three acceptable readings using the spirometer provided by SB. ***(Note: Please follow instructions in the Spirometry Manual).*** *For each set of three FEV_1 measurements, one FEV_1 must be within 10% of the highest. Please record the results of the effort with the highest FEV_1 below.*

Measurement	Time	FEV_1 (L)	FVC (L)	FEF_{25-75} (L/sec)	PEF (L/min)
1	☐☐ 24hr:min	☐.☐☐	☐.☐☐	☐.☐☐	☐☐☐

Has the patient's absolute value of FEV_1 increased or decreased by > 20% between Visits 1 and 2?

☐ No

☐ Yes

Place the spirometry reports in the plasic wallet at the back of this book.

POST-IPRATROPIUM PULMONARY FUNCTION TESTS

Provide the patient with an ipratropium MDI and spacer. Administer 80 mcg (2 puffs) of ipratropium via MDI with a spacer.

Record the time of ipratropium inhalation : ☐☐ 24hr:min

Wait for 30 minutes.

Measure the patient's pulmonary function up to 8 times to obtain 3 acceptable readings using the spirometer provided by SB (note - please follow instructions in the Spirometry Manual). For each set of 3 FEV_1 measurements, 1 FEV_1 must be within 10% of the highest. Please record the results of the effort with the highest FEV_1 below.

Measurement	Time	FEV_1 (L)	FVC (L)	FEF_{25-75} (L/sec)	PEF (L/min)
1	☐☐ 24hr:min	☐.☐☐	☐.☐☐	☐.☐☐	☐☐☐

$$\text{Reversibility} = \frac{\text{Highest post-ipratropium } FEV_1 - \text{Highest pre-ipratropium } FEV_1}{\text{Highest pre-ipratropium } FEV_1} \times 100$$

☐☐ (% reversibility to ipratropium)

Place the spirometry reports in the plasic wallet at the back of this book.

Protocol 207499/157		Patient Number [redacted]			Visit 2 Single-blind Run-in Week -2

STUDY MEDICATION RE-ISSUE

Re-issue the container of **single-blind study medication** returned at this visit and a salbutamol MDI and spacer for 'as required' use if applicable (remind the patient to use this inhaler rather than any salbutamol inhaler they may have at home). The morning dose of study medication should be taken at this visit in the clinic with food. Remind the patient that each day they must take one tablet in the morning immediately after breakfast and one tablet immediately after their evening meal.

Record the start date in the Study Medication Record section and number of tablets re-dispensed in the Study Medication Compliance section of the next visit.

Date and time visit dose was taken ☐☐ ☐☐ ☐☐ ☐☐ ☐☐
Day Month Yr 24hr:min

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 2

	(tick if done)
• *If the patient is not continuing in the study, please **complete the Study Continuation/ Withdrawal page** at the back of this book.*	
• *If the patient is continuing in the study, please:*	☑
• *Re-issue the patient's diary card and remind the patient to complete the diary each morning until the next visit.*	☐
• *Ask the patient to return for the next visit in 14 +/- 3 days at the same time of day.*	☐
• ***Remind the patient:***	
i ***not** to take their dose of study medication for at least 8 hours prior to their next study visit appointment.*	☐
ii *to refrain from using salbutamol or anticholinergic agents during the **4 hours** immediately preceding the next visit.*	☐
iii *to refrain from smoking for **2 hours** immediately preceding the visit.*	☐
iv *to bring any remaining study medication or study medication containers, the study salbutamol inhaler and spacer, and the diary card.*	☐
v *to continue to take the anticholinergic medication, if prescribed, at a constant dose, and salbutamol when needed to control symptoms.*	☐
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 occurrence.*	☐
vii *to complete the faecal occult blood test(s) by the next visit if not already done.*	☐

Protocol		Patient Number			Visit 3 Baseline
207499/157		[redacted]			

PRE-SALBUTAMOL PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed at least 4 hours after the last dose of inhaled beta$_2$-agonist or anticholinergic agent.

NOTE: If the patient is eligible to be randomised, additional pulmonary function tests will be performed 30 minutes after a dose of study salbutamol is given in the clinic AND prior to the first dose of randomised study medication.

Measure the patient's pulmonary function up to eight times to obtain three acceptable readings using the spirometer provided by SB. ***(Note: Please follow instructions in the Spirometry Manual).*** *For each set of three FEV$_1$ measurements, one FEV$_1$ must be within 10% of the highest. Please record the results of the effort with the highest FEV$_1$ below.*

Measurement	Time	FEV$_1$ (L)	FVC (L)	FEF$_{25-75}$ (L/sec)	PEF (L/min)
1	☐☐ 24hr:min	☐.☐☐	☐.☐☐	☐.☐☐	☐☐☐

Place the spirometry reports in the plasic wallet at the back of this book.

POST-SALBUTAMOL PULMONARY FUNCTION TESTS

Provide the patient with a salbutamol MDI and spacer. Administer 400 mcg (4 puffs) of salbutamol via MDI with a spacer. Remind the patient to use this inhaler (with or without the spacer), rather than any salbutamol inhaler they may have at home, for "as required" rescue-medication use during the study. ***Record the start date for this prn salbutamol use in the Prior and Concomitant medication section.***

Record the time of salbutamol inhalation ☐☐ 24hr:min

Wait 30 minutes

Measure the patient's pulmonary function up to eight times to obtain three acceptable readings using the spirometer provided by SB. ***(Note: Please follow instructions in the Spirometry Manual).*** *For each set of three FEV$_1$ measurements, one FEV$_1$ must be within 10% of the highest. Please record the results of the effort with the highest FEV$_1$ below.*

Measurement	Time	FEV$_1$ (L)	FVC (L)	FEF$_{25-75}$ (L/sec)	PEF (L/min)
1	☐☐ 24hr:min	☐.☐☐	☐.☐☐	☐.☐☐	☐☐☐

Reversibility = $\frac{\text{Highest post-salbutamol FEV}_1 - \text{Highest pre-salbutamol FEV}_1}{\text{Predicted normal FEV}_1} \times 100$

☐☐ (% reversibility to salbutamol)

Does the patient have an increase in FEV$_1$ of ≤ 10% relative to predicted normal and/or ≤ 200ml after administration of salbutamol?

☐ No ⟶ *If 'No' please withdraw the patient and* ***complete the Study Continuation / Withdrawal page*** *at the back of this book.*

☐ Yes

Place spirometry reports in the plastic wallets at the back of this book.

Protocol Amendment 2, Approved 14-Aug-02

Protocol		Patient Number			Visit 3 Baseline
207499/157		[redacted]			

(AT SELECTED CENTRES ONLY) RESIDUAL VOLUME BY BODY PLETHYSMOGRAPHY (PRE- AND POST-SALBUTAMOL)

Time of pre-salbutamol RV assessment: ☐☐ 24hr:min

Time of post-salbutamol RV assessment: ☐☐ 24hr:min

Pre-Salbutamol

$RV_{Box} = TLC_{Box} – max(|SVC|, |FVC|)$

$RV_{(Box)}$ = ☐.☐☐ (L)

Post-Salbutamol

$RV_{Box} = TLC_{Box} – max(|SVC|, |FVC|)$

$RV_{(Box)}$ = ☐.☐☐ (L)

Please attach plethysmography source data to the back of this page.

ADDITIONAL INCLUSION CRITERIA

Complete the following inclusion criteria.	**Yes**	**No**
1A. Subjects with poor reversibility of airways obstruction, defined by an increase of ≤ 10% in FEV_1 relative to predicted normal or ≤ 200ml (or both) after the administration of salbutamol 400mcg via MDI at Visit 3.	☐	☐
2A. Less than 20% change (increase or decrease) in pre-bronchodilator FEV_1 between Visit 2 and Baseline (Visit 3).	☐	☐
3. Between 80-120% compliance in taking single-blind study medication during the run-in.	☐	☐

Do not admit the patient to this study if any "NO" box has been marked

If any 'No' box has been marked, please withdraw the patient and ***complete the Study Continuation/Withdrawal page*** *at the back of this book.*

ADDITIONAL EXCLUSION CRITERIA

Complete the following exclusion criteria.	**Yes**	**No**
1. Patient has had any changes to their COPD medication (other than 'as required' use of salbutamol), received corticosteroids (oral or inhaled) for respiratory disease, or hospitalised for COPD/lower respiratory tract infections during the run-in period.	☐	☐
2. Patient is receiving any other medication during the run-in period which in the opinion of the investigator, is judged as likely to affect baseline assessments.	☐	☐
3. The patient has had a positive faecal occult blood test result between Visit 1 and 3.	☐	☐

Do not admit the patient to this study if any "YES" box has been marked

If any 'Yes' box has been marked, please withdraw the patient and ***complete the Study Continuation/Withdrawal page*** *at the back of this book.*

00000

SmithKline Beecham
Pharmaceuticals

Protocol **207499/157**		**Patient Number** [redacted]			**Visit 3 Baseline**

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 3

Is the patient continuing in the study?

☐ No ⟶ *Go to '1' below.*

☐ Yes ⟶ *Go to '2' below.*

1. If the patient is not continuing in the study, is the patient willing to return for scheduled visits?

*If 'No', please **complete the Study Continuation/Withdrawal page** at the back of this book and record the date of last dose on the Study Conclusion record.*

If 'Yes', please ask the patient to return for the next visit in 14 (+/-2) days time for essential assessments.

(tick if done)

2. If the patient is continuing in the study, please : ☑

- *Issue the patient a new diary card and remind the patient to complete the card each morning.* ☐
- *Ask the patient to return for Visit 4 in 14 +/- 2 days at the same time of day.* ☐
- ***Remind the patient:***
  - i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after their breakfast.* ☐
  - ii ***not** to take their dose of study medication for at least 8 hours prior to their next study visit appointment.* ☐
  - iii *to refrain from using salbutamol or anticholinergic agents during the **4 hours** immediately preceding 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, the study salbutamol inhaler and spacer, and the diary card.* ☐
  - vi *to continue to take the anticholinergic medication, if prescribed, at a constant dose, and salbutamol when needed to control symptoms.* ☐
  - vii *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 occurrence.* ☐

Protocol	Centre Number	Patient Number
207499/157		[redacted]

CONFIDENTIAL

SmithKline Beecham
Pharmaceuticals

PROTOCOL 207499/157

BOOK 1 : SCREENING TO RANDOMISATION

A RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL GROUP STUDY TO EVALUATE THE EFFICACY, SAFETY AND TOLERABILITY OF ORAL CILOMILAST (15 MG BD) WHEN GIVEN AS MAINTENANCE TREATMENT FOR 12 MONTHS TO SUBJECTS 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 and centre number on all pages 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 | *= 1st January 2001*
Day Month Year

TIME

Unless specified otherwise, please use the 24 hour clock

e.g. | 1 5 | 3 0 | *= 3.30 p.m*
24hr:min

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*

SCHEDULE OF ASSESSMENTS

Visit	1	2	3	4	5	6	7	8	9	10	11	12		13
	Screen		Base-line									End of DB	Early With-drawal	Follow -up
Time relative to baseline (weeks)	-4	-2	0	+2	+4	+8	+12	+20	+28	+36	+44	+52		+53
Signed written informed consent	x													
Medical & surgical history	x													
Pulmonary symptoms	x													
Postero-anterior chest X-ray[1]	x													
Medication history including influenza vaccination	x[15]													
Health Status Assessments: SGRQ and EQ-5D			x						x			x	x	
Patient global assessment			x						x			x	x	
Investigator global assessment			x						x			x	x	
Physical examination [2]	x		x									x	x	x[8]
Smoking status	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Exacerbation assessment	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Resource utilisation				x	x	x	x	x	x	x	x	x	x	x
Diary Card Review		x	x	x	x	x	x	x	x	x	x	x	x	
Baseline signs and symptoms [3]	x	x	x											
Adverse experiences [3]				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
Study medication compliance		x	x	x	x	x	x	x	x	x	x	x	x	
Resting 12-lead ECG	x		x				x		x			x	x	x[8]
Vital signs (BP, HR)[4]	x[4]	x	x[4]	x	x	x	x[4]	x	x[4]	x	x	x[4]	x[4]	x
PFTs pre and post salbutamol: Pre-dose [5]	x		x		x	x	x	x	x	x	x	x	x	x
PFTs: salbutamol reversibility [6]	x													
PFTs: ipratropium reversibility		x												
Residual Volume (body box) pre-/ post-salbutamol Selected sites only			x						x			x	x	
Laboratory tests	x		x[7]		x	x	x	x	x	x	x	x[7]	x[7]	x[8]
Faecal occult blood test	x[14]	x[14]	x[14]									x[14]	x[14]	
Dispense single-blind med	x[9]	x[10]												
Dispense double-blind med			x[11]	x[10]	x[12]	x[12]	x[12]	x[12]	x[12]	x[12]	x[12]			
Study conclusion record														x[13]

1 Chest X-ray to be taken at entry to the run-in period or in the 3 months prior to entry to the run-in period

2 Includes respiratory examination.

3 Does not include COPD exacerbations

4 Orthostatic vital signs to be measured at Visits 1, 3, 7, 9, and 12

5 Includes FEV1, FVC, FEF25-75, PEF measured by spirometry by the same study personnel at each visit before dose of study medication is taken.

6 Includes FEV1, FVC, FEF25-75, measured by spirometry by the same study personnel at each visit 30 minutes after administration of 400 mcg of salbutamol via MDI with or without a spacer, and before dose of study medication is taken.

7 Includes Blood CD4+/CD8+ ratio and serum protein C

8 Only if abnormalities are present at Visit 12.

9 Register the patient with RAMOS.

10 The container of study medication issued at the previous visit will be re-issued at this visit

11 Call RAMOS to randomise the patient and to obtain study medication assignment and container number.

12 Call RAMOS to obtain study medication container number(s)

13 Or earlier if the subject withdraws from the study prior to Visit 12.

14 In addition to the usual laboratory tests, three faecal occult blood tests will be performed between Visits 1 and 3, at the end of the treatment period or at early withdrawal.

15 Influenza vaccination status will be reviewed at every visit.

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			
207499/157		[redacted]			

2 0 7 4 9 9 1 5 7

MOD1

Please do not split modules

Module 1 : **Visit 1 Screening**

CRF Pages **1 - 15**

Unprocessed Forms : **Within this module the following occur which will generate attachments that need to be brought in-house.**

None

FOR OFFICE USE ONLY Module Comments:

Sent to Data Mngt	Review Complete Date: User:	First Entry Complete Date: User:
Second Entry Complete Date: User:	Validation Complete Date: User:	**Clintrial PID:**

CIGARETTE CONVERSION TABLE

Cigarettes	Cigars	Tobacco
35 cigs/wk for 40 yrs	5 cigars/wk for 40 yrs	33gms of tobacco/wk for 40 yrs
53cigs/wk for 30 yrs	7-8 cigars/wk for 30 yrs	57gms of tobacco/wk for 30 yrs
70cigs/wk for 20 yrs	10 cigars/wk for 20 yrs	65gms of tobacco/wk for 20 yrs
105cigs/wk for 15 yrs	15 cigars/wk for 15 yrs	98gms of tobacco/wk for 15 yrs
140cigs/wk for 10 yrs	20 cigars/wk for 10 yrs	130gms of tobacco/wk for 10 yrs
280cigs/wk for 5 yrs	40 cigars/wk for 5 yrs	260gms of tobacco/wk for 5 yrs

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number		Visit Date (Day Month Year)	
207499/157		[redacted]			Visit 1 Screening

PRESENTATION TO CLINIC

Note: ***Patients must wait for 8 hours after beta$_2$-agonist and / or anticholinergic administration before the pulmonary function tests are performed.***

Did the patient take a dose of beta$_2$ agonist in the past 24 hours?

☐ No

☐ Yes → Record date and time of the patient's last dose of beta$_2$ agonist: Day Month Yr 24hr:min

Did the patient take a dose of anticholinergic in the past 24 hours?

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: Day Month Yr 24hr:min

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes → Date and time of patient's last cigarette Day Month Yr 24hr:min

SMOKING STATUS

Does the patient currently smoke?

☐ No → *If 'No'*, has the patient previously smoked cigarettes?

☐ No → *If 'No' please withdraw the patient and **complete the Study Continuation / Withdrawal page** at the back of this book.*

☐ Yes

☐ Yes → *If 'Yes', please record the average number of cigarettes per day:* ☐☐

For pipe and cigar smokers, please use the conversion table on the facing page.

CIGARETTE SMOKING HISTORY

Please enter number of pack years * ☐☐☐.☐

** The number of pack years is calculated as follows :*

$$\frac{\text{Average number of cigarettes smoked per day}}{20} \times \text{number of years smoked}$$

Note: The patient must have a smoking history of ≥ 10 pack years to be eligible for the study.

00000

SmithKline Beecham
Pharmaceuticals

Protocol 207499/157		**Patient Number** [redacted]			**Visit 1 Screening**

DEMOGRAPHY

Date of Birth Day Month Year

Race
[1] ☐ White
[2] ☐ Black
[3] ☐ Oriental
[4] ☐ Other → *specify:* _ _ _ _ _ _ _ _ _ _ _ _ _ _ _

Gender
[M] ☐ Male
[F] ☐ Female

g_demog_01

EXAMPLE SIGNIFICANT MEDICAL/SURGICAL HISTORY AND PHYSICAL EXAMINATION
(INCLUDING RESPIRATORY EXAMINATION)

Is the subject suffering from or has he/she ever suffered from any **significant** medical or surgical condition?

☐ No

☑ Yes ⟶ If 'Yes' , please list below one diagnosis per line. (Please print clearly)

Note: COPD has been entered below for your convenience. Please complete year of diagnosis.

Only in the absence of a diagnosis, record the signs and symptoms on separate lines.

Diagnosis	Year of first diagnosis (if known)	Past+Ongoing= [3]	
		Past [1]	**Ongoing** [2]
CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)	1996	☐	☑
For SB			
SINUSITIS	1987	☑	☐
For SB			

00000

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number			Visit 1 Screening
207499/157		[redacted]			

SIGNIFICANT MEDICAL/SURGICAL HISTORY AND PHYSICAL EXAMINATION
(INCLUDING RESPIRATORY EXAMINATION)

Is the subject suffering from or has he/she ever suffered from any **significant** medical or surgical condition?

☐ No

☑ Yes ⟶ If 'Yes' , please list below one diagnosis per line. (Please print clearly)

Note: COPD has been entered below for your convenience. Please complete year of diagnosis.

Only in the absence of a diagnosis, record the signs and symptoms on separate lines.

Diagnosis	Year of first diagnosis (if known)	Past+Ongoing= [3] Past [1]	Past+Ongoing= [3] Ongoing [2]
CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)	☐☐☐☐	☐	☑
For SB			
	☐☐☐☐	☐	☐
For SB			
	☐☐☐☐	☐	☐
For SB			
	☐☐☐☐	☐	☐
For SB			
	☐☐☐☐	☐	☐
For SB			
	☐☐☐☐	☐	☐
For SB			
	☐☐☐☐	☐	☐
For SB			

g_sig_med_phys_ex_po_01

00000

SmithKline Beecham
Pharmaceuticals

Protocol 207499/157		Patient Number [redacted]			Visit 1 Screening

SIGNIFICANT MEDICAL/SURGICAL HISTORY AND PHYSICAL EXAMINATION (cont)

Only in the absence of a diagnosis, record the signs and symptoms on separate lines.		Past+Ongoing= [3]	
Diagnosis	**Year of first diagnosis (if known)**	**Past** [1]	**Ongoing** [2]
	☐☐☐☐	☐	☐
For SB			
	☐☐☐☐	☐	☐
For SB			
	☐☐☐☐	☐	☐
For SB			
	☐☐☐☐	☐	☐
For SB			
	☐☐☐☐	☐	☐
For SB			
	☐☐☐☐	☐	☐
For SB			
	☐☐☐☐	☐	☐
For SB			
	☐☐☐☐	☐	☐
For SB			
	☐☐☐☐	☐	☐
For SB			

g_sig_med_phys_ex_po_01

PROHIBITED MEDICATION

The following medications for respiratory disease are not permitted during the study and should have been withdrawn prior to or at Visit 1 :

Medication Class	Examples of Trade Names *(this is not a complete list)*
Inhaled corticosteroids	Aerobid®, Azmacort®, Flovent®, Pulmicort®, Vanceril®
Oral corticosteroids	prednisone, Medrol®, Decadron®, Sterapred®
Combination of inhaled short-acting beta$_2$-agonists & anticholinergics	Combivent®, Duovent®
Selected short-acting inhaled beta$_2$-agonists	All **except** Ventolin®
Long-acting inhaled beta$_2$-agonists	Serevent®, Foradil
Oral beta$_2$-agonists	Ventolin®, Volmax®, Bricanyl®
Nebulized beta$_2$-agonists	salbutamol, metaproterenol, Alupent®, Isuprel®, Ventolin®
Nebulized anticholinergics	Atrovent®
Inhaled cromolyn sodium	Intal®
Inhaled nedocromil	Tilade®
Oral xanthines	Slo-Bid®, Theo-Dur®
Leukotriene modifiers	Accolate®, Singulair®
Long-term oxygen therapy (LTOT)*	N/A
Mucolytics (carbocysteine)	Mucodyne®

* Several puffs of supplemental oxygen after exercise testing or when clinically indicated, at the investigator's discretion, would be acceptable. However, daily or prolonged use of supplemental oxygen is **not** permitted.

In addition, patients must not have used oral corticosteroids in the four weeks prior to Visit 1.

Any patient using non-permitted medication other than for COPD exacerbations between Visits 1 and 10 must be withdrawn from the study after consultation with the Medical Monitor. Theophylline is not permitted at any time.

EXAMPLE PRIOR AND CONCOMITANT MEDICATION

If the patient is taking 2 puffs (100mcg per puff) twice a day, record as below.

Drug Name (Trade Name preferred)	**Unit Dose** (e.g. 500mg)	**Frequency** (e.g. bd, 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	
TRADE NAME HERE	***200mcg***	***bd***	***IH***	***COPD***	15 JUN 00		✓
For SB							

00000

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number			Visit 1 Screening
207499/157		[redacted]			

PRIOR AND CONCOMITANT MEDICATION

Has the patient taken:
- medication for COPD (including inhalers) in the last 3 months?

AND/OR
- any other medication in the 2 weeks prior to study entry?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below (Please print clearly)*

*Medical indications recorded here **must** correlate with either:*
- diagnoses (or symptoms) listed in the Significant Medical/Surgical History and Physical Examination section OR
*- a documented baseline sign and symptom **or** adverse experience prior to receiving double-blind or active medication*
and must be expressed using the same terminology.

Drug Name *(Trade Name Preferred)*	**Unit Dose** (e.g. 500mg)	**Frequency** (e.g. bd, 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	
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							

** For Route, see General Instructions for acceptable abbreviations.*

g_prior_conmed_01

Protocol		Patient Number			Visit 1 Screening
207499/157		[redacted]			

PRIOR AND CONCOMITANT MEDICATION - Continued

Medical illness/diagnosis recorded here must correlate with conditions listed on the Significant Medical / Surgical History and Physical Examination page and must be expressed using the same terminology.

Drug Name *(Trade Name Preferred)*	**Unit Dose** (e.g. 500mg)	**Frequency** (e.g. bd, 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	
For SB							
For SB							
For SB							
For SB							
For SB							
For SB							
For SB							
For SB							
For SB							
For SB							
For SB							

** For Route, see General Instructions for acceptable abbreviations.*

g_prior_conmed_01

SmithKline Beecham
Pharmaceuticals

Protocol		**Patient Number**			**Visit 1 Screening**
207499/157		[redacted]			

AVERAGE ALCOHOL INTAKE

Number of units per week ☐☐

Note : A unit of alcohol is defined as 250 mL of beer (half a pint), 125 mL of wine (a medium-sized glass) or 24mL of spirits (a single measure).

CHEST X-RAY

Perform a postero-anterior (PA) chest X-ray (unless one has been performed in the previous 3 months and the film is available to the investigator) to exclude the possibility of any abnormalities that may mimic or co-exist with COPD (e.g. pneumothorax, bronchial carcinoma, active pulmonary TB). The results must be available by Visit 3.

Date performed ☐☐☐☐☐☐
Day Month Yr

Please mark appropriate box below:

[1] ☐ Normal - **within normal limits for COPD patients**

[2] ☐ Abnormal - *please record any clinically significant abnormalities* ***not related to diagnosis of COPD*** *on the Significant Medical/Surgical History and Physical Examination page.*

INFLUENZA VACCINATION

Has the patient had a vaccination for influenza during the past 12 months?

N.B. It is not necessary to record vaccinations on the Concomitant Medication or Medical Procedures page.

☐ No

☐ Yes ⟶ *If 'Yes', record date of most recent vaccination :* ☐☐☐☐☐☐
Day Month Yr

00000

SmithKline Beecham
Pharmaceuticals

Protocol		**Patient Number**			**Visit 1 Screening**
207499/157		[redacted]			

PULMONARY HISTORY

1. Has the patient had chronic bronchitis ? (i.e. had a chronic productive cough for at least 3 months in each of 2 successive years)

   ☐ No

   ☐ Yes ⟶ *If 'Yes' record details on the Significant Medical/Surgical History and Physical Examination page.*

2. Has the patient had previous lung reduction surgery for COPD ?

   ☐ No

   ☐ Yes ⟶ *If 'Yes' record details on the Significant Medical/Surgical History and Physical Examination page.*

3. Has the patient participated in a Pulmonary Rehabilitation Program in the 4 weeks prior to this visit, or is planning to enter a program during the study ?

   ☐ No

   ☐ Yes ⟶ *If 'Yes' please withdraw the patient and **complete the Study Continuation / Withdrawal page** at the back of this book.*

4. Has the patient experienced any COPD exacerbations in the last 2 weeks that were managed by self-treatment with corticosteroids, that required treatment to be prescribed by a physician, or for which the patient was hospitalised?

   ☐ No

   ☐ Yes ⟶ *If 'Yes' please withdraw the patient and **complete the Study Continuation / Withdrawal page** at the back of this book.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number			Visit 1 Screening
207499/157		[redacted]			

INVESTIGATOR INSTRUCTIONS

The following procedures (Vital Signs, ECG and Pulmonary Function Tests) must be performed greater than 8 hours after the patient's last salbutamol administration.

VITAL SIGNS

Time of assessment : ☐☐ 24hr:min

Height (cm)	Weight (kg) (light clothes, no shoes)	After Sitting for 5 Minutes	
		Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
☐☐☐.☐	☐☐☐.☐	☐☐☐/☐☐☐	☐☐☐

Were any clinically significant abnormalities noted?

☐ No

☐ Yes ⟶ *Record on the Significant Medical/Surgical History and Physical Examination page*

VITAL SIGNS - ORTHOSTATIC CHANGE

Time of assessment : ☐☐ 24hr:min

1st Measurement: After 5 Minutes Supine		2nd Measurement: 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)
☐☐☐/☐☐☐	☐☐☐	☐☐☐/☐☐☐	☐☐☐

At the second measurement (i.e. after sitting with Legs Dependent for 1 minute) does the patient have a decrease of ≥ 20 mmHg in systolic blood pressure **or** a decrease of ≥10 mmHg in diastolic blood pressure **or** an increase of ≥ 20 beats/min in heart rate?

☐ No

☐ Yes⟶ *If 'Yes' withdraw the patient and **complete the Study Continuation / Withdrawal page** at the back of this book. The primary cause of withdrawal should be 'Does not meet inclusion exclusion criteria'.*

00000

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number			Visit 1 Screening
207499/157		[redacted]			

12 LEAD ELECTROCARDIOGRAM

Time of assessment : ☐☐ 24hr:min **The ECG should be performed after the patient has been semi-supine for 5 minutes**

Date ECG Performed (Day Month Year)	Atrial Rate (beats/min)	Ventricular Rate (beats/min)	PR (msec)	QRS (msec)	☐ Uncorrected QT ☐ Corrected QT (msec)	Axis
☐☐☐☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐ + ☐ - ☐☐☐

Interpretation

☐ **(F74301) Within normal limits**

☐ **Abnormal** ⟶ ***Mark appropriate boxes below***

Rhythm
- ☐ (F73360) Sinus arrhythmia
- ☐ (F73310) Sinus bradycardia
- ☐ (F73380) Sinus tachycardia
- ☐ (F73440) Wandering atrial pacemaker
- ☐ (F73450) Premature atrial contractions
- ☐ (F73510) Paroxysmal atrial tachycardia
- ☐ (F73530) Chronic ectopic atrial tachycardia
- ☐ (F73550) Multifocal atrial tachycardia
- ☐ (F73560) Atrial flutter
- ☐ (F73570) Atrial fibrillation
- ☐ (F73610) Junctional (AV nodal) premature contractions
- ☐ (F73650) Junctional (AV nodal) tachycardia
- ☐ (F73150) Supraventricular tachycardia
- ☐ (F73860) Accelerated idioventricular rhythm
- ☐ (F73710) Premature Ventricular Contractions (NOS)
- ☐ (F73720) Unifocal PVC's
- ☐ (F73730) Multifocal PVC's
- ☐ (F73711) Ventricular couplets
- ☐ (F73750) Bigeminy
- ☐ (F73870) Ventricular tachycardia
- ☐ (F73880) Ventricular fibrillation
- ☐ (F73340) Sick sinus syndrome
- ☐ (F73190) Pacemaker rhythm

P-Wave Morphology
- ☐ (F74214) Left atrial hypertrophy, P mitrale
- ☐ (F74213) Right atrial hypertrophy, P pulmonale

Conduction
- ☐ (F73930) First degree AV block
- ☐ (F73950) Second degree AV block, Type 1
- ☐ (F73960) Second degree AV block, Type 11
- ☐ (F73970) Third degree AV block
- ☐ (F74090) Wolff-Parkinson-White syndrome

Axis
- ☐ (F74120) Right Axis deviation
- ☐ (F74130) Left Axis deviation

QRS
- ☐ (F74010) Right bundle branch block
- ☐ (F74020) Left bundle branch block
- ☐ (F74030) Left anterior hemiblock
- ☐ (F74040) Left posterior hemiblock
- ☐ (F74002) Intraventricular conduction delay
- ☐ (F74212) Left ventricular hypertrophy
- ☐ (F74211) Right ventricular hypertrophy
- ☐ (F74308) Q-wave > 0.04 sec
- ☐ (F74222) R-wave amplitude increased
- ☐ (F74225) R-wave amplitude decreased
- ☐ (F74313) Prolonged QT-interval
- ☐ (F74318) Poor R-wave progression
- ☐ (M54750) Myocardial infarction, old
  - ☐ (M54751) Anterior ☐ (M54754) Inferior
  - ☐ (M54752) Lateral ☐ (M54755) Septal
  - ☐ (M54753) Posterior

ST-T
- ☐ (F74291) Nonspecific ST-T changes
- ☐ (F74294) ST segment depression > 1 mm
- ☐ (F74295) ST segment elevation > 1 mm
- ☐ (F74350) T-wave flat
- ☐ (F74351) T-wave inversion
- ☐ (F74352) T-wave peaked
- ☐ (F74340) U-wave
- ☐ (F74360) Digitalis effect
- ☐ (F74260) Myocardial ischemia
  - ☐ (F74261) Anterior ☐ (F74264) Inferior
  - ☐ (F74262) Lateral ☐ (F74265) Septal
  - ☐ (F74263) Posterior
- ☐ (M54720) Myocardial infarction, acute
  - ☐ (M54721) Anterior ☐ (M54724) Inferior
  - ☐ (M54722) Lateral ☐ (M54725) Septal
  - ☐ (M54723) Posterior

Other interpretations not listed _

Were any clinically significant abnormalities noted at this examination?

[1] ☐ Normal

[2] ☐ Abnromal ⟶ *If 'Abnormal', enter details on the Significant Medical/Surgical History and Physical Examination page.*

Place the ECG trace in the plastic wallet a the back of this module Page amended 05/11/01

Protocol		Patient Number			Visit 1 Screening
207499/157		[redacted]			

PRE-SALBUTAMOL PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed at least 8 hours after the last dose of inhaled beta$_2$-agonist or anticholinergic agent.

Measure the patient's pulmonary function up to eight times to obtain three acceptable readings using the spirometer provided by SB. ***(Note: Please follow instructions in the Spirometry Manual).*** *For each set of three FEV_1 measurements, one FEV_1 must be within 10% of the highest. Please record the results of the effort with the highest FEV_1 below.*

Measurement	Time	FEV_1 (L)	FVC (L)	FEF_{25-75} (L/sec)	PEF (L/min)
1	24hr:min	.	.	.	

Is the patient's pre-salbutamol FEV_1 to FVC ratio (FEV_1:FVC) ≤ 0.7 ?

☐ No ⟶ *If 'No' please withdraw the patient and* ***complete the Study Continuation / Withdrawal page*** *at the back of this book.*

☐ Yes ⟶ *If 'Yes' continue with the Post-salbutamol Pulmonary Function Tests.*

Place the spirometry reports in the plasic wallet at the back of this book.

Protocol		Patient Number			Visit 1 Screening
207499/157		[redacted]			

POST-SALBUTAMOL PULMONARY FUNCTION TESTS

Provide the patient with a salbutamol MDI and spacer. Administer 400 mcg (4 puffs) of salbutamol via MDI with a spacer. Remind the patient to use this inhaler (with or without the spacer), rather than any salbutamol inhaler they may have at home, for "as required" rescue-medication use during the study. ***Record the start date for this prn salbutamol use in the Prior and Concomitant medication section.***

Record the time of salbutamol inhalation ☐☐ 24hr:min

Wait 30 minutes

Measure the patient's pulmonary function up to eight times to obtain three acceptable readings using the spirometer provided by SB. ***(Note: Please follow instructions in the Spirometry Manual).*** *For each set of three FEV_1 measurements, one FEV_1 must be within 10% of the highest. Please record the results of the effort with the highest FEV_1 below.*

Measurement	Time	FEV_1 (L)	FVC (L)	FEF_{25-75} (L/sec)	PEF (L/min)
1	☐☐ 24hr:min	☐.☐☐	☐.☐☐	☐.☐☐	☐☐☐

Reversibility = $\frac{\text{Highest post-salbutamol } FEV_1 - \text{Highest pre-salbutamol } FEV_1}{\text{Highest pre-salbutamol } FEV_1} \times 100$

☐☐ (% reversibility to salbutamol)

Does the patient have a ≤ 15% and/or ≤ 200ml increase in FEV_1 after administration of salbutamol?

☐ No ⟶ *If 'No' please withdraw the patient and* ***complete the Study Continuation / Withdrawal page*** *at the back of this book.*

☐ Yes

Is the patient's post-salbutamol FEV_1 30% to 70% (inclusive) of predicted normal for height, age and gender?

☐ No ⟶ *If 'No' please withdraw the patient and* ***complete the Study Continuation / Withdrawal page*** *at the back of this book.*

☐ Yes

Place spirometry reports in the plastic wallets at the back of this book.

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number			Visit 1 Screening
207499/157		[redacted]			

INCLUSION CRITERIA

Complete the following inclusion criteria.

	Yes	No
1. Male or female adults between 40 and 80 years of age (inclusive). ***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®) for at least 1 month prior to Visit 1 (Screening) and should continue using the same contraceptive measure during the study.*	☐	☐
2. Subjects with a clinical diagnosis of COPD, as defined by GOLD guidelines. (A diagnosis of COPD should be considered in any patient who has symptoms of cough, sputum production, or dyspnoea, and/or a history of exposure to risk factors for the disease. The diagnosis is confirmed by spirometry. The presence of a post-bronchodilator FEV_1 < 80% of the predicted value in combination with an FEV_1/FVC <70% confirms the presence of airflow limitation that is not fully reversible).	☐	☐
3. Subjects with a smoking history of ≥ 10 pack years (1 pack year = 20 cigarettes smoked per day for 1 year or equivalent). Ex-smokers are eligible to enter the study provided they have at least 10 pack years smoking history.	☐	☐
4. Subjects with a pre-bronchodilator FEV_1 to FVC ratio (FEV_1:FVC) ≤ 0.7 at Visit 1.	☐	☐
5. Subjects with poor reversibility of airway obstruction, defined by ≤15% or ≤200 ml (or both) increase in FEV_1 after the administration of salbutamol 400 mcg via MDI at Visit 1 (Screening).	☐	☐
6. Subjects with a post-salbutamol FEV_1 of ≥ 30% and ≤ 70% of predicted normal for height, age and gender at Visit 1.	☐	☐
7. Subjects who are willing and able to complete a Daily Record Card (DRC) and use a peak expiratory flow meter satisfactorily.	☐	☐
8. Subjects who give their signed and dated written informed consent to participate.	☐	☐
9. Subjects who, in the opinion of the Investigator, are not at risk of severe or life-threatening exacerbations of COPD and will be able to stop all COPD medications apart from short-acting anti-cholinergics and salbutamol from Visit 1.	☐	☐

Do not admit the patient to this study if any "NO" box has been marked.

SmithKline Beecham
Pharmaceuticals

Protocol 207499/157		Patient Number [redacted]			Visit 1 Screening

EXCLUSION CRITERIA

Complete the following exclusion criteria.	**Yes**	**No**
1. Women who are pregnant or lactating.	☐	☐
2. Patients with asthma as the main component of their obstructive airways disease.	☐	☐
3. Subjects with poorly controlled COPD, defined as the occurrence of a Level 2 or Level 3 exacerbation of COPD, or a hospitalisation or emergency room visit for the treatment of COPD or patients who self-medicate with oral corticosteroids in the 2 weeks prior to Visit 1.	☐	☐
4. Subjects with a diagnosis or suspicion of sleep apnoea.	☐	☐
5. Subjects with known active tuberculosis, lung cancer, clinically overt bronchiectasis, or other known specific pulmonary disease.	☐	☐
6. Subjects with sinusitis which in the investigator's opinion may interfere with the study objectives.	☐	☐
7. Subjects with a chest X-ray indicating diagnosis other than COPD that might interfere with the study (chest X-ray to be taken at entry to the run-in period or in the 3 months prior to entry to the run-in period).	☐	☐
8. Subjects with clinically significant cardiovascular, neurological, renal, endocrine, gastrointestinal, hepatic or haematological abnormalities that are uncontrolled on permitted therapy.	☐	☐
9. Subjects with clinically significant gastrointestinal or hepatic abnormalities.	☐	☐
10. Subjects who have participated in the acute phase of a Pulmonary Rehabilitation Program within 4 weeks prior to Visit 1 (Screening) or who will enter a Pulmonary Rehabilitation Program during the study.	☐	☐
11. Subjects with a history of hypersensitivity to PDE4 inhibitors.	☐	☐
12. Subjects with a history (or suspected history) of alcohol abuse or any other recreational substance abuse.	☐	☐
13. Subjects receiving treatment with inhaled cromolyn sodium or nedocromil, inhaled long-acting beta2-agonists, and/or oral beta2-agonists, combination short acting beta2-agonists and anticholinergics, xanthines, leukotriene modifiers, mucolytics or oral/inhaled corticosteroids. **All COPD medications except short acting anticholinergic medication or salbutamol via MDI should be withdrawn prior to or at Visit 1 (Screening)** (Section 6.11.2).	☐	☐
14. Subjects receiving treatment with long term oxygen therapy (LTOT) or those subjects who require supplemental oxygen more often than on an occasional (prn) basis, or subjects who require nocturnal positive pressure for sleep apnoea. Patients who are in the maintenance phase of a Pulmonary Rehabilitation program are not excluded.	☐	☐
15. Subjects who have received an investigational drug within 30 days of entry into this study (Visit 1), or within 5 drug half-lives of the investigational drug (whichever is longer).	☐	☐
16. Subjects who have previously participated in a cilomilast study and who received double-blind or open-label study medication.	☐	☐
17. Subjects who are unable or unwilling to comply with all protocol specified procedures, including the completion of the quality of life questionnaires.	☐	☐
18. The patient has a clinically significant orthostatic change in blood pressure or heart rate at Visit 1.	☐	☐

Do not admit the patient to this study if any "YES" box has been marked.

Protocol		Patient Number			Visit 1 Screening
207499/157		[redacted]			

LABORATORY TESTS

Please take blood samples for hematology and blood chemistry (including serum beta-HCG for women of child-bearing potential) and a urine sample for urinalysis. Please refer to the instructions on the Quest shipping form and manual.

Sample Date ☐☐ ☐☐☐ ☐☐ Day Month Yr

Please attach Central Lab CRF label here

(Attach label when sample is sent to central lab.)

Laboratory reports will stay at the site as part of the patient's source documentation.

Request βhCG test on Quest requisition for women of child-bearing potential.

Are there any **clinically significant abnormal** laboratory values?

☐ No

☐ Yes ⟶ *If 'Yes', please record the findings and/or diagnosis in the Significant Medical Surgical History and Physical Examination section (If a re-test is necessary, please use the Repeat Lab page at the end of this book)*

STUDY MEDICATION LABEL

Register the patient with SB's Registration and Medication Ordering System (RAMOS) by calling the number listed on the RAMOS worksheet. Issue the patient with 1 container of **single-blind study medication (weeks -4 to 0)**. The first dose of study medication should be taken at this visit in the clinic with food. Remind the patient that each day they must take one tablet in the morning with food and one tablet in the evening with food.

Attach the tear-off labels from the study medication container dispensed at this visit in the space below. Record the start date in the Study Medication Record section in the next visit.

Attach label here

Date and time visit dose was taken ☐☐ ☐☐☐ ☐☐ ☐☐ ☐☐ Day Month Yr 24hr:min

BASELINE SIGNS AND SYMPTOMS

If the patient suffers any adverse experiences following administration of the first dose of study medication, please record details in the Baseline Signs and Symptoms section at the back of this book.

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 1

	(tick if done)
• *If the patient is not continuing in the study, please **complete the Study Continuation/ Withdrawal page** at the back of this book.*	
• *If the patient is continuing in the study, please:*	☑
• *Issue the patient with a diary card and remind the patient to complete the diary card each morning and to bring the diary card with them to the next visit.*	☐
• *Demonstrate how to measure peak flow using the miniWright Peak Flow Meter. Issue the patient a miniWright peak flow meter with instructions to measure peak flow each morning and to record details in the diary card.*	☐
• *Issue the patient with the faecal occult blood test kit. Instruct the patient to follow the Patient Instructions provided with the kit. In particular, patients are not to collect samples during or until 3 days after a menstrual period or while they have bleeding hemorrhoids or blood in the urine. In addition, patients are not to take aspirin or other non-steroidal anti-inflammatory drugs for 7 days prior to and during the test period, and they are 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. Samples should be collected as specified and returned by the next visit if possible.*	☐
• *Ask the patient to return for the next visit in 14 + / - 3 days for a morning visit..*	☐
• ***Remind the patient:***	
i ***not** to take the morning dose of study medication at home on the day of the next clinic visit.*	☐
ii *to refrain from using salbutamol or anticholinergic agents during the **8 hours** immediately preceding the next visit.*	☐
iii *to refrain from smoking for **2 hours** immediately preceding the visit.*	☐
iv *to bring any remaining study medication or study medication containers, the study salbutamol inhaler and spacer, and the diary card, with them to the next visit.*	☐
v *to continue to take the anticholinergic medication, if prescribed, at a constant dose, and salbutamol when needed to control symptoms.*	☐
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 occurrence.*	☐

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			
207499/157		[redacted]			

2 0 7 4 9 9 1 5 7

MOD2

Please do not split modules

Module 2 : **Visit 2, Visit 3, Baseline Signs and Symptoms, Concomitant Medications, Medical Procedures, COPD Exacerbations**

CRF Pages **16 - 53**

Unprocessed Forms : **Within this module the following occur which will generate attachments that need to be brought in-house.**

None

FOR OFFICE USE ONLY Module Comments:

Sent to Data Mngt	Review Complete Date: User:	First Entry Complete Date: User:
Second Entry Complete Date: User:	Validation Complete Date: User:	**Clintrial PID:**

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number		Visit Date (Day Month Year)	Visit 2 Single-blind Run-in Week -2
207499/157		[redacted]			

PRESENTATION TO CLINIC

Note: ***Patients must wait for 8 hours after beta$_2$-agonist and / or anticholinergic administration before the pulmonary function tests are performed.***

Did the patient take a dose of beta$_2$ agonist in the past 24 hours?

☐ No

☐ Yes → Record date and time of the patient's last dose of beta$_2$ agonist: Day Month Yr 24hr:min

Did the patient take a dose of anticholinergic in the past 24 hours?

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: Day Month Yr 24hr:min

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes → Date and time of patient's last cigarette Day Month Yr 24hr:min

SMOKING STATUS

Does the patient currently smoke?

☐ No

☐ Yes → If 'Yes' please record the average number of cigarettes per day :

Protocol		Patient Number			Visit 2 Single-blind Run-in Week -2
207499/157		[redacted]			

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes ⟶ *If 'Yes', please record details in the COPD Exacerbation section at the back of this book.*

Level 1 (Mild-self treated): Acute worsening of COPD that is self-managed by the patient at home by increasing the dose of relief salbutamol medication by > 2 occasions/24 hour period on two or more consecutive days compared with their baseline (baseline = mean of last 10 days of run-in period) or use of other additional bronchodilator medication

Level 2 (Moderate- physician, investigator treated): Acute worsening of symptoms (cough, sputum production, breathlessness) requiring treatment with oral corticosteroids prescribed by a physician or primary care doctor, or as a result of hospital out-patient visit (including Emergency Room).

Exacerbations requiring oral corticosteroids will be treated with a standardised course of prednisolone or prednisone tablets 30mg/day for 10 days, or methylprednisolone tablets 24mg/day for 10 days.

Level 3 (Severe - attendance at hospital): Acute worsening of COPD that requires the patient to be admitted to hospital for treatment.

If a patient experienced a COPD exacerbation that was treated with corticosteroids, please withdraw the patient and complete the Study Continuation/Withdrawal page at the back of this book. All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this book, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations, including an increase in usual COPD medications, must be recorded in the COPD Medications or Procedures pages.

RESOURCE UTILISATION

If the patient has received any COPD exacerbation-related medical care since the last visit, record details in the Resource Utilisation section at the back of this book.

DIARY CARD REVIEW

Review the diary card in the presence of the patient. Question any increased symptoms for possible COPD exacerbations. Re-issue the diary card and ask the patient to continue completing it until the next visit.

BASELINE SIGNS AND SYMPTOMS

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 Baseline Signs and Symptoms 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.

00000

SmithKline Beecham Pharmaceuticals

Protocol 207499/157		Patient Number [redacted]			Visit 2 Single-blind Run-in Week -2

INFLUENZA VACCINATION

Has the patient had a vaccination for influenza since the last visit?
N.B. It is not necessary to record vaccinations on the Concomitant Medication or Medical Procedures page.

☐ No

☐ Yes ⟶ *If 'Yes', record date of vaccination :* ☐☐ ☐☐☐ ☐☐ Day Month Yr

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.

FAECAL OCCULT BLOOD TEST

The faecal occult blood test should be performed on three consecutive bowel movements or on bowel movements closely spaced in time between Visits 1 and 3. If 3 tests have not been completed at Visit 2, ask the patient to use the remaining tests by Visit 3. Patients were not to collect samples during or until 3 days after a menstrual period or while they had bleeding hemorrhoids or blood in the urine. They were not to take aspirin or other non-steroidal anti-inflammatory drugs for 7 days prior to and during the test period, and they were 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.

Did the patient follow these instructions?

☐ No ⟶ *If 'No', please specify:* _

☐ Yes

Test	Date of Collection Day Mth Yr	Result of faecal occult blood test
1	☐☐ ☐☐☐ ☐☐	[NEG] ☐ Negative [POS] ☐ Positive
2	☐☐ ☐☐☐ ☐☐	[NEG] ☐ Negative [POS] ☐ Positive
3	☐☐ ☐☐☐ ☐☐	[NEG] ☐ Negative [POS] ☐ Positive

*If any one of the tests is positive, please withdraw the patient and **complete the Study Continuation/Withdrawal page** at the back of this book. The primary cause of withdrawal should be 'Does not meet inclusion/exclusion criteria'.*

SmithKline Beecham
Pharmaceuticals

Protocol **207499/157**		**Patient Number** [redacted]			**Visit 2 Single-blind Run-in Week -2**

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. bd)

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
7 0					

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance ≥ 80% and ≤120%?

☐ No → *If 'No' please remind the patient of the importance of taking study medication according to the protocol.*

☐ Yes

00000

SmithKline Beecham
Pharmaceuticals

Protocol 207499/157		Patient Number [redacted]			Visit 2 Single-blind Run-in Week -2

PULMONARY REHABILITATION PROGRAM

Has the patient entered a Pulmonary Rehabilitation Program since the last visit?

☐ No

☐ Yes

INVESTIGATOR INSTRUCTIONS

The following procedures (Vital Signs) must be performed greater than 8 hours after the patient's last salbutamol administration.

VITAL SIGNS

Time of assessment : ☐☐ 24hr:min

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
☐☐☐/☐☐☐	☐☐☐

Are there any **clinically significant worsenings** since Screening?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Baseline Signs and Symptoms section at the back of this book.*

Protocol		Patient Number			Visit 2 Single-blind Run-in Week -2
207499/157		[redacted]			

PRE-IPRATROPIUM PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed at least 8 hours after the last dose of inhaled beta$_2$-agonists or anticholinergic agent.

Measure the patient's pulmonary function up to eight times to obtain three acceptable readings using the spirometer provided by SB. ***(Note: Please follow instructions in the Spirometry Manual).*** *For each set of three FEV_1 measurements, one FEV_1 must be within 10% of the highest. Please record the results of the effort with the highest FEV_1 below.*

Measurement	Time	FEV_1 (L)	FVC (L)	FEF_{25-75} (L/sec)	PEF (L/min)
1	24hr:min	.	.	.	

Has the patient's absolute value of FEV_1 increased or decreased by > 20% between Visits 1 and 2?

☐ No ⟶ *If 'No' continue with the post-ipratropium Pulmonary Function Tests.*

☐ Yes ⟶ *If 'Yes' please withdraw the patient and* ***complete the Study Continuation/Withdrawal page*** *at the back of this book.*

Place the spirometry reports in the plasic wallet at the back of this book.

POST-IPRATROPIUM PULMONARY FUNCTION TESTS

Provide the patient with an ipratropium MDI and spacer. Administer 80 mcg (2 puffs) of ipratropium via MDI with a spacer.

Record the time of ipratropium inhalation : 24hr:min

Wait for 30 minutes.

Measure the patient's pulmonary function up to 8 times to obtain 3 acceptable readings using the spirometer provided by SB (note - please follow instructions in the Spirometry Manual). For each set of 3 FEV_1 measurements, 1 FEV_1 must be within 10% of the highest. Please record the results of the effort with the highest FEV_1 below.

Measurement	Time	FEV_1 (L)	FVC (L)	FEF_{25-75} (L/sec)	PEF (L/min)
1	24hr:min	.	.	.	

$$\text{Reversibility} = \frac{\text{Highest post-ipratropium } FEV_1 - \text{Highest pre-ipratropium } FEV_1}{\text{Highest pre-ipratropium } FEV_1} \times 100$$

☐☐ (% reversibility to ipratropium)

Place the spirometry reports in the plasic wallet at the back of this book.

Protocol		Patient Number			Visit 2 Single-blind Run-in Week -2
207499/157		[redacted]			

STUDY MEDICATION RE-ISSUE

Re-issue the container of **single-blind study medication** returned at this visit and a salbutamol MDI and spacer for 'as required' use if applicable (remind the patient to use this inhaler rather than any salbutamol inhaler they may have at home). The morning dose of study medication should be taken at this visit in the clinic with food. Remind the patient that each day they must take one tablet in the morning immediately after breakfast and one tablet immediately after their evening meal.

Record the start date in the Study Medication Record section and number of tablets re-dispensed in the Study Medication Compliance section of the next visit.

Date and time visit dose was taken ☐☐ ☐☐ ☐☐ ☐☐ ☐☐
Day Month Yr 24hr:min

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 2

	(tick if done)
• *If the patient is not continuing in the study, please **complete the Study Continuation/ Withdrawal page** at the back of this book.*	
• *If the patient is continuing in the study, please:*	☑
• *Re-issue the patient's diary card and remind the patient to complete the diary each morning until the next visit.*	☐
• *Ask the patient to return for the next visit in 14 +/- 3 days for a morning visit.*	☐
• ***Remind the patient:***	
i ***not** to take the morning dose of study medication at home on the day of the next clinic visit.*	☐
ii *to refrain from using salbutamol or anticholinergic agents during the **4 hours** immediately preceding the next visit.*	☐
iii *to refrain from smoking for **2 hours** immediately preceding the visit.*	☐
iv *to bring any remaining study medication or study medication containers, the study salbutamol inhaler and spacer, and the diary card.*	☐
v *to continue to take the anticholinergic medication, if prescribed, at a constant dose, and salbutamol when needed to control symptoms.*	☐
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 occurrence.*	☐
vii *to complete the faecal occult blood test(s) by the next visit if not already done.*	☐

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number		Visit Date (Day Month Year)	
207499/157		[redacted]			**Visit 3 Baseline**

PRESENTATION TO CLINIC

Note: ***Patients must wait for 4 hours after beta$_2$-agonist and / or anticholinergic administration before the pulmonary function tests are performed.***

Did the patient take a dose of beta$_2$ agonist in the past 24 hours?

☐ No

☐ Yes → Record date and time of the patient's last dose of beta$_2$ agonist: Day Month Yr 24hr:min

Did the patient take a dose of anticholinergic in the past 24 hours?

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: Day Month Yr 24hr:min

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes → Date and time of patient's last cigarette: Day Month Yr 24hr:min

If the patient is no longer a smoker, please provide date stopped: Day Month Yr

SMOKING STATUS

Does the patient currently smoke?

☐ No

☐ Yes → If 'Yes' please record the average number of cigarettes per day :

00000

SmithKline Beecham
Pharmaceuticals

Protocol **207499/157**		**Patient Number** [redacted]			**Visit 3 Baseline**

ST. GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND EQ-5D

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

INFLUENZA VACCINATION

Has the patient had a vaccination for influenza since the last visit?

N.B. It is not necessary to record vaccinations on the Concomitant Medication or Medical Procedures page.

☐ No

☐ Yes ⟶ *If 'Yes', record date of vaccination :* ☐☐ ☐☐☐ ☐☐
Day Month Yr

00000

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number			Visit 3 Baseline
207499/157		[redacted]			

INVESTIGATOR GLOBAL EVALUATION OF IMPROVEMENT

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

PATIENT GLOBAL EVALUATION OF IMPROVEMENT

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			Visit 3 Baseline
207499/157		[redacted]			

RESOLUTION OF COPD EXACERBATIONS

Have any COPD Exacerbations resolved since the last visit?

☐ No

☐ Yes ⟶ *If 'Yes', please record details in the COPD Exacerbation section at the back of this book.*

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes ⟶ *If 'Yes', please record details in the COPD Exacerbation section at the back of this book.*

Level 1 (Mild-self treated): Acute worsening of COPD that is self-managed by the patient at home by increasing the dose of relief salbutamol medication by > 2 occasions/24 hour period on two or more consecutive days compared with their baseline (baseline = mean of last 10 days of run-in period) or use of other additional bronchodilator medication

Level 2 (Moderate- physician, investigator treated): Acute worsening of symptoms (cough, sputum production, breathlessness) requiring treatment with oral corticosteroids prescribed by a physician or primary care doctor, or as a result of hospital out-patient visit (including Emergency Room).

Exacerbations requiring oral corticosteroids will be treated with a standardised course of prednisolone or prednisone tablets 30mg/day for 10 days, or methylprednisolone tablets 24mg/day for 10 days.

Level 3 (Severe - attendance at hospital): Acute worsening of COPD that requires the patient to be admitted to hospital for treatment.

If a patient experienced a COPD exacerbation that was treated with corticosteroids, please withdraw the patient and complete the Study Continuation/Withdrawal page at the back of this book. All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this book, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations, including an increase in usual COPD medications, must be recorded in the COPD Medications or Procedures pages.

00000

SmithKline Beecham
Pharmaceuticals

Protocol **207499/157**		**Patient Number** [redacted]			**Visit 3 Baseline**

DIARY CARD REVIEW

Review the diary card in the presence of the patient. Question any increased symptoms for possible COPD exacerbations. Place diary in the plastic wallet at the back of this book and re-issue another diary card.

BASELINE SIGNS AND SYMPTOMS

Please complete the Baseline Signs and Symptoms section at the back of this book.

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 Baseline Signs and Symptoms 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.

FAECAL OCCULT BLOOD TEST

If not completed previously, record results from the test(s) in the Faecal Occult Blood Test section in Visit 2.

Has the patient had a positive faecal occult blood test?

☐ No

☐ Yes ⟶ *If 'Yes' please withdraw the patient and **complete the Study Continuation/Withdrawal page** at the back of this book. The primary cause of withdrawal should be 'Does not meet inclusion/exclusion criteria'.*

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 Baseline Signs and Symptoms section at the back of this book.*

Protocol		Patient Number			Visit 3 Baseline
207499/157		[redacted]			

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. bd)

Date and time of last dose of study medication prior to the study visit ☐☐☐☐☐☐ Day Month Yr ☐☐☐☐ 24hr:min

STUDY MEDICATION COMPLIANCE

Note : Tablets re-dispensed should be entered as the number of tablets returned from the previous visit.

Tablets Re-dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
☐☐	☐☐	☐☐	☐☐	☐☐	☐☐☐

$$\% \text{ Compliance} = \frac{\textit{Number of Tablets Taken}}{\textit{2 x Days Since Last Visit}} \times 100$$

Is compliance ≥ 80% and ≤120%?

☐ No ⟶ *If 'No', please withdraw the patient and complete the Study Continuation/Withdrawal page at the back of this book. The cause of withdrawal should be recorded as 'does not meet inclusion/exclusion criteria'.*

☐ Yes

PULMONARY REHABILITATION PROGRAM

Has the patient entered a Pulmonary Rehabilitation Program since the last visit?

☐ No

☐ Yes

Page amended 05/11/01

Protocol		Patient Number			Visit 3 Baseline
207499/157		[redacted]			

INVESTIGATOR INSTRUCTIONS

The following procedures (Vital Signs, ECG and Pulmonary Function Tests) must be performed greater than 4 hours after the patient's last salbutamol administration.

VITAL SIGNS

Time of assessment : ☐☐ 24hr:min

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
☐☐☐/☐☐☐	☐☐☐

Are there any **clinically significant worsenings** since Screening?

☐ No

☐ Yes ⟶ *If 'Yes' please record the findings and/or diagnosis in the Baseline Signs and Symptoms section at the back of this book.*

VITAL SIGNS - ORTHOSTATIC CHANGE

Time of assessment : ☐☐ 24hr:min

1st Measurement: After 5 Minutes Supine		2nd Measurement: 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)
☐☐☐/☐☐☐	☐☐☐	☐☐☐/☐☐☐	☐☐☐

At the second measurement (i.e. after sitting with Legs Dependent for 1 minute) does the patient have a decrease of ≥ 20 mmHg in systolic blood pressure **or** a decrease of ≥10 mmHg in diastolic blood pressure **or** an increase of ≥ 20 beats/min in heart rate?

☐ No

☐ Yes ⟶ *If 'Yes' withdraw the patient and **complete the Study Continuation/Withdrawal page** at the back of this book. The primary cause of withdrawal should be 'Does not meet inclusion/exclusion criteria'.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number			Visit 3 Baseline
207499/157		[redacted]			

12 LEAD ELECTROCARDIOGRAM

Time of assessment : ☐☐ 24hr:min **The ECG should be performed after the patient has been semi-supine for 5 minutes**

Date ECG Performed (Day Month Year)	Atrial Rate (beats/min)	Ventricular Rate (beats/min)	PR (msec)	QRS (msec)	☐ Uncorrected QT ☐ Corrected QT (msec)	Axis
☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐ + ☐ - ☐☐☐

Interpretation

☐ **(F74301) Within normal limits**

☐ **Abnormal** ⟶ ***Mark appropriate boxes below***

Rhythm
- ☐ (F73360) Sinus arrhythmia
- ☐ (F73310) Sinus bradycardia
- ☐ (F73380) Sinus tachycardia
- ☐ (F73440) Wandering atrial pacemaker
- ☐ (F73450) Premature atrial contractions
- ☐ (F73510) Paroxysmal atrial tachycardia
- ☐ (F73530) Chronic ectopic atrial tachycardia
- ☐ (F73550) Multifocal atrial tachycardia
- ☐ (F73560) Atrial flutter
- ☐ (F73570) Atrial fibrillation
- ☐ (F73610) Junctional (AV nodal) premature contractions
- ☐ (F73650) Junctional (AV nodal) tachycardia
- ☐ (F73150) Supraventricular tachycardia
- ☐ (F73860) Accelerated idioventricular rhythm
- ☐ (F73710) Premature Ventricular Contractions (NOS)
- ☐ (F73720) Unifocal PVC's
- ☐ (F73730) Multifocal PVC's
- ☐ (F73711) Ventricular couplets
- ☐ (F73750) Bigeminy
- ☐ (F73870) Ventricular tachycardia
- ☐ (F73880) Ventricular fibrillation
- ☐ (F73340) Sick sinus syndrome
- ☐ (F73190) Pacemaker rhythm

P-Wave Morphology
- ☐ (F74214) Left atrial hypertrophy, P mitrale
- ☐ (F74213) Right atrial hypertrophy, P pulmonale

Conduction
- ☐ (F73930) First degree AV block
- ☐ (F73950) Second degree AV block, Type 1
- ☐ (F73960) Second degree AV block, Type 11
- ☐ (F73970) Third degree AV block
- ☐ (F74090) Wolff-Parkinson-White syndrome

Axis
- ☐ (F74120) Right Axis deviation
- ☐ (F74130) Left Axis deviation

QRS
- ☐ (F74010) Right bundle branch block
- ☐ (F74020) Left bundle branch block
- ☐ (F74030) Left anterior hemiblock
- ☐ (F74040) Left posterior hemiblock
- ☐ (F74002) Intraventricular conduction delay
- ☐ (F74212) Left ventricular hypertrophy
- ☐ (F74211) Right ventricular hypertrophy
- ☐ (F74308) Q-wave > 0.04 sec
- ☐ (F74222) R-wave amplitude increased
- ☐ (F74225) R-wave amplitude decreased
- ☐ (F74313) Prolonged QT-interval
- ☐ (F74318) Poor R-wave progression
- ☐ (M54750) Myocardial infarction, old
  - ☐ (M54751) Anterior ☐ (M54754) Inferior
  - ☐ (M54752) Lateral ☐ (M54755) Septal
  - ☐ (M54753) Posterior

ST-T
- ☐ (F74291) Nonspecific ST-T changes
- ☐ (F74294) ST segment depression > 1 mm
- ☐ (F74295) ST segment elevation > 1 mm
- ☐ (F74350) T-wave flat
- ☐ (F74351) T-wave inversion
- ☐ (F74352) T-wave peaked
- ☐ (F74340) U-wave
- ☐ (F74360) Digitalis effect
- ☐ (F74260) Myocardial ischemia
  - ☐ (F74261) Anterior ☐ (F74264) Inferior
  - ☐ (F74262) Lateral ☐ (F74265) Septal
  - ☐ (F74263) Posterior
- ☐ (M54720) Myocardial infarction, acute
  - ☐ (M54721) Anterior ☐ (M54724) Inferior
  - ☐ (M54722) Lateral ☐ (M54725) Septal
  - ☐ (M54723) Posterior

Other interpretations not listed _

Were there any new clinically important changes observed since the last assessment?

[1] ☐ No

[2] ☐ Yes ⟶ *If 'Yes', enter details on the Baseline Signs and Symptoms page.*

Place the ECG trace in the plastic wallet a the back of this module

Page amended 05/11/01

Protocol		Patient Number			Visit 3 Baseline
207499/157		[redacted]			

PRE-SALBUTAMOL PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed at least 4 hours after the last dose of inhaled beta$_2$-agonist or anticholinergic agent.
NOTE: If the patient is eligible to be randomised, additional pulmonary function tests will be performed 30 minutes after a dose of study salbutamol is given in the clinic AND prior to the first dose of randomised study medication.
Measure the patient's pulmonary function up to eight times to obtain three acceptable readings using the spirometer provided by SB. ***(Note: Please follow instructions in the Spirometry Manual).*** *For each set of three FEV$_1$ measurements, one FEV$_1$ must be within 10% of the highest. Please record the results of the effort with the highest FEV$_1$ below.*

Measurement	Time	FEV$_1$ (L)	FVC (L)	FEF$_{25-75}$ (L/sec)	PEF (L/min)
1	☐☐ 24hr:min	☐.☐☐	☐.☐☐	☐.☐☐	☐☐☐

Place the spirometry reports in the plasic wallet at the back of this book.

POST-SALBUTAMOL PULMONARY FUNCTION TESTS

Provide the patient with a salbutamol MDI and spacer. Administer 400 mcg (4 puffs) of salbutamol via MDI with a spacer. Remind the patient to use this inhaler (with or without the spacer), rather than any salbutamol inhaler they may have at home, for "as required" rescue-medication use during the study. ***Record the start date for this prn salbutamol use in the Prior and Concomitant medication section.***

Record the time of salbutamol inhalation ☐☐ 24hr:min

Wait 30 minutes

Measure the patient's pulmonary function up to eight times to obtain three acceptable readings using the spirometer provided by SB. ***(Note: Please follow instructions in the Spirometry Manual).*** *For each set of three FEV$_1$ measurements, one FEV$_1$ must be within 10% of the highest. Please record the results of the effort with the highest FEV$_1$ below.*

Measurement	Time	FEV$_1$ (L)	FVC (L)	FEF$_{25-75}$ (L/sec)	PEF (L/min)
1	☐☐ 24hr:min	☐.☐☐	☐.☐☐	☐.☐☐	☐☐☐

Reversibility = $\frac{\text{Highest post-salbutamol FEV}_1 - \text{Highest pre-salbutamol FEV}_1}{\text{Highest pre-salbutamol FEV}_1} \times 100$

☐☐ (% reversibility to salbutamol)

Does the patient have a ≤ 15% and/or ≤ 200ml increase in FEV$_1$ after administration of salbutamol?

☐ No ⟶ *If 'No' please withdraw the patient and* ***complete the Study Continuation / Withdrawal page*** *at the back of this book.*

☐ Yes

Place spirometry reports in the plastic wallets at the back of this book.

Page amended 05/11/01

00000

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number			Visit 3 Baseline
207499/157		[redacted]			

(AT SELECTED CENTRES ONLY) RESIDUAL VOLUME BY BODY PLETHYSMOGRAPHY (PRE- AND POST-SALBUTAMOL)

Date: ☐☐ ☐☐☐ ☐☐ (Day Month Yr) Time of first measurement: ☐☐ ☐☐ (24hr:min)

Pre-Salbutamol

$RV_{Box} = TLC_{Box} - \max(|SVC|, |FVC|)$

$RV_{(Box)} =$ ☐.☐☐ (L)

Post-Salbutamol

$RV_{Box} = TLC_{Box} - \max(|SVC|, |FVC|)$

$RV_{(Box)} =$ ☐.☐☐ (L)

Please attach plethysmography source data to the back of this page.

ADDITIONAL INCLUSION CRITERIA

Complete the following inclusion criteria.	**Yes**	**No**
1. Subjects with poor reversibility of airway obstruction, defined by ≤15% or ≤200ml (or both) increase in FEV_1 after the administration of salbutamol 400mcg via MDI at Visit 3.	☐	☐
2. Less than 20% change (increase or decrease) in pre-bronchodilator FEV_1 between Screening (Visit 1) and Baseline (Visit 3).	☐	☐
3. Between 80-120% compliance in taking single-blind study medication during the run-in.	☐	☐

Do not admit the patient to this study if any "NO" box has been marked

If any 'No' box has been marked, please withdraw the patient and ***complete the Study Continuation/Withdrawal page*** *at the back of this book.*

ADDITIONAL EXCLUSION CRITERIA

Complete the following exclusion criteria.	**Yes**	**No**
1. Patient has had any changes to their COPD medication (other than 'as required' use of salbutamol), received corticosteroids (oral or inhaled) for respiratory disease, or hospitalised for COPD/lower respiratory tract infections during the run-in period.	☐	☐
2. Patient is receiving any other medication during the run-in period which in the opinion of the investigator, is judged as likely to affect baseline assessments.	☐	☐
3. The patient has had a positive faecal occult blood test result between Visit 1 and 3.	☐	☐

Do not admit the patient to this study if any "YES" box has been marked

If any 'Yes' box has been marked, please withdraw the patient and ***complete the Study Continuation/Withdrawal page*** *at the back of this book.*

Page amended 05/11/01

00000

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number			Visit 3 Baseline
207499/157		[redacted]			

LABORATORY TESTS

Please take blood samples for haematology and blood chemistry (including serum beta-HCG for women of child-bearing potential, CD4/CD8 ratio, serum protein C) and a urine sample for urinalysis. Please refer to the instructions on the Quest shipping form and manual.

Blood Sample Date ☐☐ ☐☐☐ ☐☐
Day Month Yr

Attach a label from the 'Routine' laboratory requisition form used at this visit in the space below.

Attach label here

Are there any **clinically significant worsenings** since Screening?

☐ No

☐ Yes ⟶ *If 'Yes' please record the findings and/or diagnosis in the Baseline Signs and Symptoms section at the back of this book.*

PATIENT RANDOMISATION

Following completion of all preceding assessments, complete the RAMOS worksheet and contact RAMOS to obtain the container and randomisation numbers assigned to the patient.

Please enter the 5-digit randomisation number assigned by RAMOS ☐☐☐☐☐

Please enter the 6-digit container number assigned by RAMOS: ☐☐☐☐☐☐

STUDY MEDICATION LABEL

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 section.

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

00000

SmithKline Beecham
Pharmaceuticals

Protocol **207499/157**		**Patient Number** [redacted]			**Visit 3 Baseline**

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 3

Is the patient continuing in the study?

☐ No

☐ Yes

If the patient is not continuing in the study, is the patient willing to return for scheduled visits?

*If 'No', please **complete the Study Continuation/Withdrawal page** at the back of this book and record the date of last dose on the Study Conclusion record.*

If 'Yes', please ask the patient to return for the next visit in 14 (+/-2) days time for essential assessments.

(tick if done)

If the patient is continuing in the study, please : ☑

- *Issue the patient a new diary card and remind the patient to complete the card each morning.* ☐
- *Ask the patient to return for Visit 4 in 14 +/- 2 days at the same time of day as Visit 3.* ☐
- ***Remind the patient:***
  - i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after their breakfast.* ☐
  - ii ***not** to take the morning dose of study medication at home on the day of the next clinic visit.* ☐
  - iii *to refrain from using salbutamol or anticholinergic agents during the **4 hours** immediately preceding 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, the study salbutamol inhaler and spacer, and the diary card.* ☐
  - vi *to continue to take the anticholinergic medication, if prescribed, at a constant dose, and salbutamol when needed to control symptoms.* ☐
  - vii *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 occurrence.* ☐

BASELINE SIGNS AND SYMPTOMS

DEFINITIONS

INTENSITY (Maximum)

MILD	*An event which is easily tolerated*
MODERATE	*An event which is sufficiently discomforting to interfere with daily activity*
SEVERE	*An event which prevents normal everyday activities*

RELATIONSHIP TO INVESTIGATIONAL STUDY PROCEDURES

NOT RELATED	*The event is definitely not related to the study procedures*
UNLIKELY	*There are other more likely causes and the study procedures are not suspected as a cause*
SUSPECTED (REASONABLE POSSIBILITY)	*A direct cause and effect relationship between the study procedures and the event has not been demonstrated but there is a reasonable possibility that the study procedures were involved*
PROBABLE	*There probably is a direct cause and effect relationship between the event and the study procedures*

SERIOUS BASELINE EVENT

A serious baseline event 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 A SERIOUS BASELINE EVENT OCCURS, PLEASE GO TO SAE SECTION IMMEDIATELY AND FOLLOW THE INSTRUCTIONS GIVEN THERE

Use each form for a maximum of two events

PLEASE REMEMBER ALL QUESTIONS ON BASELINE SIGNS AND SYMPTOMS FORM SHOULD BE COMPLETED

g_bss_instr_01

SmithKline Beecham Pharmaceuticals

Protocol	Centre Number	Patient Number			Baseline Signs and Symptoms
207499/157		[redacted]			

BASELINE SIGNS AND SYMPTOMS (or events, or diagnoses)

*Record any baseline events (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Have you felt different in any way since the last visit?"*
Do not record COPD exacerbations here, record them in the COPD Exacerbation section.
*Provide the diagnosis, **not** symptoms where possible. One baseline event per column.*

If you consider this to be a serious baseline event (SBE), please do not enter on this page but enter in the Serious Adverse Experience section (SAE) (See opposite for definitions of an SBE)

☐ Please mark this box if no baseline events occurred prior to randomisation into study.

Baseline Event *(please print clearly)*		
For SB		
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 SAE section and follow instructions given there***	[1] ☐ Resolved [2] ☐ Ongoing [3] ☐ Died	[1] ☐ Resolved [2] ☐ Ongoing [3] ☐ Died
Event Course	[1] ☐ Intermittent → No. of episodes ☐ [2] ☐ Constant	[1] ☐ Intermittent → No. of episodes ☐ [2] ☐ Constant
Intensity (maximum)	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Relationship to study procedures performed prior to randomisation	[1] ☐ Not related [2] ☐ Unlikely [3] ☐ Suspected (reasonable possibility) [4] ☐ Probable	[1] ☐ Not related [2] ☐ Unlikely [3] ☐ Suspected (reasonable possibility) [4] ☐ Probable
Corrective Therapy *If 'Yes', record details in Prior and Concomitant Medication and / or Medical procedures section as appropriate*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific event?	☐ Yes ☐ No	☐ Yes ☐ No

g_bss_01

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number			Baseline Signs and Symptoms
207499/157		[redacted]			

BASELINE SIGNS AND SYMPTOMS (or events, or diagnoses)

*Record any baseline events (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Have you felt different in any way since the last visit?"*
Do not record COPD exacerbations here, record them in the COPD Exacerbation section.
*Provide the diagnosis, **not** symptoms where possible. One baseline event per column.*

If you consider this to be a serious baseline event (SBE), please do not enter on this page but enter in the Serious Adverse Experience section (SAE) (See opposite for definitions of an SBE)

Baseline Event *(please print clearly)*		
For SB		
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 SAE section and follow instructions given there***	[1] Resolved [2] Ongoing [3] Died	[1] Resolved [2] Ongoing [3] Died
Event Course	[1] Intermittent → No. of episodes [2] Constant	[1] Intermittent → No. of episodes [2] Constant
Intensity (maximum)	[1] Mild [2] Moderate [3] Severe	[1] Mild [2] Moderate [3] Severe
Relationship to study procedures performed prior to randomisation	[1] Not related [2] Unlikely [3] Suspected (reasonable possibility) [4] Probable	[1] Not related [2] Unlikely [3] Suspected (reasonable possibility) [4] Probable
Corrective Therapy *If 'Yes', record details in Prior and Concomitant Medication and / or Medical procedures section as appropriate*	Yes No	Yes No
Was patient withdrawn due to this specific event?	Yes No	Yes No

g_bss_01

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number			Baseline Signs and Symptoms
207499/157		[redacted]			

BASELINE SIGNS AND SYMPTOMS (or events, or diagnoses)

*Record any baseline events (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Have you felt different in any way since the last visit?"*
Do not record COPD exacerbations here, record them in the COPD Exacerbation section.
*Provide the diagnosis, **not** symptoms where possible. One baseline event per column.*

If you consider this to be a serious baseline event (SBE), please do not enter on this page but enter in the Serious Adverse Experience section (SAE) (See opposite for definitions of an SBE)

Baseline Event *(please print clearly)*		
For SB		
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 SAE section and follow instructions given there***	[1] Resolved [2] Ongoing [3] Died	[1] Resolved [2] Ongoing [3] Died
Event Course	[1] Intermittent → No. of episodes [2] Constant	[1] Intermittent → No. of episodes [2] Constant
Intensity (maximum)	[1] Mild [2] Moderate [3] Severe	[1] Mild [2] Moderate [3] Severe
Relationship to study procedures performed prior to randomisation	[1] Not related [2] Unlikely [3] Suspected (reasonable possibility) [4] Probable	[1] Not related [2] Unlikely [3] Suspected (reasonable possibility) [4] Probable
Corrective Therapy *If 'Yes', record details in Prior and Concomitant Medication and / or Medical procedures section as appropriate*	Yes No	Yes No
Was patient withdrawn due to this specific event?	Yes No	Yes No

g_bss_01

Protocol	Centre Number	Patient Number			Concomitant Medication
207499/157		[redacted]			

CONCOMITANT MEDICATION

Record any changes in concomitant medication taken since the Screening Visit. (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. At the patient's final study visit, record the end date for prn study rescue medication (salbutamol) use, using the date the study inhaler was returned.

☐ No concomitant medication changes since the Screening Visit

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded in the Baseline Signs and Symptoms 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** (eg 500mg)	**Frequency** (eg bd, 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	
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							

** For Route, see general instructions for acceptable abbreviations.*

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			Concomitant Medication
207499/157		[redacted]			

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. At the patient's final study visit, record the end date for prn study rescue medication (salbutamol) use, using the date the study inhaler was returned.

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded in the Baseline Signs and Symptoms 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** (eg 500mg)	**Frequency** (eg bd, 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	
For SB							
For SB							
For SB							
For SB							
For SB							
For SB							
For SB							
For SB							

** For Route, see general instructions for acceptable abbreviations.*

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			Medical Procedures
207499/157		[redacted]			

MEDICAL PROCEDURES

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 Screening Visit?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below using standard medical terminology*

All indications for procedures should be recorded on the Baseline Signs and Symptoms Form.

Procedure	Indication	Procedure Start Date Day Mth Yr	Procedure End Date Day Mth Yr
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number			COPD Exacerbations (AE)
207499/157		[redacted]			

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 Screening 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***

Has the patient suffered any COPD Exacerbations since Screening?

☐ No

☐ Yes → *If 'Yes', please complete page below*

Baseline Event	COPD EXACERBATION
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, STOP: delete details of this exacerbation and go to SAE COPD Exacerbation pages.***	[1] ☐ Resolved [2] ☐ Ongoing [3] ☐ Died
Event Course	[1] ☐ Intermittent → No. of episodes ☐☐ [2] ☐ Constant
Intensity (maximum) *See definitions page for Baseline Signs & Symptoms form.*	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Relationship to study procedures performed prior to randomisation	[1] ☐ Not related [2] ☐ Unlikely [3] ☐ Suspected (reasonable possibility) [4] ☐ Probable
Corrective Therapy *If 'Yes', record details on the COPD Medications or Procedures page*	☐ Yes ☐ No
Was patient withdrawn due to this specific event?	☐ Yes ☐ No

DEFINITIONS OF LEVELS OF EXACERBATION OF COPD

Level 1 (Mild-self treated): Acute worsening of COPD that is self-managed by the patient at home by increasing the dose of relief salbutamol medication by > 2 occasions/24 hour period on two or more consecutive days compared with their baseline (baseline = mean of last 10 days of run-in period) or use of other additional bronchodilator medication

Level 2 (Moderate- physician, investigator treated): Acute worsening of symptoms (cough, sputum production, breathlessness) requiring treatment with oral corticosteroids prescribed by a physician or primary care doctor, or as a result of hospital out-patient visit (including Emergency Room).

Exacerbations requiring oral corticosteroids will be treated with a standardised course of prednisolone or prednisone tablets 30mg/day for 10 days, or methylprednisolone tablets 24mg/day for 10 days.

Level 3 (Severe - attendance at hospital): Acute worsening of COPD that requires the patient to be admitted to hospital for treatment.

00000

SmithKline Beecham
Pharmaceuticals

Protocol **207499/157**		**Patient Number** [redacted]			**COPD Exacerbations (AE)**

FURTHER DETAILS OF COPD EXACERBATIONS

COPD exacerbation onset date : ☐☐ ☐☐ ☐☐ Day Month Yr

Level of exacerbation (see definitions on facing page):

[1] ☐ Level 1
[2] ☐ Level 2
[3] ☐ Level 3

Pumonary function test result (FEV_1) (if done):

☐.☐☐ L

Did the patient suffer from any of the following during the exacerbation:

[1] ☐ Chest pain
[2] ☐ Upper Respiratory Tract Infection
[3] ☐ Confusion
[4] ☐ Change in alertness
[5] ☐ Pneumonia
[6] ☐ Oedema
[7] ☐ Ankle swelling

ARTERIAL BLOOD GASES (only for COPD exacerbations)

Where feasible, an arterial blood gas sample is to be taken for analysis

COPD exacerbation onset date : ☐☐ ☐☐ ☐☐ Day Month Yr

PO_2 (mmHg)	**PCO_2** (mmHg)	**pH**	**Resting SaO_2** (%)
☐☐☐	☐☐	☐.☐☐	☐☐☐

Page amended 05/11/01

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number			COPD Exacerbations (AE)
207499/157		[redacted]			

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 Screening 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***

Has the patient suffered any COPD Exacerbations since Screening?

☐ No

☐ Yes → *If 'Yes', please complete page below*

Baseline Event	COPD EXACERBATION
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, STOP: delete details of this exacerbation and go to SAE COPD Exacerbation pages.***	[1] ☐ Resolved [2] ☐ Ongoing [3] ☐ Died
Event Course	[1] ☐ Intermittent → No. of episodes ☐ [2] ☐ Constant
Intensity (maximum) *See definitions page for Baseline Signs & Symptoms form.*	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Relationship to study procedures performed prior to randomisation	[1] ☐ Not related [2] ☐ Unlikely [3] ☐ Suspected (reasonable possibility) [4] ☐ Probable
Corrective Therapy *If 'Yes', record details on the COPD Medications or Procedures page*	☐ Yes ☐ No
Was patient withdrawn due to this specific event?	☐ Yes ☐ No

DEFINITIONS OF LEVELS OF EXACERBATION OF COPD

Level 1 (Mild-self treated): Acute worsening of COPD that is self-managed by the patient at home by increasing the dose of relief salbutamol medication by > 2 occasions/24 hour period on two or more consecutive days compared with their baseline (baseline = mean of last 10 days of run-in period) or use of other additional bronchodilator medication

Level 2 (Moderate- physician, investigator treated): Acute worsening of symptoms (cough, sputum production, breathlessness) requiring treatment with oral corticosteroids prescribed by a physician or primary care doctor, or as a result of hospital out-patient visit (including Emergency Room).

Exacerbations requiring oral corticosteroids will be treated with a standardised course of prednisolone or prednisone tablets 30mg/day for 10 days, or methylprednisolone tablets 24mg/day for 10 days.

Level 3 (Severe - attendance at hospital): Acute worsening of COPD that requires the patient to be admitted to hospital for treatment.

00000

SmithKline Beecham
Pharmaceuticals

Protocol **207499/157**		**Patient Number** [redacted]			**COPD Exacerbations (AE)**

FURTHER DETAILS OF COPD EXACERBATIONS

COPD exacerbation onset date : ☐☐ ☐☐☐ ☐☐ Day Month Yr

Level of exacerbation (see definitions on facing page):

[1] ☐ Level 1
[2] ☐ Level 2
[3] ☐ Level 3

Pumonary function test result (FEV_1) (if done):

☐.☐☐ L

Did the patient suffer from any of the following during the exacerbation:

[1] ☐ Chest pain
[2] ☐ Upper Respiratory Tract Infection
[3] ☐ Confusion
[4] ☐ Change in alertness
[5] ☐ Pneumonia
[6] ☐ Oedema
[7] ☐ Ankle swelling

ARTERIAL BLOOD GASES (only for COPD exacerbations)

Where feasible, an arterial blood gas sample is to be taken for analysis

COPD exacerbation onset date : ☐☐ ☐☐☐ ☐☐ Day Month Yr

PO_2 (mmHg)	**PCO_2** (mmHg)	**pH**	**Resting SaO_2** (%)
☐☐☐	☐☐	☐.☐☐	☐☐☐

Page amended 05/11/01

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number			COPD Exacerbations (AE)
207499/157		[redacted]			

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 Screening 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***

Has the patient suffered any COPD Exacerbations since Screening?

☐ No

☐ Yes → *If 'Yes', please complete page below*

Baseline Event	COPD EXACERBATION
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, STOP: delete details of this exacerbation and go to SAE COPD Exacerbation pages.***	[1] ☐ Resolved [2] ☐ Ongoing [3] ☐ Died
Event Course	[1] ☐ Intermittent → No. of episodes ☐☐ [2] ☐ Constant
Intensity (maximum) *See definitions page for Baseline Signs & Symptoms form.*	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Relationship to study procedures performed prior to randomisation	[1] ☐ Not related [2] ☐ Unlikely [3] ☐ Suspected (reasonable possibility) [4] ☐ Probable
Corrective Therapy *If 'Yes', record details on the COPD Medications or Procedures page*	☐ Yes ☐ No
Was patient withdrawn due to this specific event?	☐ Yes ☐ No

DEFINITIONS OF LEVELS OF EXACERBATION OF COPD

Level 1 (Mild-self treated): Acute worsening of COPD that is self-managed by the patient at home by increasing the dose of relief salbutamol medication by > 2 occasions/24 hour period on two or more consecutive days compared with their baseline (baseline = mean of last 10 days of run-in period) or use of other additional bronchodilator medication

Level 2 (Moderate- physician, investigator treated): Acute worsening of symptoms (cough, sputum production, breathlessness) requiring treatment with oral corticosteroids prescribed by a physician or primary care doctor, or as a result of hospital out-patient visit (including Emergency Room).

Exacerbations requiring oral corticosteroids will be treated with a standardised course of prednisolone or prednisone tablets 30mg/day for 10 days, or methylprednisolone tablets 24mg/day for 10 days.

Level 3 (Severe - attendance at hospital): Acute worsening of COPD that requires the patient to be admitted to hospital for treatment.

00000

SmithKline Beecham
Pharmaceuticals

Protocol **207499/157**		**Patient Number** [redacted]			**COPD Exacerbations (AE)**

FURTHER DETAILS OF COPD EXACERBATIONS

COPD exacerbation onset date : ☐☐ ☐☐ ☐☐ Day Month Yr

Level of exacerbation (see definitions on facing page):

[1] ☐ Level 1
[2] ☐ Level 2
[3] ☐ Level 3

Pumonary function test result (FEV_1) (if done):

☐.☐☐ L

Did the patient suffer from any of the following during the exacerbation:

[1] ☐ Chest pain
[2] ☐ Upper Respiratory Tract Infection
[3] ☐ Confusion
[4] ☐ Change in alertness
[5] ☐ Pneumonia
[6] ☐ Oedema
[7] ☐ Ankle swelling

ARTERIAL BLOOD GASES (only for COPD exacerbations)

Where feasible, an arterial blood gas sample is to be taken for analysis

COPD exacerbation onset date : ☐☐ ☐☐ ☐☐ Day Month Yr

PO_2 (mmHg)	**PCO_2** (mmHg)	**pH**	**Resting SaO_2** (%)
☐☐☐	☐☐	☐.☐☐	☐☐☐

Page amended 05/11/01

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number			COPD Exacerbations (AE)
207499/157		[redacted]			

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 Screening 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***

Has the patient suffered any COPD Exacerbations since Screening?

☐ No

☐ Yes → *If 'Yes', please complete page below*

Baseline Event	COPD EXACERBATION
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, STOP: delete details of this exacerbation and go to SAE COPD Exacerbation pages.***	[1] ☐ Resolved [2] ☐ Ongoing [3] ☐ Died
Event Course	[1] ☐ Intermittent → No. of episodes ☐ [2] ☐ Constant
Intensity (maximum) *See definitions page for Baseline Signs & Symptoms form.*	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Relationship to study procedures performed prior to randomisation	[1] ☐ Not related [2] ☐ Unlikely [3] ☐ Suspected (reasonable possibility) [4] ☐ Probable
Corrective Therapy *If 'Yes', record details on the COPD Medications or Procedures page*	☐ Yes ☐ No
Was patient withdrawn due to this specific event?	☐ Yes ☐ No

DEFINITIONS OF LEVELS OF EXACERBATION OF COPD

Level 1 (Mild-self treated): Acute worsening of COPD that is self-managed by the patient at home by increasing the dose of relief salbutamol medication by > 2 occasions/24 hour period on two or more consecutive days compared with their baseline (baseline = mean of last 10 days of run-in period) or use of other additional bronchodilator medication

Level 2 (Moderate- physician, investigator treated): Acute worsening of symptoms (cough, sputum production, breathlessness) requiring treatment with oral corticosteroids prescribed by a physician or primary care doctor, or as a result of hospital out-patient visit (including Emergency Room).

Exacerbations requiring oral corticosteroids will be treated with a standardised course of prednisolone or prednisone tablets 30mg/day for 10 days, or methylprednisolone tablets 24mg/day for 10 days.

Level 3 (Severe - attendance at hospital): Acute worsening of COPD that requires the patient to be admitted to hospital for treatment.

00000

SmithKline Beecham
Pharmaceuticals

Protocol **207499/157**		**Patient Number** [redacted]			**COPD Exacerbations (AE)**

FURTHER DETAILS OF COPD EXACERBATIONS

COPD exacerbation onset date : ☐☐ ☐☐ ☐☐ Day Month Yr

Level of exacerbation (see definitions on facing page):

[1] ☐ Level 1
[2] ☐ Level 2
[3] ☐ Level 3

Pumonary function test result (FEV_1) (if done):

☐.☐☐ L

Did the patient suffer from any of the following during the exacerbation:

[1] ☐ Chest pain
[2] ☐ Upper Respiratory Tract Infection
[3] ☐ Confusion
[4] ☐ Change in alertness
[5] ☐ Pneumonia
[6] ☐ Oedema
[7] ☐ Ankle swelling

ARTERIAL BLOOD GASES (only for COPD exacerbations)

Where feasible, an arterial blood gas sample is to be taken for analysis

COPD exacerbation onset date : ☐☐ ☐☐ ☐☐ Day Month Yr

PO_2 (mmHg)	**PCO_2** (mmHg)	**pH**	**Resting SaO_2** (%)
☐☐☐	☐☐	☐.☐☐	☐☐☐

Page amended 05/11/01

SmithKline Beecham Pharmaceuticals

Protocol	Centre Number	Patient Number		SB Receipt Date (Day Month Year)	COPD Exacerbations (SAE)
207499/157		[redacted]			

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation

Person Reporting SAE _____ *(Please print clearly)*

AEGIS Number _____ . _____

Serious Adverse Experience	**COPD Exacerbation**
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*	[1] Resolved [2] Ongoing [3] Died
Experience Course	[1] Intermittent → No. of episodes [2] Constant
Intensity *(maximum)*	[1] Mild [2] Moderate [3] Severe
Action Taken with Respect to Investigational Drug	[1] None [2] Dose reduced [3] Dose increased [4] Drug interrupted/ restarted [5] Drug stopped
Relationship to Investigational Drug	[1] Not related [2] Unlikely [3] Suspected (reasonable possibility) [4] Probable
Corrective Therapy *If 'Yes', record details in the COPD Concomitant Medication section*	Yes No
Was patient withdrawn due to this specific SAE ?	Yes No

→ *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

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 _____

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number		SB Receipt Date (Day Month Year)	COPD Exacerbations (SAE)
207499/157		[redacted]			

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation

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 Number (please do NOT enter the container number): ☐☐☐☐☐

Investigator's Signature: _____ Date ☐☐ ☐☐ ☐☐☐☐
(confirming that the above data are accurate and complete) Day Month Year

Please PRINT Name _____

SB Medical Monitor's Signature: _____ Date ☐☐ ☐☐ ☐☐☐☐
Day Month Year

Please PRINT Name _____

DEFINITIONS OF LEVELS OF EXACERBATION OF COPD

Level 1 (Mild-self treated): Acute worsening of COPD that is self-managed by the patient at home by increasing the dose of relief salbutamol medication by > 2 occasions/24 hour period on two or more consecutive days compared with their baseline (baseline = mean of last 10 days of run-in period) or use of other additional bronchodilator medication

Level 2 (Moderate- physician, investigator treated): Acute worsening of symptoms (cough, sputum production, breathlessness) requiring treatment with oral corticosteroids prescribed by a physician or primary care doctor, or as a result of hospital out-patient visit (including Emergency Room).

Exacerbations requiring oral corticosteroids will be treated with a standardised course of prednisolone or prednisone tablets 30mg/day for 10 days, or methylprednisolone tablets 24mg/day for 10 days.

Level 3 (Severe - attendance at hospital): Acute worsening of COPD that requires the patient to be admitted to hospital for treatment.

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number		SB Receipt Date (Day Month Year)	COPD Exacerbations (SAE)
207499/157		[redacted]			

FURTHER DETAILS OF SERIOUS COPD EXACERBATIONS

COPD exacerbation onset date : Day Month Yr

Level of exacerbation (see definitions on facing page):

[1] ☐ Level 1
[2] ☐ Level 2
[3] ☐ Level 3

Pumonary function test result (FEV_1) (if done):

☐.☐☐ L

Did the patient suffer from any of the following during the exacerbation:

[1] ☐ Chest pain
[2] ☐ URTI
[3] ☐ Confusion
[4] ☐ Change in alertness
[5] ☐ Pneumonia
[6] ☐ Oedema
[7] ☐ Ankle swelling

ARTERIAL BLOOD GASES (only for serious COPD exacerbations)

Where feasible, an arterial blood gas sample is to be taken for analysis

COPD exacerbation onset date : Day Month Yr

PO_2 (mmHg)	**PCO_2** (mmHg)	**pH**	**Resting SaO_2** (%)
☐☐☐	☐☐	☐.☐☐	☐☐☐

Protocol	Centre Number	Patient Number			COPD Exacerbations (ConMed)
207499/157		[redacted]			

MEDICATION FOR COPD EXACERBATIONS

Has the patient taken any medication for COPD exacerbations since Screening?

☐ No

☐ Yes → *If 'Yes', please record details below*

Drug Name *(Trade Name Preferred)*	**Unit Dose** (eg 500mg)	**Freq.** (eg bd, prn)	**Route***	**Medical Illness/ Diag.**	**Start Date** *(be as precise as possible)* Day Mth Yr	**End Date** *(or if Continuing mark box)* Day Mth Yr		COPD Exacerbation Onset Date
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								

** For Route, see General Instructions for acceptable abbreviations.*

Protocol	Centre Number	Patient Number			COPD Exacerbations (ConMed)
207499/157		[redacted]			

MEDICAL PROCEDURES FOR COPD EXACERBATIONS

Have any non-medication, therapeutic, diagnostic or surgical procedures been performed for COPD exacerbations since Screening?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below using standard medical terminology*

Procedure	Indication	Procedure Start Date Day Mth Yr	Procedure End Date Day Mth Yr	COPD Exacerbation Onset Date
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			
207499/157					

2 0 7 4 9 9 1 5 7

CONC1

Please do not split modules

Module: **Study Continuation / Withdrawal**

CRF Pages: **54**

Unprocessed Forms: **Within this module, the following occur which will generate attachments that need to be brought in-house.**

None

FOR OFFICE USE ONLY Module Comments:

Sent to Data Mngt	Review Complete Date: User:	First Entry Complete Date: User:
Second Entry Complete Date: User:	Validation Complete Date: User:	**Clintrial PID:**

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			Study Continuation/ Withdrawal
207499/157		[redacted]			

STUDY CONTINUATION/WITHDRAWAL

Is the patient continuing in the study?

☐ Yes ⟶ *If 'Yes', please sign in the appropriate space below and continue to Book 2 for the next visit.*

☐ No ⟶ If 'No', please mark the **primary** cause of withdrawal. *(Mark one box only).*

[1] ☐ Baseline sign and symptom *(please complete Baseline Signs and Symptoms page)*

[10] ☐ Does not meet inclusion/exclusion criteria

[3] ☐ Protocol deviation (including non-compliance)

[4] ☐ Lost to follow-up

[7] ☐ Other - *specify*: _

g_cont_wthd_01

INVESTIGATOR SIGNATURE

I certify that I have reviewed the data on this case report form, including laboratory data and that in the Baseline Signs and Symptoms, Adverse Experiences and Serious Adverse Experiences sections (if appropriate) and that all information is complete and accurate.

Investigator's Signature _

Date ☐☐ ☐☐☐ ☐☐ Day Month Yr

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			
207499/157		[redacted]			

2 0 7 4 9 9 1 5 7

SAE1

Please do not split modules

Module: **Serious Adverse Experiences**

CRF Pages: **55 - 56**

FOR OFFICE USE ONLY Module Comments:

Sent to Data Mngt	Date: / User: Review Complete	Date: / User: First Entry Complete
Date: / User: Second Entry Complete	Date: / User: Validation Complete	**Clintrial PID:**

REPORTING SERIOUS ADVERSE EXPERIENCES (SAE)

INSTRUCTIONS

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

g_sae_instr_01

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number		SB Receipt Date (Day Month Year)	Serious Adverse Experiences
207499/157		[redacted]			

SERIOUS ADVERSE EXPERIENCE (SAE)

Person Reporting SAE *(Please print clearly)* _

AEGIS Number _ _ _ _ _ _ _ _ . _

Serious Adverse Experience *(Please print clearly)*

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*
[1] Resolved
[2] Ongoing
[3] Died

Experience Course
[1] Intermittent → No. of episodes
[2] Constant

Intensity *(maximum)*
[1] Mild
[2] Moderate
[3] Severe

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

Action Taken with Respect to Investigational Drug
[1] None
[2] Dose reduced
[3] Dose increased
[4] Drug interrupted restarted
[5] 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
[1] Not related
[2] Unlikely
[3] Suspected (reasonable possibility)
[4] 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

g_sae_01

00000

SmithKline Beecham Pharmaceuticals

Protocol	Centre Number	Patient Number		SB Receipt Date (Day Month Year)	Serious Adverse Experiences
207499/157		[redacted]			

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 Number (please do NOT enter the container number): ☐☐☐☐☐

Investigator's Signature: _____ Date ☐☐ ☐☐ ☐☐☐☐
(confirming that the above data are accurate and complete) Day Month Year

Please PRINT Name _____

SB Medical Monitor's Signature: _____ Date ☐☐ ☐☐ ☐☐☐☐

Please PRINT Name _____ Day Month Year

g_sae_01

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			
207499/157					

2 0 7 4 9 9 1 5 7

RPLAB1

Please do not split modules

Module: **Repeat / unscheduled laboratory assessments**

CRF Pages: **57**

Unprocessed Forms: **Within this module, the following tests / procedures occur which may generate attachments.**

None

FOR OFFICE USE ONLY Module Comments:

Sent to Data Mngt	Date: / User: Review Complete	Date: / User: First Entry Complete
Date: / User: Second Entry Complete	Date: / User: Validation Complete	**Clintrial PID:**

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			Repeat / Unscheduled Lab Tests
207499/157		[redacted]			

REPEAT / UNSCHEDULED LABORATORY TESTS

Visit Number (or last scheduled visit number): ☐☐ Sample Date ☐☐ ☐☐ ☐☐ Day Month Yr

Please take blood samples for hematology and/or blood chemistry (including serum beta-HCG for women of child-bearing potential) and/or a urine sample for urinalysis. Please refer to the instructions on the Quest shipping form and manual.

Please attach Central Lab CRF label here

(Attach label when sample is sent to central lab.)

Laboratory reports will stay at the site as part of the patient's source documentation.

Request βhCG test on Quest requisition for women of child-bearing potential. If the pregnancy test is positive, please withdraw the patient and complete the Serious Adverse Experiences form and forward it to SB within 24 hours.

Are there any **clinically significant** worsenings since the last assessment?

☐ No

☐ Yes ⟶ *If 'Yes', please record the findings and/or diagnosis in the Baseline Signs and Symptoms section.*

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			
207499/157					

2 0 7 4 9 9 1 5 7

RPLAB2

Please do not split modules

Module: **Repeat / unscheduled laboratory assessments**

CRF Pages: **58**

Unprocessed Forms: **Within this module, the following tests / procedures occur which may generate attachments.**

None

FOR OFFICE USE ONLY Module Comments:

Sent to Data Mngt	Review Complete Date: User:	First Entry Complete Date: User:
Second Entry Complete Date: User:	Validation Complete Date: User:	**Clintrial PID:**

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			Repeat / Unscheduled Lab Tests
207499/157		[redacted]			

REPEAT / UNSCHEDULED LABORATORY TESTS

Visit Number (or last scheduled visit number): ☐☐ Sample Date ☐☐ ☐☐ ☐☐
Day Month Yr

Please take blood samples for hematology and/or blood chemistry (including serum beta-HCG for women of child-bearing potential) and/or a urine sample for urinalysis. Please refer to the instructions on the Quest shipping form and manual.

Please attach Central Lab CRF label here

(Attach label when sample is sent to central lab.)

Laboratory reports will stay at the site as part of the patient's source documentation.

Request βhCG test on Quest requisition for women of child-bearing potential. If the pregnancy test is positive, please withdraw the patient and complete the Serious Adverse Experiences form and forward it to SB within 24 hours.

Are there any **clinically significant** worsenings since the last assessment?

☐ No

☐ Yes ⟶ *If 'Yes', please record the findings and/or diagnosis in the Baseline Signs and Symptoms section.*

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number		Investigator
207499/157		[redacted]		_ _

CRF TRACKING/REVIEW FORM (TRF)

Please submit COMPLETE modules only. Do not submit whole blank modules.

☐ Screening Failure (archive only)

- *Mark the **Unused** box for all remaining modules that will **not** be completed and sent in-house*
- *Ensure the Missing Pages field is completed if pages are missing from modules*
- *Ensure the Patient Number and Patient Initials entered match the information on the CRF*
- *Complete one TRF per batch of modules to be sent in-house*
- *Ensure all sections of the TRF are legible*

Module	Module Description	Page Range	Modules		Missing pages (if applicable)
			Sent to DM	Unused	
MOD1	Visit 1 Screening	1 - 15	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
ECG1	Visit 1 ECG trace	n/a	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
PFT1	Visit 1 PFT printout	n/a	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
MOD2	V2, V3, BSS, CM, MP, COPD	16 - 53	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
PFT2	Visit 2 PFT printout	n/a	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
ECG2	Visit 3 ECG trace	n/a	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
PFT3	Visit 3 PFT printout	n/a	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
SGRQ1	Visit 3 SGRQ	SG1-SG5	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
EQ5D1	Visit 3 EQ-5D	EQ1-EQ2	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
CONC1	Continuation/Withdrawal	54	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
SAE1	Serious Adverse Experiences	55 - 56	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
RPLAB1	Repeat Labs	57	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
RPLAB2	Repeat Labs	58	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
FORMD	Form D	n/a	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _

If multiple modules are submitted together, please ensure they are sorted according to the order above

Site Monitor's Name _ *(Print clearly)*

Site Monitor's Signature _ **Date Submitted** ☐☐ ☐☐ ☐☐
Day Month Yr

g_trf_01

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number		Investigator
207499/157		[redacted]		_____

CRF TRACKING/REVIEW FORM (TRF)

DIA1	Diary 1	n/a	☐	☐	_____
DIA2	Diary 2	n/a	☐	☐	_____
DIA3	Diary 3	n/a	☐	☐	_____

Site Monitor's comments (eg. protocol violations or deviations)

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

Site Monitor's Name _____ *(Print clearly)*

Site Monitor's Signature _____ **Date Submitted** ☐☐ ☐☐ ☐☐
Day Month Yr

g_trf_01

00000

SmithKline Beecham
Pharmaceuticals

Protocol **207499/157**		**Patient Number** [redacted]			**Visit 4 Week 2**

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 4

Is the patient continuing in the study?

☐ No ⟶ *Go to '1' below.*

☐ Yes ⟶ *Go to '2' below.*

*1. If the patient is **not** continuing in the study, is the patient willing to return for essential assessments?*

If 'No', please complete the assessments for Visit 4, the additional assessments for patients withdrawing at Visit 4 and the Study Continuation/Withdrawal page at the back of this book. Please schedule a safety follow-up visit in 7 days (+/- 3 days).

If 'Yes', please complete the assessments for Visit 4, the additional assessments for patients withdrawing at Visit 4 and the Study Continuation/Withdrawal page at the back of this book. Ask the patient to return for a safety follow-up visit in 7 days (+/- 3 days) and then for their next scheduled visit 7 days later for essential assessments only.

*2. If the patient **is** continuing in the study, please:*	(tick if done)
	☑
• *Issue the patient a new diary card and remind the patient to complete the diary each morning until the next visit.*	☐
• *Ask the patient to return for the next visit in 14 +/- 3 days at the same time of day.*	☐
• ***Remind the patient:***	
i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after their breakfast.*	☐
ii ***not** to take their dose of study medication for at least 8 hours prior to their next study visit appointment.*	☐
iii *to refrain from using salbutamol or anticholinergic agents during the **4 hours** immediately preceding 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, the study salbutamol inhaler and spacer, and the diary card.*	☐
vi *to continue to take the anticholinergic medication, if prescribed, at a constant dose, and salbutamol when needed to control symptoms.*	☐
vii *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 occurrence.*	☐

00000

SmithKline Beecham
Pharmaceuticals

Protocol **207499/157**		**Patient Number** [redacted]			**Visit 5 Week 4**

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 5

Is the patient continuing in the study?

☐ No ⟶ *Go to '1' below.*

☐ Yes ⟶ *Go to '2' below.*

*1. If the patient is **not** continuing in the study, is the patient willing to return for essential assessments?*

If 'No', please complete the assessments for Visit 5, the additional assessments for patients withdrawing at Visit 5 and the Study Continuation/Withdrawal page at the back of this book. Please schedule a safety follow-up visit in 7 days (+/- 3 days).

If 'Yes', please complete the assessments for Visit 5, the additional assessments for patients withdrawing at Visit 5 and the Study Continuation/Withdrawal page at the back of this book. Ask the patient to return for a safety follow-up visit in 7 days (+/- 3 days) and then for their next scheduled visit 21 (+/- 6 days) later for essential assessments only.

*2. If the patient **is** continuing in the study, please:*	(tick if done)
• *Issue the patient a new diary card and remind the patient to complete the diary each morning until the next visit.*	☐
• *Ask the patient to return for the next visit in 28 +/- 6 days at the same time of day.*	☐
• ***Remind the patient:***	
i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after their breakfast.*	☐
ii ***not** to take their dose of study medication for at least 8 hours prior to their next study visit appointment.*	☐
iii *to refrain from using salbutamol or anticholinergic agents during the **4 hours** immediately preceding 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, the study salbutamol inhaler and spacer, and the diary card.*	☐
vi *to continue to take the anticholinergic medication, if prescribed, at a constant dose, and salbutamol when needed to control symptoms.*	☐
vii *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 occurrence.*	☐

00000

SmithKline Beecham
Pharmaceuticals

Protocol **207499/157**		**Patient Number** [redacted]			**Visit 6 Week 8**

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 6

Is the patient continuing in the study?

☐ No ⟶ *Go to '1' below.*

☐ Yes ⟶ *Go to '2' below.*

*1. If the patient is **not** continuing in the study, is the patient willing to return for essential assessments?*

If 'No', please complete the assessments for Visit 6, the additional assessments for patients withdrawing at Visit 6 and the Study Continuation/Withdrawal page at the back of this book. Please schedule a safety follow-up visit in 7 days (+/- 3 days).

If 'Yes', please complete the assessments for Visit 6, the additional assessments for patients withdrawing at Visit 6 and the Study Continuation/Withdrawal page at the back of this book. Ask the patient to return for a safety follow-up visit in 7 days (+/- 3 days) and then for their next scheduled visit 21 (+/- 6 days) later for essential assessments only.

*2. If the patient **is** continuing in the study, please:* (tick if done)

- *Issue the patient a new diary card and remind the patient to complete the diary each morning until the next visit.* ☐
- *Ask the patient to return for the next visit in 28 +/- 6 days at the same time of day.* ☐
- ***Remind the patient:***
  - i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after their breakfast.* ☐
  - ii ***not** to take their dose of study medication for at least 8 hours prior to their next study visit appointment.* ☐
  - iii *to refrain from using salbutamol or anticholinergic agents during the **4 hours** immediately preceding 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, the study salbutamol inhaler and spacer, and the diary card.* ☐
  - vi *to continue to take the anticholinergic medication, if prescribed, at a constant dose, and salbutamol when needed to control symptoms.* ☐
  - vii *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 occurrence.* ☐

00000

SmithKline Beecham
Pharmaceuticals

Protocol **207499/157**		**Patient Number** [redacted]			**Visit 7 Week 12**

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 7

Is the patient continuing in the study?

☐ No ⟶ *Go to '1' below.*

☐ Yes ⟶ *Go to '2' below.*

*1. If the patient is **not** continuing in the study, is the patient willing to return for essential assessments?*

If 'No', please complete the assessments for Visit 7, the additional assessments for patients withdrawing at Visit 7 and the Study Continuation/Withdrawal page at the back of this book. Please schedule a safety follow-up visit in 7 days (+/- 3 days).

If 'Yes', please complete the assessments for Visit 7, the additional assessments for patients withdrawing at Visit 7 and the Study Continuation/Withdrawal page at the back of this book. Ask the patient to return for a safety follow-up visit in 7 days (+/- 3 days) and then for their next scheduled visit 49 (+/- 6 days) later for essential assessments only.

*2. If the patient **is** continuing in the study, please:*	(tick if done)
	☑
• *Issue the patient a new diary card and remind the patient to complete the diary each morning until the next visit.*	☐
• *Ask the patient to return for the next visit in 56 +/- 6 days at the same time of day.*	☐
• ***Remind the patient:***	
i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after their breakfast.*	☐
ii ***not** to take their dose of study medication for at least 8 hours prior to their next study visit appointment.*	☐
iii *to refrain from using salbutamol or anticholinergic agents during the **4 hours** immediately preceding 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, the study salbutamol inhaler and spacer, and the diary card.*	☐
vi *to continue to take the anticholinergic medication, if prescribed, at a constant dose, and salbutamol when needed to control symptoms.*	☐
vii *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 occurrence.*	☐

Protocol	Centre Number	Patient Number
207499/157		[redacted]

CONFIDENTIAL

SmithKline Beecham
Pharmaceuticals

PROTOCOL 207499/157

BOOK 2 : VISIT 4 TO VISIT 7

A RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL GROUP STUDY TO EVALUATE THE EFFICACY, SAFETY AND TOLERABILITY OF ORAL CILOMILAST (15 MG BD) WHEN GIVEN AS MAINTENANCE TREATMENT FOR 12 MONTHS TO SUBJECTS 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 and centre number on all pages 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 | *= 1st January 2001*
Day Month Year

TIME

Unless specified otherwise, please use the 24 hour clock

e.g. | 1 5 | 3 0 | *= 3.30 p.m*
24hr:min

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*

SCHEDULE OF ASSESSMENTS

Visit	1	2	3	4	5	6	7	8	9	10	11	12		13
	Screen		Base-line									End of DB	Early With-drawal	Follow -up
Time relative to baseline (weeks)[1]	-4	-2	0	+2	+4	+8	+12	+20	+28	+36	+44	+52		+53
Signed written informed consent	x													
Medical & surgical history	x													
Pulmonary symptoms	x													
Postero-anterior chest X-ray[2]	x													
Medication history including influenza vaccination[3]	x													
Health Status Assessments: SGRQ and EQ-5D			x						x			x	x	
Patient global assessment			x						x			x	x	
Investigator global assessment			x						x			x	x	
Physical examination [4]	x		x									x	x	x[5]
Smoking status	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Exacerbation assessment	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Resource utilisation				x	x	x	x	x	x	x	x	x	x	x
Diary Card Review		x	x	x	x	x	x	x	x	x	x	x	x	
Baseline signs and symptoms [6]	x	x	x											
Adverse experiences [6]				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
Study medication compliance		x	x	x	x	x	x	x	x	x	x	x	x	
Resting 12-lead ECG	x		x				x		x			x	x	x[5]
Vital signs (BP, HR)[7]	x[7]	x	x[7]	x	x	x	x[7]	x	x[7]	x	x	x[7]	x[7]	x
PFTs pre and post salbutamol: Pre-dose [8]	x		x		x	x	x	x	x	x	x	x	x	x
PFTs: salbutamol reversibility [9]	x		x											
PFTs: ipratropium reversibility		x												
Residual Volume (body box) pre-/ post-salbutamol Selected sites only			x						x			x	x	
Laboratory tests	x		x[10]		x	x	x	x	x	x	x	x[10]	x[10]	x[5]
Faecal occult blood test [11]	x	x										x	x	
Dispense single-blind med	x[12]	x[13]												
Dispense double-blind med			x[14]	x[13]	x[15]	x[15]	x[15]	x[15]	x[15]	x[15]	x[15]			
Study conclusion record														x[16]

1 All visit dates must be scheduled at the visit interval listed here using the Baseline visit as Day 0.
2 Chest X-ray to be taken at entry to the run-in period or in the 3 months prior to entry to the run-in period
3 Details of 'flu vaccinations will be recorded at every visit
4 Includes respiratory examination.
5 Only if abnormalities are present at Visit 12/Early Withdrawal.
6 Does not include COPD exacerbations
7 Orthostatic vital signs to be measured at Visits 1, 3, 7, 9, and 12
8 Includes FEV_1, FVC, FEF_{25-75} and PEF measured by spirometry by the same study personnel at each visit before dose of study medication is taken.
9 Includes FEV_1, FVC, FEF_{25-75} and PEF measured by spirometry by the same study personnel at each visit 30 minutes after administration of 400 mcg of salbutamol via MDI with or without a spacer, and before dose of study medication is taken.
10 Includes Blood CD4+/CD8+ ratio and serum C Reactive Protein
11 In addition to the usual laboratory tests, three faecal occult blood tests will be performed between Visits 1 and 3, at the end of the treatment period and at Early Withdrawal
12 Register the patient with RAMOS.
13 The container of study medication issued at the previous visit will be re-issued at this visit
14 Call RAMOS to randomise the patient and to obtain study medication assignment and container number.
15 Call RAMOS to obtain study medication container number(s)
16 Or earlier if the subject withdraws from the study prior to Visit 12.

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			
207499/157		[redacted]			

2 0 7 4 9 9 1 5 7

MOD3

Please do not split modules

Module 3 : **Visit 4, Visit 5, Adverse Experiences, Concomitant Medication, Medical Procedures, COPD Exacerbations, Resource Utilisation**

CRF Pages **59 - 101**

Unprocessed Forms : **Within this module the following occur which will generate attachments that need to be brought in-house.**

None

FOR OFFICE USE ONLY Module Comments:

Sent to Data Mngt	Review Complete Date: User:	First Entry Complete Date: User:
Second Entry Complete Date: User:	Validation Complete Date: User:	**Clintrial PID:**

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number		Visit Date (Day Month Year)	
207499/157		[redacted]			**Visit 4 Week 2**

PRESENTATION TO CLINIC

Note: ***Patients must wait for 4 hours after beta$_2$-agonist and / or anticholinergic administration before the pulmonary function tests are performed.***

Did the patient take a dose of beta$_2$ agonist in the past 24 hours?

☐ No

☐ Yes ⟶ Record date and time of the patient's last dose of beta$_2$ agonist: Day Month Yr 24hr:min

Did the patient take a dose of anticholinergic in the past 24 hours?

☐ No

☐ Yes ⟶ Record date and time of patient's last dose of anticholinergic: Day Month Yr 24hr:min

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes ⟶ Date and time of patient's last cigarette Day Month Yr 24hr:min

SMOKING STATUS

Does the patient currently smoke?

☐ No

☐ Yes ⟶ If 'Yes' please record the average number of cigarettes per day : ☐☐

INFLUENZA VACCINATION

Has the patient had a vaccination for influenza since the last visit?

N.B. It is not necessary to record vaccinations on the Concomitant Medication or Medical Procedures page.

☐ No

☐ Yes ⟶ *If 'Yes', record date of vaccination :* Day Month Yr

Protocol		Patient Number			Visit 4 Week 2
207499/157		[redacted]			

RESOLUTION OF COPD EXACERBATIONS

Have any COPD Exacerbations resolved since the last visit?

☐ No

☐ Yes ⟶ *If 'Yes', please record details in the COPD Exacerbation section at the back of this module.*

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes ⟶ *If 'Yes' please record details in the COPD Exacerbation section at the back of this module.*

Level 1 (Mild-self treated): Acute worsening of COPD that is self-managed by the patient at home by increasing the dose of relief salbutamol medication by > 2 occasions/24 hour period on two or more consecutive days compared with their baseline (baseline = mean of last 10 days of run-in period) or use of other additional bronchodilator medication

Level 2 (Moderate- physician, investigator treated): Acute worsening of symptoms (cough, sputum production, breathlessness) requiring treatment with oral corticosteroids prescribed by a physician or primary care doctor, or as a result of hospital out-patient visit (including Emergency Room).

Exacerbations requiring oral corticosteroids will be treated with a standardised course of prednisolone or prednisone tablets 30mg/day for 10 days, or methylprednisolone tablets 24mg/day for 10 days.

Level 3 (Severe - attendance at hospital): Acute worsening of COPD that requires the patient to be admitted to hospital for treatment.

If a patient experienced a COPD exacerbation that was treated with corticosteroids, please withdraw the patient and complete the Study Continuation/Withdrawal page at the back of this book. 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, including an increase in usual COPD medications, must be recorded in the COPD Medications or Procedures pages.

00000

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number			Visit 4 Week 2
207499/157		[redacted]			

RESOURCE UTILISATION

If the patient has received any COPD exacerbation-related medical care since the last visit, record details on the Resource Utilisation pages of the COPD Exacerbation section at the back of this module.

DIARY CARD REVIEW

Review the diary card in the presence of the patient. Question any increased symptoms for possible COPD exacerbations. Place diary in the plastic wallet at the back of this module and re-issue another diary card.

ADVERSE EXPERIENCES

Please complete the Adverse Experiences 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 Experiences 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.

SmithKline Beecham
Pharmaceuticals

Protocol **207499/157**		**Patient Number** [redacted]			**Visit 4 Week 2**

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. bd)

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	☐☐	☐☐	☐☐	☐☐	☐☐☐

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance ≥ 80% and ≤120%?

☐ No → *If 'No' please remind the patient of the importance of taking study medication according to the protocol.*

☐ Yes

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number			Visit 4 Week 2
207499/157		[redacted]			

PULMONARY REHABILITATION PROGRAM

Has the patient entered a Pulmonary Rehabilitation Program since the last visit?

☐ No

☐ Yes

INVESTIGATOR INSTRUCTIONS

The following procedures (Vital Signs) must be performed greater than 4 hours after the patient's last salbutamol administration.

VITAL SIGNS

Time of assessment : ☐☐ 24hr:min

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
☐☐☐/☐☐☐	☐☐☐

Are there any **clinically significant worsenings** since the previous visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experiences section at the back of this module.*

STUDY MEDICATION RE-ISSUE

Re-issue the container of **study medication** returned at this visit and a salbutamol MDI and spacer for 'as required' use if applicable (remind the patient to use this inhaler rather than any salbutamol inhaler they may have at home). The morning dose of study medication should be taken at this visit in the clinic with food. Remind the patient that each day they must take one tablet in the morning immediately after breakfast and one tablet immediately after their evening meal.

Record the start date in the Study Medication Record section and number of tablets re-dispensed in the Study Medication Compliance section of the next visit.

Date and time visit dose was taken ☐☐ ☐☐ ☐☐ Day Month Yr ☐☐ 24hr:min

00000

SmithKline Beecham
Pharmaceuticals

Protocol **207499/157**		**Patient Number** [redacted]			**Visit 4 Week 2**

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 4

Is the patient continuing in the study?

☐ No

☐ Yes

*If the patient is **not** continuing in the study, is the patient willing to return for essential assessments?*

If 'No', please complete the assessments for Visit 4 and the additional assessments for patients withdrawing at Visit 4 and the Study Continuation/Withdrawal page at the back of this book.

If 'Yes', please complete the assessments for Visit 4, the assessments for patients withdrawing at Visit 4 and the Study Continuation/Withdrawal page at the back of this book. Ask the patient to return in 14 +/-3 days time for essential assessments only.

*If the patient **is** continuing in the study, please:*	(tick if done)
	☑
• *Issue the patient a new diary card and remind the patient to complete the diary each morning until the next visit.*	☐
• *Ask the patient to return for the next visit in 14 +/- 3 days for a morning visit.*	☐
• ***Remind the patient:***	
i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after their breakfast.*	☐
ii ***not** to take the morning dose of study medication at home on the day of the next clinic visit.*	☐
iii *to refrain from using salbutamol or anticholinergic agents during the **4 hours** immediately preceding 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, the study salbutamol inhaler and spacer, and the diary card.*	☐
vi *to continue to take the anticholinergic medication, if prescribed, at a constant dose, and salbutamol when needed to control symptoms.*	☐
vii *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 occurrence.*	☐

00000

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number			Withdrawal at Visit 4 Week 2
207499/157		[redacted]			

ASSESSMENTS FOR PATIENTS WITHDRAWING AT VISIT 4

Complete the assessments below only for patients who are withdrawing from the study at this visit.

ST. GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND EQ-5D

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

INVESTIGATOR GLOBAL EVALUATION OF IMPROVEMENT

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

PATIENT GLOBAL EVALUATION OF IMPROVEMENT

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

00000

SmithKline Beecham
Pharmaceuticals

Protocol **207499/157**		**Patient Number** [redacted]			**Withdrawal at Visit 4 Week 2**

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 Experiences section at the back of this module.*

VITAL SIGNS - ORTHOSTATIC CHANGE

Time of assessment : ☐☐ 24hr:min

1st Measurement: After 5 Minutes Supine		**2nd Measurement: 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)
☐☐☐/☐☐☐	☐☐☐	☐☐☐/☐☐☐	☐☐☐

Have there been any clinically significant worsenings since the last assessment?

☐ No

☐ Yes⟶ *If 'Yes', please record the findings in the Adverse Experiences section at the back of this module.*

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number			Withdrawal at Visit 4 Week 2
207499/157		[redacted]			

12 LEAD ELECTROCARDIOGRAM

Time of assessment : ☐☐ 24hr:min **The ECG should be performed after the patient has been semi-supine for 5 minutes**

Date ECG Performed (Day Month Year)	Atrial Rate (beats/min)	Ventricular Rate (beats/min)	PR (msec)	QRS (msec)	☐ Uncorrected QT ☐ Corrected QT (msec)	Axis
☐☐☐☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐ + ☐ - ☐☐☐

Interpretation

☐ **(F74301) Within normal limits**

☐ **Abnormal** ⟶ ***Mark appropriate boxes below***

Rhythm
- ☐ (F73360) Sinus arrhythmia
- ☐ (F73310) Sinus bradycardia
- ☐ (F73380) Sinus tachycardia
- ☐ (F73440) Wandering atrial pacemaker
- ☐ (F73450) Premature atrial contractions
- ☐ (F73510) Paroxysmal atrial tachycardia
- ☐ (F73530) Chronic ectopic atrial tachycardia
- ☐ (F73550) Multifocal atrial tachycardia
- ☐ (F73560) Atrial flutter
- ☐ (F73570) Atrial fibrillation
- ☐ (F73610) Junctional (AV nodal) premature contractions
- ☐ (F73650) Junctional (AV nodal) tachycardia
- ☐ (F73150) Supraventricular tachycardia
- ☐ (F73860) Accelerated idioventricular rhythm
- ☐ (F73710) Premature Ventricular Contractions (NOS)
- ☐ (F73720) Unifocal PVC's
- ☐ (F73730) Multifocal PVC's
- ☐ (F73711) Ventricular couplets
- ☐ (F73750) Bigeminy
- ☐ (F73870) Ventricular tachycardia
- ☐ (F73880) Ventricular fibrillation
- ☐ (F73340) Sick sinus syndrome
- ☐ (F73190) Pacemaker rhythm

P-Wave Morphology
- ☐ (F74214) Left atrial hypertrophy, P mitrale
- ☐ (F74213) Right atrial hypertrophy, P pulmonale

Conduction
- ☐ (F73930) First degree AV block
- ☐ (F73950) Second degree AV block, Type 1
- ☐ (F73960) Second degree AV block, Type 11
- ☐ (F73970) Third degree AV block
- ☐ (F74090) Wolff-Parkinson-White syndrome

Axis
- ☐ (F74120) Right Axis deviation
- ☐ (F74130) Left Axis deviation

QRS
- ☐ (F74010) Right bundle branch block
- ☐ (F74020) Left bundle branch block
- ☐ (F74030) Left anterior hemiblock
- ☐ (F74040) Left posterior hemiblock
- ☐ (F74002) Intraventricular conduction delay
- ☐ (F74212) Left ventricular hypertrophy
- ☐ (F74211) Right ventricular hypertrophy
- ☐ (F74308) Q-wave > 0.04 sec
- ☐ (F74222) R-wave amplitude increased
- ☐ (F74225) R-wave amplitude decreased
- ☐ (F74313) Prolonged QT-interval
- ☐ (F74318) Poor R-wave progression
- ☐ (M54750) Myocardial infarction, old
  - ☐ (M54751) Anterior ☐ (M54754) Inferior
  - ☐ (M54752) Lateral ☐ (M54755) Septal
  - ☐ (M54753) Posterior

ST-T
- ☐ (F74291) Nonspecific ST-T changes
- ☐ (F74294) ST segment depression > 1 mm
- ☐ (F74295) ST segment elevation > 1 mm
- ☐ (F74350) T-wave flat
- ☐ (F74351) T-wave inversion
- ☐ (F74352) T-wave peaked
- ☐ (F74340) U-wave
- ☐ (F74360) Digitalis effect
- ☐ (F74260) Myocardial ischemia
  - ☐ (F74261) Anterior ☐ (F74264) Inferior
  - ☐ (F74262) Lateral ☐ (F74265) Septal
  - ☐ (F74263) Posterior
- ☐ (M54720) Myocardial infarction, acute
  - ☐ (M54721) Anterior ☐ (M54724) Inferior
  - ☐ (M54722) Lateral ☐ (M54725) Septal
  - ☐ (M54723) Posterior

Other interpretations not listed _

Were there any clinically important changes observed since the last assessment?

[1] ☐ No

[2] ☐ Yes ⟶ *If 'Yes', enter details on the Adverse Experiences page at the back of this module.*

Place the ECG trace in the plastic wallet a the back of this module

Protocol		Patient Number			Withdrawal at Visit 4 Week 2
207499/157		[redacted]			

PRE-SALBUTAMOL PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed at least 4 hours after the last dose of inhaled beta$_2$-agonist or anticholinergic agent.

Measure the patient's pulmonary function up to eight times to obtain three acceptable readings using the spirometer provided by SB. ***(Note: Please follow instructions in the Spirometry Manual).*** *For each set of three FEV_1 measurements, one FEV_1 must be within 10% of the highest. Please record the results of the effort with the highest FEV_1 below.*

Measurement	Time	FEV_1 (L)	FVC (L)	FEF_{25-75} (L/sec)	PEF (L/min)
1	☐☐ 24hr:min	☐.☐☐	☐.☐☐	☐.☐☐	☐☐☐

Place the spirometry reports in the plasic wallet at the back of this module.

POST-SALBUTAMOL PULMONARY FUNCTION TESTS

Provide the patient with a salbutamol MDI and spacer. Administer 400 mcg (4 puffs) of salbutamol via MDI with a spacer.

Record the time of salbutamol inhalation ☐☐ 24hr:min

Wait 30 minutes

Measure the patient's pulmonary function up to eight times to obtain three acceptable readings using the spirometer provided by SB. ***(Note: Please follow instructions in the Spirometry Manual).*** *For each set of three FEV_1 measurements, one FEV_1 must be within 10% of the highest. Please record the results of the effort with the highest FEV_1 below.*

Measurement	Time	FEV_1 (L)	FVC (L)	FEF_{25-75} (L/sec)	PEF (L/min)
1	☐☐ 24hr:min	☐.☐☐	☐.☐☐	☐.☐☐	☐☐☐

Place spirometry reports in the plastic wallets at the back of this module.

(AT SELECTED CENTRES ONLY) RESIDUAL VOLUME BY BODY PLETHYSMOGRAPHY (PRE- AND POST-SALBUTAMOL)

Time of pre-salbutamol RV assessment: ☐☐ 24hr:min

Time of post-salbutamol RV assessment: ☐☐ 24hr:min

Pre-Salbutamol

$RV_{Box} = TLC_{Box} - \max(|SVC|, |FVC|)$

$RV_{(Box)}$ = ☐.☐☐ (L)

Post-Salbutamol

$RV_{Box} = TLC_{Box} - \max(|SVC|, |FVC|)$

$RV_{(Box)}$ = ☐.☐☐ (L)

Please attach plethysmography source data to the back of this page.

Protocol		Patient Number			Withdrawal at Visit 4 Week 2
207499/157		[redacted]			

FAECAL OCCULT BLOOD TEST

The faecal occult blood test should be performed on three consecutive bowel movements between withdrawal and the next scheduled visit or the Follow-Up visit depending on whether the patient is willing, or not, to return for essential assessments. Patients are not to take samples during or up-to 3-days after a menstrual period or while having bleeding haemorrhoids or blood in the urine. Patients are not to take aspirin or other non-steroidal anti-inflammatory drugs for 7 days prior to and during the test period and they are to avoid Vitamin C in excess of 250mg 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.

Did the patient follow these instructions?

☐ No ⟶ *If 'No', please specify:* _

☐ Yes

Test	Date of Collection Day Mth Yr	Result of faecal occult blood test
1	☐☐ ☐☐☐ ☐☐	[NEG] ☐ Negative [POS] ☐ Positive
2	☐☐ ☐☐☐ ☐☐	[NEG] ☐ Negative [POS] ☐ Positive
3	☐☐ ☐☐☐ ☐☐	[NEG] ☐ Negative [POS] ☐ Positive

Are these findings clinically significant ?

☐ No

☐ Yes ⟶ *If 'Yes' please record the findings and/or diagnosis in the Adverse Experiences section at the back of this module.*

LABORATORY TESTS

Please take blood samples for haematology and blood chemistry (including serum beta-HCG for women of child-bearing potential,CD4/CD8 ratio, serum protein C) and a urine sample for urinalysis. Please refer to the instructions on the Quest shipping form and manual.

Blood Sample Date ☐☐ ☐☐☐ ☐☐
Day Month Yr

Attach a label from the 'Routine' laboratory requisition form used at this visit in the space below.

Attach label here

Are there any **clinically significant worsenings** since the last assessment?

☐ No

☐ Yes ⟶ *If 'Yes' please record the findings and/or diagnosis in the Adverse Experiences section at the back of this module.*

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number		Visit Date (Day Month Year)	
207499/157		[redacted]			**Visit 5 Week 4**

PRESENTATION TO CLINIC

Note: ***Patients must wait for 4 hours after beta$_2$-agonist and / or anticholinergic administration before the pulmonary function tests are performed.***

Did the patient take a dose of beta$_2$ agonist in the past 24 hours?

☐ No

☐ Yes ⟶ Record date and time of the patient's last dose of beta$_2$ agonist: Day Month Yr 24hr:min

Did the patient take a dose of anticholinergic in the past 24 hours?

☐ No

☐ Yes ⟶ Record date and time of patient's last dose of anticholinergic: Day Month Yr 24hr:min

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes ⟶ Date and time of patient's last cigarette Day Month Yr 24hr:min

SMOKING STATUS

Does the patient currently smoke?

☐ No

☐ Yes ⟶ If 'Yes' please record the average number of cigarettes per day :

INFLUENZA VACCINATION

Has the patient had a vaccination for influenza since the last visit?

N.B. It is not necessary to record vaccinations on the Concomitant Medication or Medical Procedures page.

☐ No

☐ Yes ⟶ *If 'Yes', record date of vaccination :* Day Month Yr

Protocol		Patient Number			Visit 5 Week 4
207499/157		[redacted]			

RESOLUTION OF COPD EXACERBATIONS

Have any COPD Exacerbations resolved since the last visit?

☐ No

☐ Yes ⟶ *If 'Yes', please record details in the COPD Exacerbation section at the back of this module.*

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes ⟶ *If 'Yes' please record details in the COPD Exacerbation section at the back of this module.*

Level 1 (Mild-self treated): Acute worsening of COPD that is self-managed by the patient at home by increasing the dose of relief salbutamol medication by > 2 occasions/24 hour period on two or more consecutive days compared with their baseline (baseline = mean of last 10 days of run-in period) or use of other additional bronchodilator medication

Level 2 (Moderate- physician, investigator treated): Acute worsening of symptoms (cough, sputum production, breathlessness) requiring treatment with oral corticosteroids prescribed by a physician or primary care doctor, or as a result of hospital out-patient visit (including Emergency Room).

Exacerbations requiring oral corticosteroids will be treated with a standardised course of prednisolone or prednisone tablets 30mg/day for 10 days, or methylprednisolone tablets 24mg/day for 10 days.

Level 3 (Severe - attendance at hospital): Acute worsening of COPD that requires the patient to be admitted to hospital for treatment.

If a patient experienced a COPD exacerbation that was treated with corticosteroids, please withdraw the patient and complete the Study Continuation/Withdrawal page at the back of this book. 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, including an increase in usual COPD medications, must be recorded in the COPD Medications or Procedures pages.

00000

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number			Visit 5 Week 4
207499/157		[redacted]			

RESOURCE UTILISATION

If the patient has received any COPD exacerbation-related medical care since the last visit, record details on the Resource Utilisation pages of the COPD Exacerbation section at the back of this module.

DIARY CARD REVIEW

Review the diary card in the presence of the patient. Question any increased symptoms for possible COPD exacerbations. Place diary in the plastic wallet at the back of this module and re-issue another diary card.

ADVERSE EXPERIENCES

Please complete the Adverse Experiences 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 Experiences 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		Patient Number			Visit 5 Week 4
207499/157		[redacted]			

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. bd)

Date and time of last dose of study medication prior to the study visit ____ ____ ____ (Day Month Yr) ____ ____ (24hr:min)

STUDY MEDICATION COMPLIANCE

Note : Tablets re-dispensed should be entered as the number of tablets returned at the previous visit.

Tablets Re-dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance

$$\% \text{ Compliance} = \frac{\textit{Number of Tablets Taken}}{\textit{2 x Days Since Last Visit}} \textit{ x100}$$

Is compliance ≥ 80% and ≤120%?

☐ No ⟶ *If 'No' please remind the patient of the importance of taking study medication according to the protocol.*

☐ Yes

00000

SmithKline Beecham
Pharmaceuticals

Protocol **207499/157**		**Patient Number** [redacted]			**Visit 5 Week 4**

INVESTIGATOR INSTRUCTIONS

The following procedures (Vital Signs and Pulmonary Function Tests) must be performed greater than 4 hours after the patient's last salbutamol administration.

VITAL SIGNS

Time of assessment : ☐☐ 24hr:min

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
☐☐☐/☐☐☐	☐☐☐

Are there any **clinically significant worsenings** since the previous visit?

☐ No

☐ Yes ⟶ *If 'Yes' please record the findings and/or diagnosis in the Adverse Experiences section at the back of this module.*

Protocol		Patient Number			Visit 5 Week 4
207499/157		[redacted]			

PRE-SALBUTAMOL PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed at least 4 hours after the last dose of inhaled beta$_2$-agonist or anticholinergic agent.

Measure the patient's pulmonary function up to eight times to obtain three acceptable readings using the spirometer provided by SB. ***(Note: Please follow instructions in the Spirometry Manual).*** *For each set of three FEV_1 measurements, one FEV_1 must be within 10% of the highest. Please record the results of the effort with the highest FEV_1 below.*

Measurement	Time	FEV_1 (L)	FVC (L)	FEF_{25-75} (L/sec)	PEF (L/min)
1	☐☐ 24hr:min	☐.☐☐	☐.☐☐	☐.☐☐	☐☐☐

Place the spirometry reports in the plasic wallet at the back of this module.

POST-SALBUTAMOL PULMONARY FUNCTION TESTS

Provide the patient with a salbutamol MDI and spacer. Administer 400 mcg (4 puffs) of salbutamol via MDI with a spacer. Remind the patient to use this inhaler (with or without the spacer), rather than any salbutamol inhaler they may have at home, for "as required" rescue-medication use during the study.

Record the time of salbutamol inhalation ☐☐ 24hr:min

Wait 30 minutes

Measure the patient's pulmonary function up to eight times to obtain three acceptable readings using the spirometer provided by SB. ***(Note: Please follow instructions in the Spirometry Manual).*** *For each set of three FEV_1 measurements, one FEV_1 must be within 10% of the highest. Please record the results of the effort with the highest FEV_1 below.*

Measurement	Time	FEV_1 (L)	FVC (L)	FEF_{25-75} (L/sec)	PEF (L/min)
1	☐☐ 24hr:min	☐.☐☐	☐.☐☐	☐.☐☐	☐☐☐

Place spirometry reports in the plastic wallets at the back of this module.

PULMONARY REHABILITATION PROGRAM

Has the patient entered a Pulmonary Rehabilitation Program since the last visit?

☐ No

☐ Yes

00000

SmithKline Beecham
Pharmaceuticals

Protocol 207499/157		**Patient Number** [redacted]			**Visit 5 Week 4**

LABORATORY TESTS

Please take blood samples for haematology and blood chemistry (including serum beta-HCG for women of child-bearing potential) and a urine sample for urinalysis. Please refer to the instructions on the Quest shipping form and manual.

Blood Sample Date ☐☐ ☐☐ ☐☐
Day Month Yr

Attach a label from the 'Routine' laboratory requisition form used at this visit in the space below.

Attach label here

Are there any **clinically significant worsenings** since the last assessment?

☐ No

☐ Yes ⟶ *If 'Yes' please record the findings and/or diagnosis in the Adverse Experiences section at the back of this module.*

STUDY MEDICATION ALLOCATION - RAMOS CALL

Following completion of all preceding assessments, complete the RAMOS worksheet appropriate for this visit and contact RAMOS to obtain the container number for this visit.

*Please enter the 5-digit **randomisation number** assigned by RAMOS* ☐☐☐☐☐

*Please enter the 6-digit **container number** as it appears on the study medication label*: ☐☐☐☐☐☐

STUDY MEDICATION LABEL

Attach the tear-off label from the study medication container 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

00000

SmithKline Beecham
Pharmaceuticals

Protocol **207499/157**		**Patient Number** [redacted]			**Visit 5 Week 4**

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 5

Is the patient continuing in the study?

☐ No

☐ Yes

*If the patient is **not** continuing in the study, is the patient willing to return for essential assessments?*

If 'No', please complete the assessments for Visit 5 and the additional assessments for patients withdrawing at Visit 5 and the Study Continuation/Withdrawal page at the back of this book.

If 'Yes', please complete the assessments for Visit 5, the assessments for patients withdrawing at Visit 5 and the Study Continuation/Withdrawal page at the back of this book. Ask the patient to return in 28 +/-6 days time for essential assessments only.

*If the patient **is** continuing in the study, please:*	(tick if done)
	☑
• *Issue the patient a new diary card and remind the patient to complete the diary each morning until the next visit.*	☐
• *Ask the patient to return for the next visit in 28 +/- 6 days for a morning visit.*	☐
• ***Remind the patient:***	
i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after their breakfast.*	☐
ii ***not** to take the morning dose of study medication at home on the day of the next clinic visit.*	☐
iii *to refrain from using salbutamol or anticholinergic agents during the **4 hours** immediately preceding 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, the study salbutamol inhaler and spacer, and the diary card.*	☐
vi *to continue to take the anticholinergic medication, if prescribed, at a constant dose, and salbutamol when needed to control symptoms.*	☐
vii *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 occurrence.*	☐

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number			Withdrawal at Visit 5 Week 4
207499/157		[redacted]			

ASSESSMENTS FOR PATIENTS WITHDRAWING AT VISIT 5

Complete the assessments below only for patients who are withdrawing from the study at this visit.

ST. GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND EQ-5D

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

INVESTIGATOR GLOBAL EVALUATION OF IMPROVEMENT

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

PATIENT GLOBAL EVALUATION OF IMPROVEMENT

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

00000

SmithKline Beecham
Pharmaceuticals

Protocol **207499/157**		**Patient Number** [redacted]			**Withdrawal at Visit 5 Week 4**

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 Experiences section at the back of this module.*

VITAL SIGNS - ORTHOSTATIC CHANGE

Time of assessment : ☐☐ 24hr:min

1st Measurement: After 5 Minutes Supine		**2nd Measurement: 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)
☐☐☐/☐☐☐	☐☐☐	☐☐☐/☐☐☐	☐☐☐

Have there been any clinically significant worsenings since the last assessment?

☐ No

☐ Yes⟶ *If 'Yes', please record the findings in the Adverse Experiences section at the back of this module.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number			Withdrawal at Visit 5 Week 4
207499/157		[redacted]			

12 LEAD ELECTROCARDIOGRAM

Time of assessment : ☐☐ 24hr:min **The ECG should be performed after the patient has been semi-supine for 5 minutes**

Date ECG Performed (Day Month Year)	Atrial Rate (beats/min)	Ventricular Rate (beats/min)	PR (msec)	QRS (msec)	☐ Uncorrected QT ☐ Corrected QT (msec)	Axis
☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐ + ☐ - ☐☐☐

Interpretation

☐ **(F74301) Within normal limits**

☐ **Abnormal** ⟶ ***Mark appropriate boxes below***

Rhythm
- ☐ (F73360) Sinus arrhythmia
- ☐ (F73310) Sinus bradycardia
- ☐ (F73380) Sinus tachycardia
- ☐ (F73440) Wandering atrial pacemaker
- ☐ (F73450) Premature atrial contractions
- ☐ (F73510) Paroxysmal atrial tachycardia
- ☐ (F73530) Chronic ectopic atrial tachycardia
- ☐ (F73550) Multifocal atrial tachycardia
- ☐ (F73560) Atrial flutter
- ☐ (F73570) Atrial fibrillation
- ☐ (F73610) Junctional (AV nodal) premature contractions
- ☐ (F73650) Junctional (AV nodal) tachycardia
- ☐ (F73150) Supraventricular tachycardia
- ☐ (F73860) Accelerated idioventricular rhythm
- ☐ (F73710) Premature Ventricular Contractions (NOS)
- ☐ (F73720) Unifocal PVC's
- ☐ (F73730) Multifocal PVC's
- ☐ (F73711) Ventricular couplets
- ☐ (F73750) Bigeminy
- ☐ (F73870) Ventricular tachycardia
- ☐ (F73880) Ventricular fibrillation
- ☐ (F73340) Sick sinus syndrome
- ☐ (F73190) Pacemaker rhythm

P-Wave Morphology
- ☐ (F74214) Left atrial hypertrophy, P mitrale
- ☐ (F74213) Right atrial hypertrophy, P pulmonale

Conduction
- ☐ (F73930) First degree AV block
- ☐ (F73950) Second degree AV block, Type 1
- ☐ (F73960) Second degree AV block, Type 11
- ☐ (F73970) Third degree AV block
- ☐ (F74090) Wolff-Parkinson-White syndrome

Axis
- ☐ (F74120) Right Axis deviation
- ☐ (F74130) Left Axis deviation

QRS
- ☐ (F74010) Right bundle branch block
- ☐ (F74020) Left bundle branch block
- ☐ (F74030) Left anterior hemiblock
- ☐ (F74040) Left posterior hemiblock
- ☐ (F74002) Intraventricular conduction delay
- ☐ (F74212) Left ventricular hypertrophy
- ☐ (F74211) Right ventricular hypertrophy
- ☐ (F74308) Q-wave > 0.04 sec
- ☐ (F74222) R-wave amplitude increased
- ☐ (F74225) R-wave amplitude decreased
- ☐ (F74313) Prolonged QT-interval
- ☐ (F74318) Poor R-wave progression
- ☐ (M54750) Myocardial infarction, old
  - ☐ (M54751) Anterior ☐ (M54754) Inferior
  - ☐ (M54752) Lateral ☐ (M54755) Septal
  - ☐ (M54753) Posterior

ST-T
- ☐ (F74291) Nonspecific ST-T changes
- ☐ (F74294) ST segment depression > 1 mm
- ☐ (F74295) ST segment elevation > 1 mm
- ☐ (F74350) T-wave flat
- ☐ (F74351) T-wave inversion
- ☐ (F74352) T-wave peaked
- ☐ (F74340) U-wave
- ☐ (F74360) Digitalis effect
- ☐ (F74260) Myocardial ischemia
  - ☐ (F74261) Anterior ☐ (F74264) Inferior
  - ☐ (F74262) Lateral ☐ (F74265) Septal
  - ☐ (F74263) Posterior
- ☐ (M54720) Myocardial infarction, acute
  - ☐ (M54721) Anterior ☐ (M54724) Inferior
  - ☐ (M54722) Lateral ☐ (M54725) Septal
  - ☐ (M54723) Posterior

Other interpretations not listed _

Were there any clinically important changes observed since the last assessment?

[1] ☐ No

[2] ☐ Yes ⟶ *If 'Yes', enter details on the Adverse Experiences page at the back of this module.*

Place the ECG trace in the plastic wallet a the back of this module

Protocol		Patient Number			Withdrawal at Visit 5 Week 4
207499/157		[redacted]			

(AT SELECTED CENTRES ONLY) RESIDUAL VOLUME BY BODY PLETHYSMOGRAPHY (PRE- AND POST-SALBUTAMOL)

Time of pre-salbutamol RV assessment: ☐☐ 24hr:min

Time of post-salbutamol RV assessment: ☐☐ 24hr:min

Pre-Salbutamol

$RV_{Box} = TLC_{Box} – max(|SVC|, |FVC|)$

$RV_{(Box)}$ = ☐.☐☐ (L)

Post-Salbutamol

$RV_{Box} = TLC_{Box} – max(|SVC|, |FVC|)$

$RV_{(Box)}$ = ☐.☐☐ (L)

Please attach plethysmography source data to the back of this page.

FAECAL OCCULT BLOOD TEST

The faecal occult blood test should be performed on three consecutive bowel movements between withdrawal and the next scheduled visit or the Follow-Up visit depending on whether the patient is willing, or not, to return for essential assessments. Patients are not to take samples during or up-to 3-days after a menstrual period or while having bleeding haemorrhoids or blood in the urine. Patients are not to take aspirin or other non-steroidal anti-inflammatory drugs for 7 days prior to and during the test period and they are to avoid Vitamin C in excess of 250mg 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.

Did the patient follow these instructions?

☐ No ⟶ *If 'No', please specify:* _

☐ Yes

Test	Date of Collection Day Mth Yr	Result of faecal occult blood test
1	☐☐ ☐☐ ☐☐	[NEG] ☐ Negative [POS] ☐ Positive
2	☐☐ ☐☐ ☐☐	[NEG] ☐ Negative [POS] ☐ Positive
3	☐☐ ☐☐ ☐☐	[NEG] ☐ Negative [POS] ☐ Positive

Are these findings clinically significant ?

☐ No

☐ Yes ⟶ *If 'Yes' please record the findings and/or diagnosis in the Adverse Experiences section at the back of this module.*

00000

SmithKline Beecham
Pharmaceuticals

Protocol		**Patient Number**			**Withdrawal at Visit 5 Week 4**
207499/157		[redacted]			

LABORATORY TESTS

Please take blood samples for CD4/CD8 ratio and C Reactive Protein. Please refer to the instructions on the Quest shipping form and manual.

Blood Sample Date ☐☐ ☐☐ ☐☐
Day Month Yr

Attach a label from the 'Routine' laboratory requisition form used at this visit in the space below.

Attach label here

Are there any **clinically significant worsenings** since the last assessment?

☐ No

☐ Yes ⟶ *If 'Yes' please record the findings and/or diagnosis in the Adverse Experiences section at the back of this module.*

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 study procedures should be reported as a serious event

IF AN 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

g_ae_instr_01

Protocol	Centre Number	Patient Number			Adverse Experiences
207499/157		[redacted]			

ADVERSE EXPERIENCES (Non-serious)

g_ae_01

*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 last visit?"*
*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).

☐ Please mark this box if no adverse experiences occurred since the last module

Adverse Experience *(please print clearly)*		
For SB		
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 SAE section and follow instructions given there***	[1] ☐ Resolved [2] ☐ Ongoing [3] ☐ Died	[1] ☐ Resolved [2] ☐ Ongoing [3] ☐ Died
Experience Course	[1] ☐ Intermittent → No. of episodes ☐ [2] ☐ Constant	[1] ☐ Intermittent → No. of episodes ☐ [2] ☐ Constant
Intensity (maximum)	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Action Taken with Respect to Investigational Drug	[1] ☐ None [2] ☐ Dose reduced [3] ☐ Dose increased [4] ☐ Drug interrupted/restarted [5] ☐ Drug stopped	[1] ☐ None [2] ☐ Dose reduced [3] ☐ Dose increased [4] ☐ Drug interrupted/restarted [5] ☐ Drug stopped
Relationship to Investigational Drug	[1] ☐ Not related [2] ☐ Unlikely [3] ☐ Suspected (reasonable possibility) [4] ☐ Probable	[1] ☐ Not related [2] ☐ Unlikely [3] ☐ Suspected (reasonable possibility) [4] ☐ Probable
Corrective Therapy *If 'Yes', record details in the Concomitant Medication section and/ or Medical Procedures section if appropriate*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No

SmithKline Beecham Pharmaceuticals

Protocol	Centre Number	Patient Number			Adverse Experiences
207499/157		[redacted]			

ADVERSE EXPERIENCES (Non-serious) - Continued

g_ae_01

*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 last visit?" 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).

Adverse Experience *(please print clearly)*		
For SB		
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 SAE section and follow instructions given there***	[1] Resolved [2] Ongoing [3] Died	[1] Resolved [2] Ongoing [3] Died
Experience Course	[1] Intermittent → No. of episodes [2] Constant	[1] Intermittent → No. of episodes [2] Constant
Intensity (maximum)	[1] Mild [2] Moderate [3] Severe	[1] Mild [2] Moderate [3] Severe
Action Taken with Respect to Investigational Drug	[1] None [2] Dose reduced [3] Dose increased [4] Drug interrupted/restarted [5] Drug stopped	[1] None [2] Dose reduced [3] Dose increased [4] Drug interrupted/restarted [5] Drug stopped
Relationship to Investigational Drug	[1] Not related [2] Unlikely [3] Suspected (reasonable possibility) [4] Probable	[1] Not related [2] Unlikely [3] Suspected (reasonable possibility) [4] Probable
Corrective Therapy *If 'Yes', record details in the Concomitant Medication section and/ or Medical Procedures section if appropriate*	Yes No	Yes No
Was patient withdrawn due to this specific AE?	Yes No	Yes No

SmithKline Beecham Pharmaceuticals

Protocol	Centre Number	Patient Number			Adverse Experiences
207499/157		[redacted]			

ADVERSE EXPERIENCES (Non-serious) - Continued

g_ae_01

*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 last visit?"*
*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).

Adverse Experience *(please print clearly)*		
For SB		
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 SAE section and follow instructions given there***	[1] Resolved [2] Ongoing [3] Died	[1] Resolved [2] Ongoing [3] Died
Experience Course	[1] Intermittent → No. of episodes [2] Constant	[1] Intermittent → No. of episodes [2] Constant
Intensity (maximum)	[1] Mild [2] Moderate [3] Severe	[1] Mild [2] Moderate [3] Severe
Action Taken with Respect to Investigational Drug	[1] None [2] Dose reduced [3] Dose increased [4] Drug interrupted/restarted [5] Drug stopped	[1] None [2] Dose reduced [3] Dose increased [4] Drug interrupted/restarted [5] Drug stopped
Relationship to Investigational Drug	[1] Not related [2] Unlikely [3] Suspected (reasonable possibility) [4] Probable	[1] Not related [2] Unlikely [3] Suspected (reasonable possibility) [4] Probable
Corrective Therapy *If 'Yes', record details in the Concomitant Medication section and/ or Medical Procedures section if appropriate*	Yes No	Yes No
Was patient withdrawn due to this specific AE?	Yes No	Yes No

Protocol	Centre Number	Patient Number			Concomitant Medication
207499/157		[redacted]			

CONCOMITANT MEDICATION

Record any changes in concomitant medication taken since the last 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. At the patient's final study visit, record the end date for prn study rescue medication (salbutamol) use, using the date the study inhaler was returned.

☐ No concomitant medication changes since the last module

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded in the Adverse Experiences 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** (eg 500mg)	**Frequency** (eg bd, 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	
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							

** For Route, see general instructions for acceptable abbreviations.*

Protocol	**Centre Number**	**Patient Number**			**Concomitant Medication**
207499/157		[redacted]			

CONCOMITANT MEDICATION (Cont.)

Do not record any medication taken for COPD exacerbations in this section. Record all COPD exacerbation medication in the COPD Exacerbation section. At the patient's final study visit, record the end date for prn study rescue medication (salbutamol) use, using the date the study inhaler was returned.

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded in the Adverse Experiences 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** (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	
For SB							
For SB							
For SB							
For SB							
For SB							
For SB							
For SB							
For SB							
For SB							
For SB							

** For Route, see general instructions for acceptable abbreviations.*

g_conmed_01

Protocol	Centre Number	Patient Number			Medical Procedures
207499/157		[redacted]			

MEDICAL PROCEDURES

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 last module?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below using standard medical terminology*

All indications for procedures should be recorded on the Adverse Experiences Form.

Procedure	Indication	Procedure Start Date Day Mth Yr	Procedure End Date Day Mth Yr
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			COPD Exacerbations (AE)
207499/157		[redacted]			

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 last 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***

Has the patient suffered any COPD Exacerbations since the last module ?

☐ No

☐ Yes → *If 'Yes', please complete page below*

Adverse Event	COPD EXACERBATION
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, STOP: delete details of this exacerbation and go to SAE COPD Exacerbation pages.***	[1] ☐ Resolved [2] ☐ Ongoing [3] ☐ Died
Event Course	[1] ☐ Intermittent → No. of episodes ☐ [2] ☐ Constant
Intensity (maximum) *See definitions page for Adverse Experiences form.*	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Action Taken with Respect to Investigational Drug	[1] ☐ None [2] ☐ Dose reduced [3] ☐ Dose increased [4] ☐ Drug interrupted/restarted [5] ☐ Drug stopped
Relationship to Investigational Drug	[1] ☐ Not related [2] ☐ Unlikely [3] ☐ Suspected (reasonable possibility) [4] ☐ Probable
Corrective Therapy *If 'Yes', record details on the COPD Medications or Procedures page*	☐ Yes ☐ No
Was patient withdrawn due to this specific event?	☐ Yes ☐ No

DEFINITIONS OF LEVELS OF EXACERBATION OF COPD

Level 1 (Mild-self treated): Acute worsening of COPD that is self-managed by the patient at home by increasing the dose of relief salbutamol medication by > 2 occasions/24 hour period on two or more consecutive days compared with their baseline (baseline = mean of last 10 days of run-in period) or use of other additional bronchodilator medication

Level 2 (Moderate- physician, investigator treated): Acute worsening of symptoms (cough, sputum production, breathlessness) requiring treatment with oral corticosteroids prescribed by a physician or primary care doctor, or as a result of hospital out-patient visit (including Emergency Room).

Exacerbations requiring oral corticosteroids will be treated with a standardised course of prednisolone or prednisone tablets 30mg/day for 10 days, or methylprednisolone tablets 24mg/day for 10 days.

Level 3 (Severe - attendance at hospital): Acute worsening of COPD that requires the patient to be admitted to hospital for treatment.

Protocol	Centre Number	Patient Number			COPD Exacerbations (AE)
207499/157					

FURTHER DETAILS OF COPD EXACERBATIONS

COPD exacerbation onset date : Day Month Yr

Level of exacerbation (see definitions on facing page):

[1] ☐ Level 1
[2] ☐ Level 2
[3] ☐ Level 3

Pumonary function test result (FEV_1) (if done):

☐.☐☐ L

Did the patient suffer from any of the following during the exacerbation:

[1] ☐ Chest pain
[2] ☐ Upper Respiratory Tract Infection
[3] ☐ Confusion
[4] ☐ Change in alertness
[5] ☐ Pneumonia
[6] ☐ Oedema
[7] ☐ Ankle swelling

ARTERIAL BLOOD GASES (only for COPD exacerbations)

Where feasible, an arterial blood gas sample is to be taken for analysis

COPD exacerbation onset date : Day Month Yr

PO_2 (mmHg)	**PCO_2** (mmHg)	**pH**	**Resting SaO_2** (%)
☐☐☐	☐☐	☐.☐☐	☐☐☐

RESOURCE UTILISATION

Please complete the Resource Utilisation pages for this exacerbation.

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			COPD Exacerbations (AE)
207499/157		[redacted]			

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 last 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 Event	COPD EXACERBATION
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, STOP: delete details of this exacerbation and go to SAE COPD Exacerbation pages.***	[1] ☐ Resolved [2] ☐ Ongoing [3] ☐ Died
Event Course	[1] ☐ Intermittent → No. of episodes ☐ [2] ☐ Constant
Intensity (maximum) *See definitions page for Adverse Experiences form.*	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Action Taken with Respect to Investigational Drug	[1] ☐ None [2] ☐ Dose reduced [3] ☐ Dose increased [4] ☐ Drug interrupted/restarted [5] ☐ Drug stopped
Relationship to Investigational Drug	[1] ☐ Not related [2] ☐ Unlikely [3] ☐ Suspected (reasonable possibility) [4] ☐ Probable
Corrective Therapy *If 'Yes', record details on the COPD Medications or Procedures page*	☐ Yes ☐ No
Was patient withdrawn due to this specific event?	☐ Yes ☐ No

DEFINITIONS OF LEVELS OF EXACERBATION OF COPD

Level 1 (Mild-self treated): Acute worsening of COPD that is self-managed by the patient at home by increasing the dose of relief salbutamol medication by > 2 occasions/24 hour period on two or more consecutive days compared with their baseline (baseline = mean of last 10 days of run-in period) or use of other additional bronchodilator medication

Level 2 (Moderate- physician, investigator treated): Acute worsening of symptoms (cough, sputum production, breathlessness) requiring treatment with oral corticosteroids prescribed by a physician or primary care doctor, or as a result of hospital out-patient visit (including Emergency Room).

Exacerbations requiring oral corticosteroids will be treated with a standardised course of prednisolone or prednisone tablets 30mg/day for 10 days, or methylprednisolone tablets 24mg/day for 10 days.

Level 3 (Severe - attendance at hospital): Acute worsening of COPD that requires the patient to be admitted to hospital for treatment.

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			COPD Exacerbations (AE)
207499/157					

FURTHER DETAILS OF COPD EXACERBATIONS

COPD exacerbation onset date : Day Month Yr

Level of exacerbation (see definitions on facing page):

[1] ☐ Level 1
[2] ☐ Level 2
[3] ☐ Level 3

Pumonary function test result (FEV_1) (if done):

☐.☐☐ L

Did the patient suffer from any of the following during the exacerbation:

[1] ☐ Chest pain
[2] ☐ Upper Respiratory Tract Infection
[3] ☐ Confusion
[4] ☐ Change in alertness
[5] ☐ Pneumonia
[6] ☐ Oedema
[7] ☐ Ankle swelling

ARTERIAL BLOOD GASES (only for COPD exacerbations)

Where feasible, an arterial blood gas sample is to be taken for analysis

COPD exacerbation onset date : Day Month Yr

PO_2 (mmHg)	**PCO_2** (mmHg)	**pH**	**Resting SaO_2** (%)
☐☐☐	☐☐	☐.☐☐	☐☐☐

RESOURCE UTILISATION

Please complete the Resource Utilisation pages for this exacerbation.

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			COPD Exacerbations (AE)
207499/157		[redacted]			

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 last 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 Event	COPD EXACERBATION
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, STOP: delete details of this exacerbation and go to SAE COPD Exacerbation pages.***	[1] ☐ Resolved [2] ☐ Ongoing [3] ☐ Died
Event Course	[1] ☐ Intermittent → No. of episodes ☐ [2] ☐ Constant
Intensity (maximum) *See definitions page for Adverse Experiences form.*	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Action Taken with Respect to Investigational Drug	[1] ☐ None [2] ☐ Dose reduced [3] ☐ Dose increased [4] ☐ Drug interrupted/restarted [5] ☐ Drug stopped
Relationship to Investigational Drug	[1] ☐ Not related [2] ☐ Unlikely [3] ☐ Suspected (reasonable possibility) [4] ☐ Probable
Corrective Therapy *If 'Yes', record details on the COPD Medications or Procedures page*	☐ Yes ☐ No
Was patient withdrawn due to this specific event?	☐ Yes ☐ No

DEFINITIONS OF LEVELS OF EXACERBATION OF COPD

Level 1 (Mild-self treated): Acute worsening of COPD that is self-managed by the patient at home by increasing the dose of relief salbutamol medication by > 2 occasions/24 hour period on two or more consecutive days compared with their baseline (baseline = mean of last 10 days of run-in period) or use of other additional bronchodilator medication

Level 2 (Moderate- physician, investigator treated): Acute worsening of symptoms (cough, sputum production, breathlessness) requiring treatment with oral corticosteroids prescribed by a physician or primary care doctor, or as a result of hospital out-patient visit (including Emergency Room).

Exacerbations requiring oral corticosteroids will be treated with a standardised course of prednisolone or prednisone tablets 30mg/day for 10 days, or methylprednisolone tablets 24mg/day for 10 days.

Level 3 (Severe - attendance at hospital): Acute worsening of COPD that requires the patient to be admitted to hospital for treatment.

Protocol	Centre Number	Patient Number			COPD Exacerbations (AE)
207499/157					

FURTHER DETAILS OF COPD EXACERBATIONS

COPD exacerbation onset date : Day Month Yr

Level of exacerbation (see definitions on facing page):

[1] ☐ Level 1
[2] ☐ Level 2
[3] ☐ Level 3

Pumonary function test result (FEV_1) (if done):

☐.☐☐ L

Did the patient suffer from any of the following during the exacerbation:

[1] ☐ Chest pain
[2] ☐ Upper Respiratory Tract Infection
[3] ☐ Confusion
[4] ☐ Change in alertness
[5] ☐ Pneumonia
[6] ☐ Oedema
[7] ☐ Ankle swelling

ARTERIAL BLOOD GASES (only for COPD exacerbations)

Where feasible, an arterial blood gas sample is to be taken for analysis

COPD exacerbation onset date : Day Month Yr

PO_2 (mmHg)	**PCO_2** (mmHg)	**pH**	**Resting SaO_2** (%)
☐☐☐	☐☐	☐.☐☐	☐☐☐

RESOURCE UTILISATION

Please complete the Resource Utilisation pages for this exacerbation.

SmithKline Beecham Pharmaceuticals

Protocol	Centre Number	Patient Number		SB Receipt Date (Day Month Year)	COPD Exacerbations (SAE)
207499/157		[redacted]			

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation

Person Reporting SAE _____ *(Please print clearly)*

AEGIS Number _____ . _____

Serious Adverse Experience	**COPD Exacerbation**
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*	[1] ☐ Resolved [2] ☐ Ongoing [3] ☐ Died
Experience Course	[1] ☐ Intermittent → No. of episodes ☐ [2] ☐ Constant
Intensity *(maximum)*	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Action Taken with Respect to Investigational Drug	[1] ☐ None [2] ☐ Dose reduced [3] ☐ Dose increased [4] ☐ Drug interrupted/ restarted [5] ☐ Drug stopped
Relationship to Investigational Drug	[1] ☐ Not related [2] ☐ Unlikely [3] ☐ Suspected (reasonable possibility) [4] ☐ Probable
Corrective Therapy *If 'Yes', record details in the COPD Concomitant Medication section*	☐ Yes ☐ No
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No

→ *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

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 _____

00000

SmithKline Beecham
Pharmaceuticals

Protocol	**Centre Number**	**Patient Number**		**SB Receipt Date** Day Month Year	**COPD Exacerbations (SAE)**
207499/157		[redacted]			

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation

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 Number (please do NOT enter the container number): ☐☐☐☐☐

Investigator's Signature: _____ Date ☐☐ ☐☐ ☐☐☐☐
(confirming that the above data are accurate and complete) Day Month Year

Please PRINT Name _____

SB Medical Monitor's Signature: _____ Date ☐☐ ☐☐ ☐☐☐☐

Please PRINT Name _____ Day Month Year

DEFINITIONS OF LEVELS OF EXACERBATION OF COPD

Level 1 (Mild-self treated): Acute worsening of COPD that is self-managed by the patient at home by increasing the dose of relief salbutamol medication by > 2 occasions/24 hour period on two or more consecutive days compared with their baseline (baseline = mean of last 10 days of run-in period) or use of other additional bronchodilator medication

Level 2 (Moderate- physician, investigator treated): Acute worsening of symptoms (cough, sputum production, breathlessness) requiring treatment with oral corticosteroids prescribed by a physician or primary care doctor, or as a result of hospital out-patient visit (including Emergency Room).

Exacerbations requiring oral corticosteroids will be treated with a standardised course of prednisolone or prednisone tablets 30mg/day for 10 days, or methylprednisolone tablets 24mg/day for 10 days.

Level 3 (Severe - attendance at hospital): Acute worsening of COPD that requires the patient to be admitted to hospital for treatment.

00000

SmithKline Beecham
Pharmaceuticals

Protocol	**Centre Number**	**Patient Number**		**SB Receipt Date** Day Month Year	**COPD Exacerbations (SAE)**
207499/157		[redacted]			

FURTHER DETAILS OF SERIOUS COPD EXACERBATIONS

COPD exacerbation onset date : Day Month Yr

Level of exacerbation (see definitions on facing page):

[1] ☐ Level 1
[2] ☐ Level 2
[3] ☐ Level 3

Pumonary function test result (FEV_1) (if done):

☐.☐☐ L

Did the patient suffer from any of the following during the exacerbation:

[1] ☐ Chest pain
[2] ☐ Upper Respiratory Tract Infection
[3] ☐ Confusion
[4] ☐ Change in alertness
[5] ☐ Pneumonia
[6] ☐ Oedema
[7] ☐ Ankle swelling

ARTERIAL BLOOD GASES (only for serious COPD exacerbations)

Where feasible, an arterial blood gas sample is to be taken for analysis

COPD exacerbation onset date : Day Month Yr

PO_2 (mmHg)	**PCO_2** (mmHg)	**pH**	**Resting SaO_2** (%)
☐☐☐	☐☐	☐.☐☐	☐☐☐

RESOURCE UTILISATION

Please complete the Resource Utilisation pages for this exacerbation.

Protocol	**Centre Number**	**Patient Number**			**COPD Exacerbations (ConMed)**
207499/157		[redacted]			

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)	**Freq.** (eg bd, prn)	**Route***	**Medical Illness/ Diag.**	**Start Date** *(be as precise as possible)* Day Mth Yr	**End Date** *(or if Continuing mark box)* Day Mth Yr		COPD Exacerbation Onset Date
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								

** For Route, see General Instructions for acceptable abbreviations.*

SmithKline Beecham
Pharmaceuticals

Protocol	**Centre Number**	**Patient Number**			**COPD Exacerbations (ConMed)**
207499/157		[redacted]			

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** Day Mth Yr	**Procedure End Date** Day Mth Yr	COPD Exacerbation Onset Date
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				

Protocol	Centre Number	Patient Number			Resource Utilisation For COPD Exacerbations
207499/157		[redacted]			

RESOURCE UTILISATION FOR COPD EXACERBATIONS

Has the patient had any medical care for COPD Exacerbations that have occurred since the previous module?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below*

Has the patient had any **Physician contact** (COPD care excluding scheduled protocol visits) since the previous module?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below*

Date of Contact Day Mth Yr	Telephone	Home Visit		Office/ Practice	Out-patients	Reason for contact	COPD Exacerbation Onset Date Day Mth Yr
		Day	Night				

Has the patient had any **Emergency Room (ER)/Urgent Care Visits/Procedures (i.e., lung surgery)** since the previous module?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below*

Date of Contact Day Mth Yr	**Reason for contact**	**Patient Admitted from ER?**		COPD Exacerbation Onset Date Day Mth Yr
		Yes	**No**	

Protocol	Centre Number	Patient Number			Resource Utilisation For COPD Exacerbations
207499/157		[redacted]			

RESOURCE UTILISATION FOR COPD EXACERBATIONS - (cont)

Has the patient had any **Hospitalisations** since the previous module?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below* ***(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	COPD Exacerbation Onset Date Day Mth Yr

Has the patient had any **Intensive Care Unit (ICU) stays** ***(did the patient stay in the ICU during any of the above hospitalisations?)*** since the previous module?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below*

Date Admitted to ICU Day Mth Yr	Date Discharged from ICU Day Mth Yr	Reason for ICU Admission	COPD Exacerbation Onset Date Day Mth Yr

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			
207499/157		[redacted]			

2 0 7 4 9 9 1 5 7

MOD4

Please do not split modules

Module 4 : **Visit 6, Visit 7, Adverse Experiences, Concomitant Medication, Medical Procedures, COPD Exacerbations, Resource Utilisation**

CRF Pages **102 - 145**

Unprocessed Forms : **Within this module the following occur which will generate attachments that need to be brought in-house.**

None

FOR OFFICE USE ONLY Module Comments:

Sent to Data Mngt	Review Complete Date: User:	First Entry Complete Date: User:
Second Entry Complete Date: User:	Validation Complete Date: User:	**Clintrial PID:**

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number		Visit Date (Day Month Year)	
207499/157		[redacted]			**Visit 6 Week 8**

PRESENTATION TO CLINIC

Note: ***Patients must wait for 4 hours after beta$_2$-agonist and / or anticholinergic administration before the pulmonary function tests are performed.***

Did the patient take a dose of beta$_2$ agonist in the past 24 hours?

☐ No

☐ Yes → Record date and time of the patient's last dose of beta$_2$ agonist: Day Month Yr 24hr:min

Did the patient take a dose of anticholinergic in the past 24 hours?

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: Day Month Yr 24hr:min

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes → Date and time of patient's last cigarette Day Month Yr 24hr:min

SMOKING STATUS

Does the patient currently smoke?

☐ No

☐ Yes → If 'Yes' please record the average number of cigarettes per day :

INFLUENZA VACCINATION

Has the patient had a vaccination for influenza since the last visit?

N.B. It is not necessary to record vaccinations on the Concomitant Medication or Medical Procedures page.

☐ No

☐ Yes → *If 'Yes', record date of vaccination :* Day Month Yr

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number			Visit 6 Week 8
207499/157		[redacted]			

RESOLUTION OF COPD EXACERBATIONS

Have any COPD Exacerbations resolved since the last visit?

☐ No

☐ Yes ⟶ *If 'Yes', please record details in the COPD Exacerbation section at the back of this module.*

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes ⟶ *If 'Yes' please record details in the COPD Exacerbation section at the back of this module.*

Level 1 (Mild-self treated): Acute worsening of COPD that is self-managed by the patient at home by increasing the dose of relief salbutamol medication by > 2 occasions/24 hour period on two or more consecutive days compared with their baseline (baseline = mean of last 10 days of run-in period) or use of other additional bronchodilator medication

Level 2 (Moderate- physician, investigator treated): Acute worsening of symptoms (cough, sputum production, breathlessness) requiring treatment with oral corticosteroids prescribed by a physician or primary care doctor, or as a result of hospital out-patient visit (including Emergency Room).

Exacerbations requiring oral corticosteroids will be treated with a standardised course of prednisolone or prednisone tablets 30mg/day for 10 days, or methylprednisolone tablets 24mg/day for 10 days.

Level 3 (Severe - attendance at hospital): Acute worsening of COPD that requires the patient to be admitted to hospital for treatment.

If a patient experienced a COPD exacerbation that was treated with corticosteroids, please withdraw the patient and complete the Study Continuation/Withdrawal page at the back of this book. 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, including an increase in usual COPD medications, must be recorded in the COPD Medications or Procedures pages.

00000

SmithKline Beecham
Pharmaceuticals

Protocol		**Patient Number**			**Visit 6**
207499/157		[redacted]			**Week 8**

RESOURCE UTILISATION

If the patient has received any COPD exacerbation-related medical care since the last visit, record details on the Resource Utilisation pages of the COPD Exacerbation section at the back of this module.

DIARY CARD REVIEW

Review the diary card in the presence of the patient. Question any increased symptoms for possible COPD exacerbations. Place diary in the plastic wallet at the back of this module and re-issue another diary card.

ADVERSE EXPERIENCES

Please complete the Adverse Experiences 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 Experiences 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.

00000

SmithKline Beecham
Pharmaceuticals

Protocol **207499/157**		**Patient Number** [redacted]			**Visit 6 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. bd)

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	☐☐	☐☐	☐☐	☐☐	☐☐☐

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance ≥ 80% and ≤120%?

☐ No → *If 'No' please remind the patient of the importance of taking study medication according to the protocol.*

☐ Yes

00000

SmithKline Beecham
Pharmaceuticals

Protocol		**Patient Number**			**Visit 6**
207499/157		[redacted]			**Week 8**

INVESTIGATOR INSTRUCTIONS

The following procedures (Vital Signs and Pulmonary Function Tests) must be performed greater than 4 hours after the patient's last salbutamol administration.

VITAL SIGNS

Time of assessment : ☐☐ 24hr:min

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
☐☐☐/☐☐☐	☐☐☐

Are there any **clinically significant worsenings** since the previous visit?

☐ No

☐ Yes ⟶ *If 'Yes' please record the findings and/or diagnosis in the Adverse Experiences section at the back of this module.*

Protocol		Patient Number			Visit 6 Week 8
207499/157		[redacted]			

PRE-SALBUTAMOL PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed at least 4 hours after the last dose of inhaled beta$_2$-agonist or anticholinergic agent.

Measure the patient's pulmonary function up to eight times to obtain three acceptable readings using the spirometer provided by SB. ***(Note: Please follow instructions in the Spirometry Manual).*** *For each set of three FEV_1 measurements, one FEV_1 must be within 10% of the highest. Please record the results of the effort with the highest FEV_1 below.*

Measurement	Time	FEV_1 (L)	FVC (L)	FEF_{25-75} (L/sec)	PEF (L/min)
1	☐☐:☐☐ 24hr:min	☐.☐☐	☐.☐☐	☐.☐☐	☐☐☐

Place the spirometry reports in the plasic wallet at the back of this module.

POST-SALBUTAMOL PULMONARY FUNCTION TESTS

Provide the patient with a salbutamol MDI and spacer. Administer 400 mcg (4 puffs) of salbutamol via MDI with a spacer. Remind the patient to use this inhaler (with or without the spacer), rather than any salbutamol inhaler they may have at home, for "as required" rescue-medication use during the study.

Record the time of salbutamol inhalation ☐☐:☐☐ 24hr:min

Wait 30 minutes

Measure the patient's pulmonary function up to eight times to obtain three acceptable readings using the spirometer provided by SB. ***(Note: Please follow instructions in the Spirometry Manual).*** *For each set of three FEV_1 measurements, one FEV_1 must be within 10% of the highest. Please record the results of the effort with the highest FEV_1 below.*

Measurement	Time	FEV_1 (L)	FVC (L)	FEF_{25-75} (L/sec)	PEF (L/min)
1	☐☐:☐☐ 24hr:min	☐.☐☐	☐.☐☐	☐.☐☐	☐☐☐

Place spirometry reports in the plastic wallets at the back of this module.

PULMONARY REHABILITATION PROGRAM

Has the patient entered a Pulmonary Rehabilitation Program since the last visit?

☐ No

☐ Yes

SmithKline Beecham
Pharmaceuticals

Protocol 207499/157		**Patient Number** [redacted]			**Visit 6 Week 8**

LABORATORY TESTS

Please take blood samples for haematology and blood chemistry (including serum beta-HCG for women of child-bearing potential) and a urine sample for urinalysis. Please refer to the instructions on the Quest shipping form and manual.

Blood Sample Date ☐☐ ☐☐ ☐☐
Day Month Yr

Attach a label from the 'Routine' laboratory requisition form used at this visit in the space below.

Attach label here

Are there any **clinically significant worsenings** since the last assessment?

☐ No

☐ Yes ⟶ *If 'Yes' please record the findings and/or diagnosis in the Adverse Experiences section at the back of this module.*

STUDY MEDICATION ALLOCATION - RAMOS CALL

Following completion of all preceding assessments, complete the RAMOS worksheet appropriate for this visit and contact RAMOS to obtain the container number for this visit.

*Please enter the 5-digit **randomisation number** assigned by RAMOS* ☐☐☐☐☐

*Please enter the 6-digit **container number** as it appears on the study medication label*: ☐☐☐☐☐☐

STUDY MEDICATION LABEL

Attach the tear-off label from the study medication container 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

00000

SmithKline Beecham
Pharmaceuticals

Protocol **207499/157**		**Patient Number** [redacted]			**Visit 6 Week 8**

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 6

Is the patient continuing in the study?

☐ No

☐ Yes

*If the patient is **not** continuing in the study, is the patient willing to return for essential assessments?*

If 'No', please complete the assessments for Visit 6 and the additional assessments for patients withdrawing at Visit 6 and the Study Continuation/Withdrawal page at the back of this book.

If 'Yes', please complete the assessments for Visit 6, the assessments for patients withdrawing at Visit 6 and the Study Continuation/Withdrawal page at the back of this book. Ask the patient to return in 28 +/-6 days time for essential assessments only.

*If the patient **is** continuing in the study, please:* (tick if done)

- *Issue the patient a new diary card and remind the patient to complete the diary each morning until the next visit.* ☐
- *Ask the patient to return for the next visit in 28 +/- 6 days for a morning visit.* ☐
- ***Remind the patient:***
  - i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after their breakfast.* ☐
  - ii ***not** to take the morning dose of study medication at home on the day of the next clinic visit.* ☐
  - iii *to refrain from using salbutamol or anticholinergic agents during the **4 hours** immediately preceding 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, the study salbutamol inhaler and spacer, and the diary card.* ☐
  - vi *to continue to take the anticholinergic medication, if prescribed, at a constant dose, and salbutamol when needed to control symptoms.* ☐
  - vii *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 occurrence.* ☐

Protocol		Patient Number			Withdrawal at Visit 6 Week 8
207499/157		[redacted]			

ASSESSMENTS FOR PATIENTS WITHDRAWING AT VISIT 6

Complete the assessments below only for patients who are withdrawing from the study at this visit.

ST. GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND EQ-5D

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

INVESTIGATOR GLOBAL EVALUATION OF IMPROVEMENT

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

PATIENT GLOBAL EVALUATION OF IMPROVEMENT

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

Protocol 207499/157		Patient Number [redacted]			Withdrawal at Visit 6 Week 8

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 Experiences section at the back of this module.*

VITAL SIGNS - ORTHOSTATIC CHANGE

Time of assessment : ☐☐ 24hr:min

1st Measurement: After 5 Minutes Supine		**2nd Measurement: 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)
☐☐☐/☐☐☐	☐☐☐	☐☐☐/☐☐☐	☐☐☐

Have there been any clinically significant worsenings since the last assessment?

☐ No

☐ Yes⟶ *If 'Yes', please record the findings in the Adverse Experiences section at the back of this module.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number			Withdrawal at Visit 6 Week 8
207499/157		[redacted]			

12 LEAD ELECTROCARDIOGRAM

Time of assessment : ☐☐ 24hr:min **The ECG should be performed after the patient has been semi-supine for 5 minutes**

Date ECG Performed (Day Month Year)	Atrial Rate (beats/min)	Ventricular Rate (beats/min)	PR (msec)	QRS (msec)	☐ Uncorrected QT ☐ Corrected QT (msec)	Axis
☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐ + ☐ - ☐☐☐

Interpretation

☐ **(F74301) Within normal limits**

☐ **Abnormal** ⟶ ***Mark appropriate boxes below***

Rhythm
- ☐ (F73360) Sinus arrhythmia
- ☐ (F73310) Sinus bradycardia
- ☐ (F73380) Sinus tachycardia
- ☐ (F73440) Wandering atrial pacemaker
- ☐ (F73450) Premature atrial contractions
- ☐ (F73510) Paroxysmal atrial tachycardia
- ☐ (F73530) Chronic ectopic atrial tachycardia
- ☐ (F73550) Multifocal atrial tachycardia
- ☐ (F73560) Atrial flutter
- ☐ (F73570) Atrial fibrillation
- ☐ (F73610) Junctional (AV nodal) premature contractions
- ☐ (F73650) Junctional (AV nodal) tachycardia
- ☐ (F73150) Supraventricular tachycardia
- ☐ (F73860) Accelerated idioventricular rhythm
- ☐ (F73710) Premature Ventricular Contractions (NOS)
- ☐ (F73720) Unifocal PVC's
- ☐ (F73730) Multifocal PVC's
- ☐ (F73711) Ventricular couplets
- ☐ (F73750) Bigeminy
- ☐ (F73870) Ventricular tachycardia
- ☐ (F73880) Ventricular fibrillation
- ☐ (F73340) Sick sinus syndrome
- ☐ (F73190) Pacemaker rhythm

P-Wave Morphology
- ☐ (F74214) Left atrial hypertrophy, P mitrale
- ☐ (F74213) Right atrial hypertrophy, P pulmonale

Conduction
- ☐ (F73930) First degree AV block
- ☐ (F73950) Second degree AV block, Type 1
- ☐ (F73960) Second degree AV block, Type 11
- ☐ (F73970) Third degree AV block
- ☐ (F74090) Wolff-Parkinson-White syndrome

Axis
- ☐ (F74120) Right Axis deviation
- ☐ (F74130) Left Axis deviation

QRS
- ☐ (F74010) Right bundle branch block
- ☐ (F74020) Left bundle branch block
- ☐ (F74030) Left anterior hemiblock
- ☐ (F74040) Left posterior hemiblock
- ☐ (F74002) Intraventricular conduction delay
- ☐ (F74212) Left ventricular hypertrophy
- ☐ (F74211) Right ventricular hypertrophy
- ☐ (F74308) Q-wave > 0.04 sec
- ☐ (F74222) R-wave amplitude increased
- ☐ (F74225) R-wave amplitude decreased
- ☐ (F74313) Prolonged QT-interval
- ☐ (F74318) Poor R-wave progression
- ☐ (M54750) Myocardial infarction, old
  - ☐ (M54751) Anterior ☐ (M54754) Inferior
  - ☐ (M54752) Lateral ☐ (M54755) Septal
  - ☐ (M54753) Posterior

ST-T
- ☐ (F74291) Nonspecific ST-T changes
- ☐ (F74294) ST segment depression > 1 mm
- ☐ (F74295) ST segment elevation > 1 mm
- ☐ (F74350) T-wave flat
- ☐ (F74351) T-wave inversion
- ☐ (F74352) T-wave peaked
- ☐ (F74340) U-wave
- ☐ (F74360) Digitalis effect
- ☐ (F74260) Myocardial ischemia
  - ☐ (F74261) Anterior ☐ (F74264) Inferior
  - ☐ (F74262) Lateral ☐ (F74265) Septal
  - ☐ (F74263) Posterior
- ☐ (M54720) Myocardial infarction, acute
  - ☐ (M54721) Anterior ☐ (M54724) Inferior
  - ☐ (M54722) Lateral ☐ (M54725) Septal
  - ☐ (M54723) Posterior

Other interpretations not listed _

Were there any clinically important changes observed since the last assessment?

[1] ☐ No

[2] ☐ Yes ⟶ *If 'Yes', enter details on the Adverse Experiences page at the back of this module.*

Place the ECG trace in the plastic wallet a the back of this module

Protocol		Patient Number			Withdrawal at Visit 6 Week 8
207499/157		[redacted]			

(AT SELECTED CENTRES ONLY) RESIDUAL VOLUME BY BODY PLETHYSMOGRAPHY (PRE- AND POST-SALBUTAMOL)

Time of pre-salbutamol RV assessment: ☐☐ 24hr:min

Time of post-salbutamol RV assessment: ☐☐ 24hr:min

Pre-Salbutamol

$RV_{Box} = TLC_{Box} – max(|SVC|, |FVC|)$

$RV_{(Box)}$ = ☐.☐☐ (L)

Post-Salbutamol

$RV_{Box} = TLC_{Box} – max(|SVC|, |FVC|)$

$RV_{(Box)}$ = ☐.☐☐ (L)

Please attach plethysmography source data to the back of this page.

FAECAL OCCULT BLOOD TEST

The faecal occult blood test should be performed on three consecutive bowel movements between withdrawal and the next scheduled visit or the Follow-Up visit depending on whether the patient is willing, or not, to return for essential assessments. Patients are not to take samples during or up-to 3-days after a menstrual period or while having bleeding haemorrhoids or blood in the urine. Patients are not to take aspirin or other non-steroidal anti-inflammatory drugs for 7 days prior to and during the test period and they are to avoid Vitamin C in excess of 250mg 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.

Did the patient follow these instructions?

☐ No ⟶ *If 'No', please specify:* _

☐ Yes

Test	Date of Collection Day Mth Yr	Result of faecal occult blood test
1	☐☐ ☐☐ ☐☐	[NEG] ☐ Negative [POS] ☐ Positive
2	☐☐ ☐☐ ☐☐	[NEG] ☐ Negative [POS] ☐ Positive
3	☐☐ ☐☐ ☐☐	[NEG] ☐ Negative [POS] ☐ Positive

Are these findings clinically significant ?

☐ No

☐ Yes ⟶ *If 'Yes' please record the findings and/or diagnosis in the Adverse Experiences section at the back of this module.*

00000

SmithKline Beecham
Pharmaceuticals

Protocol		**Patient Number**			**Withdrawal at Visit 6 Week 8**
207499/157		[redacted]			

LABORATORY TESTS

Please take blood samples for CD4/CD8 ratio and C Reactive Protein. Please refer to the instructions on the Quest shipping form and manual.

Blood Sample Date ☐☐ ☐☐ ☐☐
Day Month Yr

Attach a label from the 'Routine' laboratory requisition form used at this visit in the space below.

Attach label here

Are there any **clinically significant worsenings** since the last assessment?

☐ No

☐ Yes ⟶ *If 'Yes' please record the findings and/or diagnosis in the Adverse Experiences section at the back of this module.*

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number		Visit Date (Day Month Year)	
207499/157		[redacted]			**Visit 7 Week 12**

PRESENTATION TO CLINIC

Note: ***Patients must wait for 4 hours after beta$_2$-agonist and / or anticholinergic administration before the pulmonary function tests are performed.***

Did the patient take a dose of beta$_2$ agonist in the past 24 hours?

☐ No

☐ Yes → Record date and time of the patient's last dose of beta$_2$ agonist: Day Month Yr 24hr:min

Did the patient take a dose of anticholinergic in the past 24 hours?

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: Day Month Yr 24hr:min

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes → Date and time of patient's last cigarette Day Month Yr 24hr:min

SMOKING STATUS

Does the patient currently smoke?

☐ No

☐ Yes → If 'Yes' please record the average number of cigarettes per day :

INFLUENZA VACCINATION

Has the patient had a vaccination for influenza since the last visit?

N.B. It is not necessary to record vaccinations on the Concomitant Medication or Medical Procedures page.

☐ No

☐ Yes → *If 'Yes', record date of vaccination :* Day Month Yr

Protocol		Patient Number			Visit 7 Week 12
207499/157		[redacted]			

RESOLUTION OF COPD EXACERBATIONS

Have any COPD Exacerbations resolved since the last visit?

☐ No

☐ Yes ⟶ *If 'Yes', please record details in the COPD Exacerbation section at the back of this module.*

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes ⟶ *If 'Yes' please record details in the COPD Exacerbation section at the back of this module.*

Level 1 (Mild-self treated): Acute worsening of COPD that is self-managed by the patient at home by increasing the dose of relief salbutamol medication by > 2 occasions/24 hour period on two or more consecutive days compared with their baseline (baseline = mean of last 10 days of run-in period) or use of other additional bronchodilator medication

Level 2 (Moderate- physician, investigator treated): Acute worsening of symptoms (cough, sputum production, breathlessness) requiring treatment with oral corticosteroids prescribed by a physician or primary care doctor, or as a result of hospital out-patient visit (including Emergency Room).

Exacerbations requiring oral corticosteroids will be treated with a standardised course of prednisolone or prednisone tablets 30mg/day for 10 days, or methylprednisolone tablets 24mg/day for 10 days.

Level 3 (Severe - attendance at hospital): Acute worsening of COPD that requires the patient to be admitted to hospital for treatment.

If a patient experienced a COPD exacerbation that was treated with corticosteroids, please withdraw the patient and complete the Study Continuation/Withdrawal page at the back of this book. 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, including an increase in usual COPD medications, must be recorded in the COPD Medications or Procedures pages.

00000

SmithKline Beecham
Pharmaceuticals

Protocol **207499/157**		**Patient Number** [redacted]			**Visit 7 Week 12**

RESOURCE UTILISATION

If the patient has received any COPD exacerbation-related medical care since the last visit, record details on the Resource Utilisation pages of the COPD Exacerbation section at the back of this module.

DIARY CARD REVIEW

Review the diary card in the presence of the patient. Question any increased symptoms for possible COPD exacerbations. Place diary in the plastic wallet at the back of this module and re-issue another diary card.

ADVERSE EXPERIENCES

Please complete the Adverse Experiences 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 Experiences 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.

00000

SmithKline Beecham
Pharmaceuticals

Protocol **207499/157**		**Patient Number** [redacted]			**Visit 7 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. bd)

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					

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance ≥ 80% and ≤120%?

☐ No → *If 'No' please remind the patient of the importance of taking study medication according to the protocol.*

☐ Yes

00000

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number			Visit 7 Week 12
207499/157		[redacted]			

INVESTIGATOR INSTRUCTIONS

The following procedures (Vital Signs, ECG and Pulmonary Function Tests) must be performed greater than 4 hours after the patient's last salbutamol administration.

VITAL SIGNS

Time of assessment : ☐☐ 24hr:min

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
☐☐☐/☐☐☐	☐☐☐

Are there any **clinically significant worsenings** since the previous visit?

☐ No

☐ Yes ⟶ *If 'Yes' please record the findings and/or diagnosis in the Adverse Experiences section at the back of this module.*

VITAL SIGNS - ORTHOSTATIC CHANGE

Time of assessment : ☐☐ 24hr:min

1st Measurement: After 5 Minutes Supine		2nd Measurement: 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)
☐☐☐/☐☐☐	☐☐☐	☐☐☐/☐☐☐	☐☐☐

Have there been any clinically significant worsenings since the last assessment?

☐ No

☐ Yes⟶ *If 'Yes', please record the findings in the Adverse Experiences section at the back of this module.*

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number			Visit 7 Week 12
207499/157		[redacted]			

12 LEAD ELECTROCARDIOGRAM

Time of assessment : ☐☐ 24hr:min **The ECG should be performed after the patient has been semi-supine for 5 minutes**

Date ECG Performed (Day Month Year)	Atrial Rate (beats/min)	Ventricular Rate (beats/min)	PR (msec)	QRS (msec)	☐ Uncorrected QT ☐ Corrected QT (msec)	Axis
☐☐☐☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐ + ☐ - ☐☐☐

Interpretation

☐ **(F74301) Within normal limits**

☐ **Abnormal** ⟶ ***Mark appropriate boxes below***

Rhythm
- ☐ (F73360) Sinus arrhythmia
- ☐ (F73310) Sinus bradycardia
- ☐ (F73380) Sinus tachycardia
- ☐ (F73440) Wandering atrial pacemaker
- ☐ (F73450) Premature atrial contractions
- ☐ (F73510) Paroxysmal atrial tachycardia
- ☐ (F73530) Chronic ectopic atrial tachycardia
- ☐ (F73550) Multifocal atrial tachycardia
- ☐ (F73560) Atrial flutter
- ☐ (F73570) Atrial fibrillation
- ☐ (F73610) Junctional (AV nodal) premature contractions
- ☐ (F73650) Junctional (AV nodal) tachycardia
- ☐ (F73150) Supraventricular tachycardia
- ☐ (F73860) Accelerated idioventricular rhythm
- ☐ (F73710) Premature Ventricular Contractions (NOS)
- ☐ (F73720) Unifocal PVC's
- ☐ (F73730) Multifocal PVC's
- ☐ (F73711) Ventricular couplets
- ☐ (F73750) Bigeminy
- ☐ (F73870) Ventricular tachycardia
- ☐ (F73880) Ventricular fibrillation
- ☐ (F73340) Sick sinus syndrome
- ☐ (F73190) Pacemaker rhythm

P-Wave Morphology
- ☐ (F74214) Left atrial hypertrophy, P mitrale
- ☐ (F74213) Right atrial hypertrophy, P pulmonale

Conduction
- ☐ (F73930) First degree AV block
- ☐ (F73950) Second degree AV block, Type 1
- ☐ (F73960) Second degree AV block, Type 11
- ☐ (F73970) Third degree AV block
- ☐ (F74090) Wolff-Parkinson-White syndrome

Axis
- ☐ (F74120) Right Axis deviation
- ☐ (F74130) Left Axis deviation

QRS
- ☐ (F74010) Right bundle branch block
- ☐ (F74020) Left bundle branch block
- ☐ (F74030) Left anterior hemiblock
- ☐ (F74040) Left posterior hemiblock
- ☐ (F74002) Intraventricular conduction delay
- ☐ (F74212) Left ventricular hypertrophy
- ☐ (F74211) Right ventricular hypertrophy
- ☐ (F74308) Q-wave > 0.04 sec
- ☐ (F74222) R-wave amplitude increased
- ☐ (F74225) R-wave amplitude decreased
- ☐ (F74313) Prolonged QT-interval
- ☐ (F74318) Poor R-wave progression
- ☐ (M54750) Myocardial infarction, old
  - ☐ (M54751) Anterior ☐ (M54754) Inferior
  - ☐ (M54752) Lateral ☐ (M54755) Septal
  - ☐ (M54753) Posterior

ST-T
- ☐ (F74291) Nonspecific ST-T changes
- ☐ (F74294) ST segment depression > 1 mm
- ☐ (F74295) ST segment elevation > 1 mm
- ☐ (F74350) T-wave flat
- ☐ (F74351) T-wave inversion
- ☐ (F74352) T-wave peaked
- ☐ (F74340) U-wave
- ☐ (F74360) Digitalis effect
- ☐ (F74260) Myocardial ischemia
  - ☐ (F74261) Anterior ☐ (F74264) Inferior
  - ☐ (F74262) Lateral ☐ (F74265) Septal
  - ☐ (F74263) Posterior
- ☐ (M54720) Myocardial infarction, acute
  - ☐ (M54721) Anterior ☐ (M54724) Inferior
  - ☐ (M54722) Lateral ☐ (M54725) Septal
  - ☐ (M54723) Posterior

Other interpretations not listed _

Were there any clinically important changes observed since the last assessment?

[1] ☐ No

[2] ☐ Yes ⟶ *If 'Yes', enter details on the Adverse Experiences page at the back of this module.*

Place the ECG trace in the plastic wallet a the back of this module

Protocol		Patient Number			Visit 7 Week 12
207499/157		[redacted]			

PRE-SALBUTAMOL PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed at least 4 hours after the last dose of inhaled beta$_2$-agonist or anticholinergic agent.

Measure the patient's pulmonary function up to eight times to obtain three acceptable readings using the spirometer provided by SB. ***(Note: Please follow instructions in the Spirometry Manual).*** *For each set of three FEV_1 measurements, one FEV_1 must be within 10% of the highest. Please record the results of the effort with the highest FEV_1 below.*

Measurement	Time	FEV_1 (L)	FVC (L)	FEF_{25-75} (L/sec)	PEF (L/min)
1	☐☐ 24hr:min	☐.☐☐	☐.☐☐	☐.☐☐	☐☐☐

Place the spirometry reports in the plasic wallet at the back of this module.

POST-SALBUTAMOL PULMONARY FUNCTION TESTS

Provide the patient with a salbutamol MDI and spacer. Administer 400 mcg (4 puffs) of salbutamol via MDI with a spacer. Remind the patient to use this inhaler (with or without the spacer), rather than any salbutamol inhaler they may have at home, for "as required" rescue-medication use during the study.

Record the time of salbutamol inhalation ☐☐ 24hr:min

Wait 30 minutes

Measure the patient's pulmonary function up to eight times to obtain three acceptable readings using the spirometer provided by SB. ***(Note: Please follow instructions in the Spirometry Manual).*** *For each set of three FEV_1 measurements, one FEV_1 must be within 10% of the highest. Please record the results of the effort with the highest FEV_1 below.*

Measurement	Time	FEV_1 (L)	FVC (L)	FEF_{25-75} (L/sec)	PEF (L/min)
1	☐☐ 24hr:min	☐.☐☐	☐.☐☐	☐.☐☐	☐☐☐

Place spirometry reports in the plastic wallets at the back of this module.

PULMONARY REHABILITATION PROGRAM

Has the patient entered a Pulmonary Rehabilitation Program since the last visit?

☐ No

☐ Yes

Protocol		Patient Number			Visit 7 Week 12
207499/157		[redacted]			

LABORATORY TESTS

Please take blood samples for haematology and blood chemistry (including serum beta-HCG for women of child-bearing potential) and a urine sample for urinalysis. Please refer to the instructions on the Quest shipping form and manual.

Blood Sample Date ☐☐ ☐☐☐ ☐☐
Day Month Yr

Attach a label from the 'Routine' laboratory requisition form used at this visit in the space below.

Attach label here

Are there any **clinically significant worsenings** since the last assessment?

☐ No

☐ Yes ⟶ *If 'Yes' please record the findings and/or diagnosis in the Adverse Experiences section at the back of this module.*

STUDY MEDICATION ALLOCATION - RAMOS CALL

Following completion of all preceding assessments, complete the RAMOS worksheet appropriate for this visit and contact RAMOS to obtain the container numbers for this visit.

*Please enter the 5-digit **randomisation number** assigned by RAMOS* ☐☐☐☐☐

*Please enter the 6-digit **container number** as it appears on the study medication label **(Container 1)**.* ☐☐☐☐☐☐

*Please enter the 6-digit **container number** as it appears on the study medication label **(Container 2)**.* ☐☐☐☐☐☐

STUDY MEDICATION LABEL

Attach the tear-off labels from the study medication containers 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

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

00000

SmithKline Beecham
Pharmaceuticals

Protocol **207499/157**		**Patient Number** [redacted]			**Visit 7 Week 12**

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 7

Is the patient continuing in the study?

☐ No

☐ Yes

*If the patient is **not** continuing in the study, is the patient willing to return for essential assessments?*

If 'No', please complete the assessments for Visit 7 and the additional assessments for patients withdrawing at Visit 7 and the Study Continuation/Withdrawal page at the back of this book.

If 'Yes', please complete the assessments for Visit 7, the assessments for patients withdrawing at Visit 7 and the Study Continuation/Withdrawal page at the back of this book. Ask the patient to return in 56 +/-6 days time for essential assessments only.

*If the patient **is** continuing in the study, please:*	(tick if done)
	☑
• *Issue the patient a new diary card and remind the patient to complete the diary each morning until the next visit.*	☐
• *Ask the patient to return for the next visit in 56 +/- 6 days for a morning visit.*	☐
• ***Remind the patient:***	
i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after their breakfast.*	☐
ii ***not** to take the morning dose of study medication at home on the day of the next clinic visit.*	☐
iii *to refrain from using salbutamol or anticholinergic agents during the **4 hours** immediately preceding 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, the study salbutamol inhaler and spacer, and the diary card.*	☐
vi *to continue to take the anticholinergic medication, if prescribed, at a constant dose, and salbutamol when needed to control symptoms.*	☐
vii *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 occurrence.*	☐

Protocol		Patient Number			Withdrawal at Visit 7 Week 12
207499/157		[redacted]			

ASSESSMENTS FOR PATIENTS WITHDRAWING AT VISIT 7

Complete the assessments below only for patients who are withdrawing from the study at this visit.

ST. GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND EQ-5D

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

INVESTIGATOR GLOBAL EVALUATION OF IMPROVEMENT

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

PATIENT GLOBAL EVALUATION OF IMPROVEMENT

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

SmithKline Beecham Pharmaceuticals

Protocol 207499/157		Patient Number [redacted]			Withdrawal at Visit 7 Week 12

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 Experiences section at the back of this module.*

(AT SELECTED CENTRES ONLY) RESIDUAL VOLUME BY BODY PLETHYSMOGRAPHY (PRE- AND POST-SALBUTAMOL)

Time of pre-salbutamol RV assessment: ☐☐ 24hr:min

Time of post-salbutamol RV assessment: ☐☐ 24hr:min

Pre-Salbutamol

$RV_{Box} = TLC_{Box} - \max(|SVC|, |FVC|)$

$RV_{(Box)}$ = ☐.☐☐ (L)

Post-Salbutamol

$RV_{Box} = TLC_{Box} - \max(|SVC|, |FVC|)$

$RV_{(Box)}$ = ☐.☐☐ (L)

Please attach plethysmography source data to the back of this page.

FAECAL OCCULT BLOOD TEST

The faecal occult blood test should be performed on three consecutive bowel movements between withdrawal and the next scheduled visit or the Follow-Up visit depending on whether the patient is willing, or not, to return for essential assessments. Patients are not to take samples during or up-to 3-days after a menstrual period or while having bleeding haemorrhoids or blood in the urine. Patients are not to take aspirin or other non-steroidal anti-inflammatory drugs for 7 days prior to and during the test period and they are to avoid Vitamin C in excess of 250mg 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.

Did the patient follow these instructions?

☐ No ⟶ *If 'No', please specify:* _

☐ Yes

Test	Date of Collection Day Mth Yr	Result of faecal occult blood test
1	☐☐ ☐☐☐ ☐☐	[NEG] ☐ Negative [POS] ☐ Positive
2	☐☐ ☐☐☐ ☐☐	[NEG] ☐ Negative [POS] ☐ Positive
3	☐☐ ☐☐☐ ☐☐	[NEG] ☐ Negative [POS] ☐ Positive

Are these findings clinically significant ?

☐ No

☐ Yes ⟶ *If 'Yes' please record the findings and/or diagnosis in the Adverse Experiences section at the back of this module.*

00000

SmithKline Beecham
Pharmaceuticals

Protocol **207499/157**		**Patient Number** [redacted]			**Withdrawal at Visit 7 Week 12**

LABORATORY TESTS

Please take blood samples for CD4/CD8 ratio and C Reactive Protein. Please refer to the instructions on the Quest shipping form and manual.

Blood Sample Date ☐☐ ☐☐ ☐☐
Day Month Yr

Attach a label from the 'Routine' laboratory requisition form used at this visit in the space below.

Attach label here

Are there any **clinically significant worsenings** since the last assessment?

☐ No

☐ Yes ⟶ *If 'Yes' please record the findings and/or diagnosis in the Adverse Experiences section at the back of this module.*

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 experience which is :-

1 - fatal
2 - life threatening
3 - disabling/incapacitating
4 - results in hospitalization (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 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

SmithKline Beecham Pharmaceuticals

Protocol	Centre Number	Patient Number			Adverse Experiences
207499/157		[redacted]			

ADVERSE EXPERIENCES (Non-serious)

g_ae_01

*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 last visit?"*
*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).

☐ Please mark this box if no adverse experiences occurred since the last module

Adverse Experience *(please print clearly)*		
For SB		
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 SAE section and follow instructions given there***	[1] ☐ Resolved [2] ☐ Ongoing [3] ☐ Died	[1] ☐ Resolved [2] ☐ Ongoing [3] ☐ Died
Experience Course	[1] ☐ Intermittent → No. of episodes ☐ [2] ☐ Constant	[1] ☐ Intermittent → No. of episodes ☐ [2] ☐ Constant
Intensity (maximum)	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Action Taken with Respect to Investigational Drug	[1] ☐ None [2] ☐ Dose reduced [3] ☐ Dose increased [4] ☐ Drug interrupted/restarted [5] ☐ Drug stopped	[1] ☐ None [2] ☐ Dose reduced [3] ☐ Dose increased [4] ☐ Drug interrupted/restarted [5] ☐ Drug stopped
Relationship to Investigational Drug	[1] ☐ Not related [2] ☐ Unlikely [3] ☐ Suspected (reasonable possibility) [4] ☐ Probable	[1] ☐ Not related [2] ☐ Unlikely [3] ☐ Suspected (reasonable possibility) [4] ☐ Probable
Corrective Therapy *If 'Yes', record details in the Concomitant Medication section and/ or Medical Procedures section if appropriate*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No

SmithKline Beecham Pharmaceuticals

Protocol	Centre Number	Patient Number			Adverse Experiences
207499/157		[redacted]			

ADVERSE EXPERIENCES (Non-serious) - Continued

g_ae_01

*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 last visit?" 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).

Adverse Experience *(please print clearly)*		
For SB		
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 SAE section and follow instructions given there***	[1] Resolved [2] Ongoing [3] Died	[1] Resolved [2] Ongoing [3] Died
Experience Course	[1] Intermittent → No. of episodes [2] Constant	[1] Intermittent → No. of episodes [2] Constant
Intensity (maximum)	[1] Mild [2] Moderate [3] Severe	[1] Mild [2] Moderate [3] Severe
Action Taken with Respect to Investigational Drug	[1] None [2] Dose reduced [3] Dose increased [4] Drug interrupted/restarted [5] Drug stopped	[1] None [2] Dose reduced [3] Dose increased [4] Drug interrupted/restarted [5] Drug stopped
Relationship to Investigational Drug	[1] Not related [2] Unlikely [3] Suspected (reasonable possibility) [4] Probable	[1] Not related [2] Unlikely [3] Suspected (reasonable possibility) [4] Probable
Corrective Therapy *If 'Yes', record details in the Concomitant Medication section and/ or Medical Procedures section if appropriate*	Yes No	Yes No
Was patient withdrawn due to this specific AE?	Yes No	Yes No

SmithKline Beecham
Pharmaceuticals

Protocol	**Centre Number**	**Patient Number**			**Adverse Experiences**
207499/157		[redacted]			

ADVERSE EXPERIENCES (Non-serious) - Continued

g_ae_01

*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 last visit?"*
*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).

Adverse Experience *(please print clearly)*		
For SB		
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 SAE section and follow instructions given there***	[1] Resolved [2] Ongoing [3] Died	[1] Resolved [2] Ongoing [3] Died
Experience Course	[1] Intermittent → No. of episodes [2] Constant	[1] Intermittent → No. of episodes [2] Constant
Intensity (maximum)	[1] Mild [2] Moderate [3] Severe	[1] Mild [2] Moderate [3] Severe
Action Taken with Respect to Investigational Drug	[1] None [2] Dose reduced [3] Dose increased [4] Drug interrupted/restarted [5] Drug stopped	[1] None [2] Dose reduced [3] Dose increased [4] Drug interrupted/restarted [5] Drug stopped
Relationship to Investigational Drug	[1] Not related [2] Unlikely [3] Suspected (reasonable possibility) [4] Probable	[1] Not related [2] Unlikely [3] Suspected (reasonable possibility) [4] Probable
Corrective Therapy *If 'Yes', record details in the Concomitant Medication section and/ or Medical Procedures section if appropriate*	Yes No	Yes No
Was patient withdrawn due to this specific AE?	Yes No	Yes No

Protocol	**Centre Number**	**Patient Number**			**Concomitant Medication**
207499/157		[redacted]			

CONCOMITANT MEDICATION

Record any changes in concomitant medication taken since the last 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. At the patient's final study visit, record the end date for prn study rescue medication (salbutamol) use, using the date the study inhaler was returned.

☐ No concomitant medication changes since the last module

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded in the Adverse Experiences 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** (eg 500mg)	**Frequency** (eg bd, 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	
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							

** For Route, see general instructions for acceptable abbreviations.*

Protocol	Centre Number	Patient Number			Concomitant Medication
207499/157		[redacted]			

CONCOMITANT MEDICATION (Cont.)

Do not record any medication taken for COPD exacerbations in this section. Record all COPD exacerbation medication in the COPD Exacerbation section. At the patient's final study visit, record the end date for prn study rescue medication (salbutamol) use, using the date the study inhaler was returned.

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded in the Adverse Experiences 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** (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	
For SB							
For SB							
For SB							
For SB							
For SB							
For SB							
For SB							
For SB							
For SB							
For SB							

** For Route, see general instructions for acceptable abbreviations.*

g_conmed_01

Protocol	Centre Number	Patient Number			Medical Procedures
207499/157		[redacted]			

MEDICAL PROCEDURES

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 last module?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below using standard medical terminology*

All indications for procedures should be recorded on the Adverse Experiences Form.

Procedure	Indication	Procedure Start Date Day Mth Yr	Procedure End Date Day Mth Yr
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			

Protocol	Centre Number	Patient Number			COPD Exacerbations (AE)
207499/157		[redacted]			

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 last 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***

Has the patient suffered any COPD Exacerbations since the last module ?

☐ No

☐ Yes → *If 'Yes', please complete page below*

Adverse Event	COPD EXACERBATION
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, STOP: delete details of this exacerbation and go to SAE COPD Exacerbation pages.***	[1] ☐ Resolved [2] ☐ Ongoing [3] ☐ Died
Event Course	[1] ☐ Intermittent → No. of episodes ☐ [2] ☐ Constant
Intensity (maximum) *See definitions page for Adverse Experiences form.*	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Action Taken with Respect to Investigational Drug	[1] ☐ None [2] ☐ Dose reduced [3] ☐ Dose increased [4] ☐ Drug interrupted/restarted [5] ☐ Drug stopped
Relationship to Investigational Drug	[1] ☐ Not related [2] ☐ Unlikely [3] ☐ Suspected (reasonable possibility) [4] ☐ Probable
Corrective Therapy *If 'Yes', record details on the COPD Medications or Procedures page*	☐ Yes ☐ No
Was patient withdrawn due to this specific event?	☐ Yes ☐ No

DEFINITIONS OF LEVELS OF EXACERBATION OF COPD

Level 1 (Mild-self treated): Acute worsening of COPD that is self-managed by the patient at home by increasing the dose of relief salbutamol medication by > 2 occasions/24 hour period on two or more consecutive days compared with their baseline (baseline = mean of last 10 days of run-in period) or use of other additional bronchodilator medication

Level 2 (Moderate- physician, investigator treated): Acute worsening of symptoms (cough, sputum production, breathlessness) requiring treatment with oral corticosteroids prescribed by a physician or primary care doctor, or as a result of hospital out-patient visit (including Emergency Room).

Exacerbations requiring oral corticosteroids will be treated with a standardised course of prednisolone or prednisone tablets 30mg/day for 10 days, or methylprednisolone tablets 24mg/day for 10 days.

Level 3 (Severe - attendance at hospital): Acute worsening of COPD that requires the patient to be admitted to hospital for treatment.

Protocol	Centre Number	Patient Number			COPD Exacerbations (AE)
207499/157		[redacted]			

FURTHER DETAILS OF COPD EXACERBATIONS

COPD exacerbation onset date : Day Month Yr

Level of exacerbation (see definitions on facing page):

[1] ☐ Level 1
[2] ☐ Level 2
[3] ☐ Level 3

Pumonary function test result (FEV_1) (if done):

☐.☐☐ L

Did the patient suffer from any of the following during the exacerbation:

[1] ☐ Chest pain
[2] ☐ Upper Respiratory Tract Infection
[3] ☐ Confusion
[4] ☐ Change in alertness
[5] ☐ Pneumonia
[6] ☐ Oedema
[7] ☐ Ankle swelling

ARTERIAL BLOOD GASES (only for COPD exacerbations)

Where feasible, an arterial blood gas sample is to be taken for analysis

COPD exacerbation onset date : Day Month Yr

PO_2 (mmHg)	**PCO_2** (mmHg)	**pH**	**Resting SaO_2** (%)
☐☐☐	☐☐	☐.☐☐	☐☐☐

RESOURCE UTILISATION

Please complete the Resource Utilisation pages for this exacerbation.

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			COPD Exacerbations (AE)
207499/157		[redacted]			

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 last 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***

Has the patient suffered any COPD Exacerbations since the last module ?

☐ No

☐ Yes → *If 'Yes', please complete page below*

Adverse Event	COPD EXACERBATION
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, STOP: delete details of this exacerbation and go to SAE COPD Exacerbation pages.***	[1] ☐ Resolved [2] ☐ Ongoing [3] ☐ Died
Event Course	[1] ☐ Intermittent → No. of episodes ☐ [2] ☐ Constant
Intensity (maximum) *See definitions page for Adverse Experiences form.*	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Action Taken with Respect to Investigational Drug	[1] ☐ None [2] ☐ Dose reduced [3] ☐ Dose increased [4] ☐ Drug interrupted/restarted [5] ☐ Drug stopped
Relationship to Investigational Drug	[1] ☐ Not related [2] ☐ Unlikely [3] ☐ Suspected (reasonable possibility) [4] ☐ Probable
Corrective Therapy *If 'Yes', record details on the COPD Medications or Procedures page*	☐ Yes ☐ No
Was patient withdrawn due to this specific event?	☐ Yes ☐ No

DEFINITIONS OF LEVELS OF EXACERBATION OF COPD

Level 1 (Mild-self treated): Acute worsening of COPD that is self-managed by the patient at home by increasing the dose of relief salbutamol medication by > 2 occasions/24 hour period on two or more consecutive days compared with their baseline (baseline = mean of last 10 days of run-in period) or use of other additional bronchodilator medication

Level 2 (Moderate- physician, investigator treated): Acute worsening of symptoms (cough, sputum production, breathlessness) requiring treatment with oral corticosteroids prescribed by a physician or primary care doctor, or as a result of hospital out-patient visit (including Emergency Room).

Exacerbations requiring oral corticosteroids will be treated with a standardised course of prednisolone or prednisone tablets 30mg/day for 10 days, or methylprednisolone tablets 24mg/day for 10 days.

Level 3 (Severe - attendance at hospital): Acute worsening of COPD that requires the patient to be admitted to hospital for treatment.

Protocol	Centre Number	Patient Number			COPD Exacerbations (AE)
207499/157		[redacted]			

FURTHER DETAILS OF COPD EXACERBATIONS

COPD exacerbation onset date : Day Month Yr

Level of exacerbation (see definitions on facing page):

[1] ☐ Level 1
[2] ☐ Level 2
[3] ☐ Level 3

Pumonary function test result (FEV_1) (if done):

☐.☐☐ L

Did the patient suffer from any of the following during the exacerbation:

[1] ☐ Chest pain
[2] ☐ Upper Respiratory Tract Infection
[3] ☐ Confusion
[4] ☐ Change in alertness
[5] ☐ Pneumonia
[6] ☐ Oedema
[7] ☐ Ankle swelling

ARTERIAL BLOOD GASES (only for COPD exacerbations)

Where feasible, an arterial blood gas sample is to be taken for analysis

COPD exacerbation onset date : Day Month Yr

PO_2 (mmHg)	**PCO_2** (mmHg)	**pH**	**Resting SaO_2** (%)
☐☐☐	☐☐	☐.☐☐	☐☐☐

RESOURCE UTILISATION

Please complete the Resource Utilisation pages for this exacerbation.

SmithKline Beecham Pharmaceuticals

Protocol	Centre Number	Patient Number			COPD Exacerbations (AE)
207499/157		[redacted]			

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 last 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***

Has the patient suffered any COPD Exacerbations since the last module ?

☐ No

☐ Yes → *If 'Yes', please complete page below*

Adverse Event	COPD EXACERBATION
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, STOP: delete details of this exacerbation and go to SAE COPD Exacerbation pages.***	[1] ☐ Resolved [2] ☐ Ongoing [3] ☐ Died
Event Course	[1] ☐ Intermittent → No. of episodes ☐ [2] ☐ Constant
Intensity (maximum) *See definitions page for Adverse Experiences form.*	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Action Taken with Respect to Investigational Drug	[1] ☐ None [2] ☐ Dose reduced [3] ☐ Dose increased [4] ☐ Drug interrupted/restarted [5] ☐ Drug stopped
Relationship to Investigational Drug	[1] ☐ Not related [2] ☐ Unlikely [3] ☐ Suspected (reasonable possibility) [4] ☐ Probable
Corrective Therapy *If 'Yes', record details on the COPD Medications or Procedures page*	☐ Yes ☐ No
Was patient withdrawn due to this specific event?	☐ Yes ☐ No

DEFINITIONS OF LEVELS OF EXACERBATION OF COPD

Level 1 (Mild-self treated): Acute worsening of COPD that is self-managed by the patient at home by increasing the dose of relief salbutamol medication by > 2 occasions/24 hour period on two or more consecutive days compared with their baseline (baseline = mean of last 10 days of run-in period) or use of other additional bronchodilator medication

Level 2 (Moderate- physician, investigator treated): Acute worsening of symptoms (cough, sputum production, breathlessness) requiring treatment with oral corticosteroids prescribed by a physician or primary care doctor, or as a result of hospital out-patient visit (including Emergency Room).

Exacerbations requiring oral corticosteroids will be treated with a standardised course of prednisolone or prednisone tablets 30mg/day for 10 days, or methylprednisolone tablets 24mg/day for 10 days.

Level 3 (Severe - attendance at hospital): Acute worsening of COPD that requires the patient to be admitted to hospital for treatment.

Protocol	Centre Number	Patient Number			COPD Exacerbations (AE)
207499/157					

FURTHER DETAILS OF COPD EXACERBATIONS

COPD exacerbation onset date : Day Month Yr

Level of exacerbation (see definitions on facing page):

[1] ☐ Level 1
[2] ☐ Level 2
[3] ☐ Level 3

Pumonary function test result (FEV_1) (if done):

☐.☐☐ L

Did the patient suffer from any of the following during the exacerbation:

[1] ☐ Chest pain
[2] ☐ Upper Respiratory Tract Infection
[3] ☐ Confusion
[4] ☐ Change in alertness
[5] ☐ Pneumonia
[6] ☐ Oedema
[7] ☐ Ankle swelling

ARTERIAL BLOOD GASES (only for COPD exacerbations)

Where feasible, an arterial blood gas sample is to be taken for analysis

COPD exacerbation onset date : Day Month Yr

PO_2 (mmHg)	**PCO_2** (mmHg)	**pH**	**Resting SaO_2** (%)
☐☐☐	☐☐	☐.☐☐	☐☐☐

RESOURCE UTILISATION

Please complete the Resource Utilisation pages for this exacerbation.

SmithKline Beecham Pharmaceuticals

Protocol	Centre Number	Patient Number		SB Receipt Date (Day Month Year)	COPD Exacerbations (SAE)
207499/157		[redacted]			

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation

Person Reporting SAE _____ *(Please print clearly)*

AEGIS Number _____ . _____

Serious Adverse Experience	**COPD Exacerbation**
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*	[1] ☐ Resolved [2] ☐ Ongoing [3] ☐ Died
Experience Course	[1] ☐ Intermittent → No. of episodes ☐ [2] ☐ Constant
Intensity *(maximum)*	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Action Taken with Respect to Investigational Drug	[1] ☐ None [2] ☐ Dose reduced [3] ☐ Dose increased [4] ☐ Drug interrupted/ restarted [5] ☐ Drug stopped
Relationship to Investigational Drug	[1] ☐ Not related [2] ☐ Unlikely [3] ☐ Suspected (reasonable possibility) [4] ☐ Probable
Corrective Therapy *If 'Yes', record details in the COPD Concomitant Medication section*	☐ Yes ☐ No
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No

→ *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

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 _____

00000

SmithKline Beecham Pharmaceuticals

Protocol	Centre Number	Patient Number		SB Receipt Date (Day Month Year)	COPD Exacerbations (SAE)
207499/157		[redacted]			

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation

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 Number (please do NOT enter the container number): ☐☐☐☐☐

Investigator's Signature: _____ Date ☐☐ ☐☐☐ ☐☐☐☐ (Day Month Year)
(confirming that the above data are accurate and complete)

Please PRINT Name _____

SB Medical Monitor's Signature: _____ Date ☐☐ ☐☐☐ ☐☐☐☐ (Day Month Year)

Please PRINT Name _____

DEFINITIONS OF LEVELS OF EXACERBATION OF COPD

Level 1 (Mild-self treated): Acute worsening of COPD that is self-managed by the patient at home by increasing the dose of relief salbutamol medication by > 2 occasions/24 hour period on two or more consecutive days compared with their baseline (baseline = mean of last 10 days of run-in period) or use of other additional bronchodilator medication

Level 2 (Moderate- physician, investigator treated): Acute worsening of symptoms (cough, sputum production, breathlessness) requiring treatment with oral corticosteroids prescribed by a physician or primary care doctor, or as a result of hospital out-patient visit (including Emergency Room).

Exacerbations requiring oral corticosteroids will be treated with a standardised course of prednisolone or prednisone tablets 30mg/day for 10 days, or methylprednisolone tablets 24mg/day for 10 days.

Level 3 (Severe - attendance at hospital): Acute worsening of COPD that requires the patient to be admitted to hospital for treatment.

00000

SmithKline Beecham
Pharmaceuticals

Protocol	**Centre Number**	**Patient Number**		**SB Receipt Date** Day Month Year	**COPD Exacerbations (SAE)**
207499/157		[redacted]			

FURTHER DETAILS OF SERIOUS COPD EXACERBATIONS

COPD exacerbation onset date : Day Month Yr

Level of exacerbation (see definitions on facing page):

[1] ☐ Level 1
[2] ☐ Level 2
[3] ☐ Level 3

Pumonary function test result (FEV_1) (if done):

☐.☐☐ L

Did the patient suffer from any of the following during the exacerbation:

[1] ☐ Chest pain
[2] ☐ URTI
[3] ☐ Confusion
[4] ☐ Change in alertness
[5] ☐ Pneumonia
[6] ☐ Oedema
[7] ☐ Ankle swelling

ARTERIAL BLOOD GASES (only for serious COPD exacerbations)

Where feasible, an arterial blood gas sample is to be taken for analysis

COPD exacerbation onset date : Day Month Yr

PO_2 (mmHg)	**PCO_2** (mmHg)	**pH**	**Resting SaO_2** (%)
☐☐☐	☐☐	☐.☐☐	☐☐☐

RESOURCE UTILISATION

Please complete the Resource Utilisation pages for this exacerbation.

Protocol	**Centre Number**	**Patient Number**			**COPD Exacerbations (ConMed)**
207499/157		[redacted]			

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)	**Freq.** (eg bd, prn)	**Route***	**Medical Illness/ Diag.**	**Start Date** *(be as precise as possible)* Day Mth Yr	**End Date** *(or if Continuing mark box)* Day Mth Yr		COPD Exacerbation Onset Date
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								

** For Route, see General Instructions for acceptable abbreviations.*

Protocol	**Centre Number**	**Patient Number**			**COPD Exacerbations (ConMed)**
207499/157		[redacted]			

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** Day Mth Yr	**Procedure End Date** Day Mth Yr	COPD Exacerbation Onset Date
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				

SmithKline Beecham
Pharmaceuticals

Protocol	**Centre Number**	**Patient Number**			**Resource Utilisation For COPD Exacerbations**
207499/157		[redacted]			

RESOURCE UTILISATION FOR COPD EXACERBATIONS

Has the patient had any medical care for COPD Exacerbations that have occurred since the previous module?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below*

Has the patient had any **Physician contact** (COPD care excluding scheduled protocol visits) since the previous module?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below*

Date of Contact Day Mth Yr	Telephone	Home Visit		Office/ Practice	Out-patients	Reason for contact	COPD Exacerbation Onset Date Day Mth Yr
		Day	Night				

Has the patient had any **Emergency Room (ER)/Urgent Care Visits/Procedures (i.e., lung surgery)** since the previous module?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below*

Date of Contact Day Mth Yr	**Reason for contact**	**Patient Admitted from ER?**		COPD Exacerbation Onset Date Day Mth Yr
		Yes	**No**	

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			Resource Utilisation For COPD Exacerbations
207499/157		[redacted]			

RESOURCE UTILISATION FOR COPD EXACERBATIONS - (cont)

Has the patient had any **Hospitalisations** since the previous module?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below* ***(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	COPD Exacerbation Onset Date Day Mth Yr

Has the patient had any **Intensive Care Unit (ICU) stays** ***(did the patient stay in the ICU during any of the above hospitalisations?)*** since the previous module?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below*

Date Admitted to ICU Day Mth Yr	Date Discharged from ICU Day Mth Yr	Reason for ICU Admission	COPD Exacerbation Onset Date Day Mth Yr

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			
207499/157		[redacted]			

2 0 7 4 9 9 1 5 7

CONC2

Please do not split modules

Module: **Study Continuation / Withdrawal**

CRF Pages **146**

Unprocessed Forms : **Within this module the following occur which will generate attachments that need to be brought in-house.**

None

FOR OFFICE USE ONLY Module Comments:

Sent to Data Mngt	Review Complete Date: User:	First Entry Complete Date: User:
Second Entry Complete Date: User:	Validation Complete Date: User:	**Clintrial PID:**

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			Study Continuation/ Withdrawal
207499/157		[redacted]			

STUDY CONTINUATION/WITHDRAWAL

Is the patient continuing in the study? ***(For patients who have withdrawn from study medication but are continuing with essential assessment visits, please mark 'No' and the primary reason for withdrawal)***

☐ Yes ⟶ *If 'Yes', please sign in the appropriate space below and continue to Book 3 for the next visit.*

☐ No ⟶ If 'No', please mark the **primary** cause of withdrawal. *(Mark one box only).*

[1] ☐ Adverse Experience *(please complete Adverse Experiences page)*

[2] ☐ Insufficient therapeutic effect

[3] ☐ Protocol deviation (including non-compliance)

[4] ☐ Lost to follow-up

[7] ☐ Other - *specify*: _

g_cont_wthd_01

INVESTIGATOR SIGNATURE

I certify that I have reviewed the data on this case report form, including laboratory data and that in the Baseline Signs and Symptoms, Adverse Experiences and Serious Adverse Experiences sections (if appropriate) 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*
- *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			
207499/157		[redacted]			

2 0 7 4 9 9 1 5 7

SAE2

Please do not split modules

Module: **Serious Adverse Experiences**

CRF Pages **147 - 148**

Unprocessed Forms : **Within this module the following occur which will generate attachments that need to be brought in-house.**

None

FOR OFFICE USE ONLY Module Comments:

Sent to Data Mngt	Date: / User: Review Complete	Date: / User: First Entry Complete
Date: / User: Second Entry Complete	Date: / User: Validation Complete	**Clintrial PID:**

00000

SmithKline Beecham
Pharmaceuticals

Protocol	**Centre Number**	**Patient Number**		**SB Receipt Date** Day Month Year	**Serious Adverse Experiences**
207499/157		[redacted]			

SERIOUS ADVERSE EXPERIENCE (SAE)

Person Reporting SAE *(Please print clearly)* _

AEGIS Number _ _ _ _ _ _ _ _ . _

Serious Adverse Experience *(Please print clearly)*

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*
[1] Resolved
[2] Ongoing
[3] Died

Experience Course
[1] Intermittent — No. of episodes
[2] Constant

Intensity *(maximum)*
[1] Mild
[2] Moderate
[3] Severe

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

Action Taken with Respect to Investigational Drug
[1] None
[2] Dose reduced
[3] Dose increased
[4] Drug interrupted restarted
[5] 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
[1] Not related
[2] Unlikely
[3] Suspected (reasonable possibility)
[4] 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

g_sae_01

00000

SmithKline Beecham Pharmaceuticals

Protocol	Centre Number	Patient Number		SB Receipt Date (Day Month Year)	Serious Adverse Experiences
207499/157		[redacted]			

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 Number (please do NOT enter the container number): ☐☐☐☐☐

Investigator's Signature: _____ Date ☐☐ ☐☐ ☐☐
(confirming that the above data are accurate and complete) Day Month Year

Please PRINT Name _____

SB Medical Monitor's Signature: _____ Date ☐☐ ☐☐ ☐☐

Please PRINT Name _____ Day Month Year

g_sae_01

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			
207499/157		[redacted]			

2 0 7 4 9 9 1 5 7

RPLAB3

Please do not split modules

Module: **Repeat / unscheduled laboratory assessments**

CRF Pages: **149**

Unprocessed Forms: **Within this module, the following tests / procedures occur which may generate attachments.**

None

FOR OFFICE USE ONLY Module Comments:

Sent to Data Mngt	Review Complete Date: User:	First Entry Complete Date: User:
Second Entry Complete Date: User:	Validation Complete Date: User:	**Clintrial PID:**

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			Repeat / Unscheduled Lab Tests
207499/157		[redacted]			

REPEAT / UNSCHEDULED LABORATORY TESTS

Visit Number (or last scheduled visit number): ☐☐ Sample Date ☐☐ ☐☐ ☐☐ Day Month Yr

Please take blood samples for hematology and/or blood chemistry (including serum beta-HCG for women of child-bearing potential) and/or a urine sample for urinalysis. Please refer to the instructions on the Quest shipping form and manual.

Please attach Central Lab CRF label here

(Attach label when sample is sent to central lab.)

Laboratory reports will stay at the site as part of the patient's source documentation.

Request βhCG test on Quest requisition for women of child-bearing potential. If the pregnancy test is positive, please withdraw the patient and complete the Serious Adverse Experiences form and forward it to SB within 24 hours.

Are there any **clinically significant** worsenings since the last assessment?

☐ No

☐ Yes ⟶ *If 'Yes', please record the findings and/or diagnosis in the Adverse Experiences section.*

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			
207499/157					

2 0 7 4 9 9 1 5 7

RPLAB4

Please do not split modules

Module: **Repeat / unscheduled laboratory assessments**

CRF Pages: **150**

Unprocessed Forms: **Within this module, the following tests / procedures occur which may generate attachments.**

None

FOR OFFICE USE ONLY Module Comments:

Sent to Data Mngt	Review Complete Date: User:	First Entry Complete Date: User:
Second Entry Complete Date: User:	Validation Complete Date: User:	**Clintrial PID:**

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			Repeat / Unscheduled Lab Tests
207499/157		[redacted]			

REPEAT / UNSCHEDULED LABORATORY TESTS

Visit Number (or last scheduled visit number): ☐☐ Sample Date ☐☐ ☐☐ ☐☐ Day Month Yr

Please take blood samples for hematology and/or blood chemistry (including serum beta-HCG for women of child-bearing potential) and/or a urine sample for urinalysis. Please refer to the instructions on the Quest shipping form and manual.

Please attach Central Lab CRF label here

(Attach label when sample is sent to central lab.)

Laboratory reports will stay at the site as part of the patient's source documentation.

Request βhCG test on Quest requisition for women of child-bearing potential. If the pregnancy test is positive, please withdraw the patient and complete the Serious Adverse Experiences form and forward it to SB within 24 hours.

Are there any **clinically significant** worsenings since the last assessment?

☐ No

☐ Yes ⟶ *If 'Yes', please record the findings and/or diagnosis in the Adverse Experiences section.*

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number		Investigator
207499/157		[redacted]		_ _

CRF TRACKING/REVIEW FORM (TRF) (BOOK 2)

Please submit COMPLETE modules only. Do not submit whole blank modules.

- *Mark the **Unused** box for all remaining modules that will **not** be completed and sent in-house*
- *Ensure the Missing Pages field is completed if pages are missing from modules*
- *Ensure the Patient Numbers entered match the information on the CRF*
- *Complete one TRF per batch of modules to be sent in-house*
- *Ensure all sections of the TRF are legible*

Module	Module Description	Page Range	Modules		Missing pages (if applicable)
			Sent to DM	Unused	
DIA3	Visit 3 Patient diary	1 - 6	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
MOD3	V4, V5, AE, CM, Med Pro, COPD, RU	59 - 101	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
DIA4	Visit 4 Patient diary	1 - 6	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
PFT4	Visit 5 PFT printout	n/a	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
DIA5	Visit 5 Patient diary	1 - 6	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
MOD4	V6, V7 , AE, CM, Med Pro, COPD, RU	102 - 145	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
PFT5	Visit 6 PFT printout	n/a	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
DIA6	Visit 6 Patient diary	1 - 6	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
ECG3	Visit 7 ECG trace	n/a	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
PFT6	Visit 7 PFT printout	n/a	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
CONC2	Continuation/Withdrawal	146	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
SAE2	Serious Adverse Experiences	147 - 148	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
RPLAB3	Repeat Labs	149	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
RPLAB4	Repeat Labs	150	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
FORMD	Form D	n/a	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _

If multiple modules are submitted together, please ensure they are sorted according to the order above

Site Monitor's Name _ *(Print clearly)*

Site Monitor's Signature _ **Date Submitted** ☐☐ ☐☐ ☐☐
Day Month Yr

g_trf_01

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number		Investigator
207499/157		[redacted]		_ _

CRF TRACKING/REVIEW FORM (TRF) (BOOK 2)

Site Monitor's comments (eg. protocol violations or deviations)

_ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number		Investigator
207499/157		[redacted]		_ _

CRF TRACKING/REVIEW FORM (TRF) (BOOK 2)

Please submit COMPLETE modules only. Do not submit whole blank modules.

- *Mark the **Unused** box for all remaining modules that will **not** be completed and sent in-house*
- *Ensure the Missing Pages field is completed if pages are missing from modules*
- *Ensure the Patient Numbers entered match the information on the CRF*
- *Complete one TRF per batch of modules to be sent in-house*
- *Ensure all sections of the TRF are legible*

Module	Module Description	Page Range	Modules		Missing pages (if applicable)
			Sent to DM	Unused	
DIA3	Visit 3 Patient diary	1 - 6	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
MOD3	V4, V5, AE, CM, Med Pro, COPD, RU	59 - 101	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
DIA4	Visit 4 Patient diary	1 - 6	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
PFT4	Visit 5 PFT printout	n/a	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
DIA5	Visit 5 Patient diary	1 - 6	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
MOD4	V6, V7 , AE, CM, Med Pro, COPD, RU	102 - 145	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
PFT5	Visit 6 PFT printout	n/a	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
DIA6	Visit 6 Patient diary	1 - 6	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
ECG3	Visit 7 ECG trace	n/a	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
PFT6	Visit 7 PFT printout	n/a	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
CONC2	Continuation/Withdrawal	146	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
SAE2	Serious Adverse Experiences	147 - 148	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
RPLAB3	Repeat Labs	149	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
RPLAB4	Repeat Labs	150	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
FORMD	Form D	n/a	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _

If multiple modules are submitted together, please ensure they are sorted according to the order above

Site Monitor's Name _ *(Print clearly)*

Site Monitor's Signature _ **Date Submitted** ☐☐ ☐☐ ☐☐
Day Month Yr

g_trf_01

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number		Investigator
207499/157		[redacted]		_ _

CRF TRACKING/REVIEW FORM (TRF) (BOOK 2)

Site Monitor's comments (eg. protocol violations or deviations)

_ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number		Investigator
207499/157		[redacted]		_ _

CRF TRACKING/REVIEW FORM (TRF) (BOOK 2)

Please submit COMPLETE modules only. Do not submit whole blank modules.

- *Mark the **Unused** box for all remaining modules that will **not** be completed and sent in-house*
- *Ensure the Missing Pages field is completed if pages are missing from modules*
- *Ensure the Patient Numbers entered match the information on the CRF*
- *Complete one TRF per batch of modules to be sent in-house*
- *Ensure all sections of the TRF are legible*

Module	Module Description	Page Range	Modules		Missing pages (if applicable)
			Sent to DM	Unused	
DIA3	Visit 3 Patient diary	1 - 6	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
MOD3	V4, V5, AE, CM, Med Pro, COPD, RU	59 - 101	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
DIA4	Visit 4 Patient diary	1 - 6	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
PFT4	Visit 5 PFT printout	n/a	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
DIA5	Visit 5 Patient diary	1 - 6	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
MOD4	V6, V7 , AE, CM, Med Pro, COPD, RU	102 - 145	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
PFT5	Visit 6 PFT printout	n/a	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
DIA6	Visit 6 Patient diary	1 - 6	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
ECG3	Visit 7 ECG trace	n/a	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
PFT6	Visit 7 PFT printout	n/a	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
CONC2	Continuation/Withdrawal	146	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
SAE2	Serious Adverse Experiences	147 - 148	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
RPLAB3	Repeat Labs	149	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
RPLAB4	Repeat Labs	150	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
FORMD	Form D	n/a	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _

If multiple modules are submitted together, please ensure they are sorted according to the order above

Site Monitor's Name _ *(Print clearly)*

Site Monitor's Signature _ **Date Submitted** ☐☐ ☐☐ ☐☐
Day Month Yr

g_trf_01

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number		Investigator
207499/157		[redacted]		_ _

CRF TRACKING/REVIEW FORM (TRF) (BOOK 2)

Site Monitor's comments (eg. protocol violations or deviations)

_ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _

00000

SmithKline Beecham
Pharmaceuticals

Protocol **207499/157**		**Patient Number** [redacted]			**Visit 8 Week 20**

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 8

Is the patient continuing in the study?

☐ No ⟶ *Go to '1' below.*

☐ Yes ⟶ *Go to '2' below.*

*1. If the patient is **not** continuing in the study, is the patient willing to return for essential assessments?*

If 'No', please complete the assessments for Visit 8, the additional assessments for patients withdrawing at Visit 8 and the Study Continuation/Withdrawal page at the back of this book. Please schedule a safety follow-up visit in 7 days (+/- 3 days).

If 'Yes', please complete the assessments for Visit 8, the additional assessments for patients withdrawing at Visit 8 and the Study Continuation/Withdrawal page at the back of this book. Ask the patient to return for a safety follow-up visit in 7 days (+/- 3 days) and then for their next scheduled visit 49 (+/- 6 days) later for essential assessments only.

*2. If the patient **is** continuing in the study, please:*	(tick if done)
	☑
• *Issue the patient a new diary card and remind the patient to complete the diary each morning until the next visit.*	☐
• *Ask the patient to return for the next visit in 56 +/- 6 days at the same time of day.*	☐
• ***Remind the patient:***	
i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after their breakfast.*	☐
ii ***not** to take their dose of study medication for at least 8 hours prior to their next study visit appointment.*	☐
iii *to refrain from using salbutamol or anticholinergic agents during the **4 hours** immediately preceding 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, the study salbutamol inhaler and spacer, and the diary card.*	☐
vi *to continue to take the anticholinergic medication, if prescribed, at a constant dose, and salbutamol when needed to control symptoms.*	☐
vii *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 occurrence.*	☐

00000

SmithKline Beecham
Pharmaceuticals

Protocol **207499/157**		**Patient Number** [redacted]			**Visit 9 Week 28**

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 9

Is the patient continuing in the study?

☐ No ⟶ *Go to '1' below.*

☐ Yes ⟶ *Go to '2' below.*

*1. If the patient is **not** continuing in the study, is the patient willing to return for essential assessments?*

If 'No', please complete the assessments for Visit 9, the additional assessments for patients withdrawing at Visit 9 and the Study Continuation/Withdrawal page at the back of this book. Please schedule a safety follow-up visit in 7 days (+/- 3 days).

If 'Yes', please complete the assessments for Visit 9, the additional assessments for patients withdrawing at Visit 9 and the Study Continuation/Withdrawal page at the back of this book. Ask the patient to return for a safety follow-up visit in 7 days (+/- 3 days) and then for their next scheduled visit 49 (+/- 6 days) later for essential assessments only.

*2. If the patient **is** continuing in the study, please:*	(tick if done)
	☑
• *Issue the patient a new diary card and remind the patient to complete the diary each morning until the next visit.*	☐
• *Ask the patient to return for the next visit in 56 +/- 6 days at the same time of day.*	☐
• ***Remind the patient:***	
i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after their breakfast.*	☐
ii ***not** to take their dose of study medication for at least 8 hours prior to their next study visit appointment.*	☐
iii *to refrain from using salbutamol or anticholinergic agents during the **4 hours** immediately preceding 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, the study salbutamol inhaler and spacer, and the diary card.*	☐
vi *to continue to take the anticholinergic medication, if prescribed, at a constant dose, and salbutamol when needed to control symptoms.*	☐
vii *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 occurrence.*	☐

00000

SmithKline Beecham
Pharmaceuticals

Protocol **207499/157**		**Patient Number** [redacted]			**Visit 10 Week 36**

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 10

Is the patient continuing in the study?

☐ No ⟶ *Go to '1' below.*

☐ Yes ⟶ *Go to '2' below.*

*1. If the patient is **not** continuing in the study, is the patient willing to return for essential assessments?*

If 'No', please complete the assessments for Visit 10, the additional assessments for patients withdrawing at Visit 10 and the Study Continuation/Withdrawal page at the back of this book. Please schedule a safety follow-up visit in 7 days (+/- 3 days).

If 'Yes', please complete the assessments for Visit 10, the additional assessments for patients withdrawing at Visit 10 and the Study Continuation/Withdrawal page at the back of this book. Ask the patient to return for a safety follow-up visit in 7 days (+/- 3 days) and then for their next scheduled visit 49 (+/- 6 days) later for essential assessments only.

*2. If the patient **is** continuing in the study, please:*	(tick if done)
	☑
• *Issue the patient a new diary card and remind the patient to complete the diary each morning until the next visit.*	☐
• *Ask the patient to return for the next visit in 56 +/- 6 days at the same time of day.*	☐
• ***Remind the patient:***	
i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after their breakfast.*	☐
ii ***not** to take their dose of study medication for at least 8 hours prior to their next study visit appointment.*	☐
iii *to refrain from using salbutamol or anticholinergic agents during the **4 hours** immediately preceding 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, the study salbutamol inhaler and spacer, and the diary card.*	☐
vi *to continue to take the anticholinergic medication, if prescribed, at a constant dose, and salbutamol when needed to control symptoms.*	☐
vii *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 occurrence.*	☐

Protocol	Centre Number	Patient Number
207499/157		[redacted]

CONFIDENTIAL

SmithKline Beecham
Pharmaceuticals

PROTOCOL 207499/157

BOOK 3 : VISIT 8 TO VISIT 10

A RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL GROUP STUDY TO EVALUATE THE EFFICACY, SAFETY AND TOLERABILITY OF ORAL CILOMILAST (15 MG BD) WHEN GIVEN AS MAINTENANCE TREATMENT FOR 12 MONTHS TO SUBJECTS 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 and centre number on all pages 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 | *= 1st January 2001*
Day Month Year

TIME

Unless specified otherwise, please use the 24 hour clock

e.g. | 1 5 | 3 0 | *= 3.30 p.m*
24hr:min

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*

SCHEDULE OF ASSESSMENTS

Visit	1	2	3	4	5	6	7	8	9	10	11	12		13
	Screen		Base-line									End of DB	Early With-drawal	Follow -up
Time relative to baseline (weeks)[1]	-4	-2	0	+2	+4	+8	+12	+20	+28	+36	+44	+52		+53
Signed written informed consent	x													
Medical & surgical history	x													
Pulmonary symptoms	x													
Postero-anterior chest X-ray[2]	x													
Medication history including influenza vaccination[3]	x													
Health Status Assessments: SGRQ and EQ-5D			x						x			x	x	
Patient global assessment			x						x			x	x	
Investigator global assessment			x						x			x	x	
Physical examination [4]	x		x									x	x	x[5]
Smoking status	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Exacerbation assessment	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Resource utilisation				x	x	x	x	x	x	x	x	x	x	x
Diary Card Review		x	x	x	x	x	x	x	x	x	x	x	x	
Baseline signs and symptoms [6]	x	x	x											
Adverse experiences [6]				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
Study medication compliance		x	x	x	x	x	x	x	x	x	x	x	x	
Resting 12-lead ECG	x		x				x		x			x	x	x[5]
Vital signs (BP, HR)[7]	x[7]	x	x[7]	x	x	x	x[7]	x	x[7]	x	x	x[7]	x[7]	x
PFTs pre and post salbutamol: Pre-dose [8]	x		x		x	x	x	x	x	x	x	x	x	x
PFTs: salbutamol reversibility [9]	x		x											
PFTs: ipratropium reversibility		x												
Residual Volume (body box) pre-/ post-salbutamol Selected sites only			x						x			x	x	
Laboratory tests	x		x[10]		x	x	x	x	x	x	x	x[10]	x[10]	x[5]
Faecal occult blood test [11]	x	x										x	x	
Dispense single-blind med	x[12]	x[13]												
Dispense double-blind med			x[14]	x[13]	x[15]	x[15]	x[15]	x[15]	x[15]	x[15]	x[15]			
Study conclusion record														x[16]

1 All visit dates must be scheduled at the visit interval listed here using the Baseline visit as Day 0.
2 Chest X-ray to be taken at entry to the run-in period or in the 3 months prior to entry to the run-in period
3 Details of 'flu vaccinations will be recorded at every visit
4 Includes respiratory examination.
5 Only if abnormalities are present at Visit 12/Early Withdrawal.
6 Does not include COPD exacerbations
7 Orthostatic vital signs to be measured at Visits 1, 3, 7, 9, and 12
8 Includes FEV_1, FVC, FEF_{25-75} and PEF measured by spirometry by the same study personnel at each visit before dose of study medication is taken.
9 Includes FEV_1, FVC, FEF_{25-75} and PEF measured by spirometry by the same study personnel at each visit 30 minutes after administration of 400 mcg of salbutamol via MDI with or without a spacer, and before dose of study medication is taken.
10 Includes Blood CD4+/CD8+ ratio and serum C Reactive Protein
11 In addition to the usual laboratory tests, three faecal occult blood tests will be performed between Visits 1 and 3, at the end of the treatment period and at Early Withdrawal
12 Register the patient with RAMOS.
13 The container of study medication issued at the previous visit will be re-issued at this visit
14 Call RAMOS to randomise the patient and to obtain study medication assignment and container number.
15 Call RAMOS to obtain study medication container number(s)
16 Or earlier if the subject withdraws from the study prior to Visit 12.

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			
207499/157		[redacted]			

2 0 7 4 9 9 1 5 7

MOD5

Please do not split modules

Module 5 : **Visit 8, Adverse Experiences, Concomitant Medications, Medical Procedures, COPD Exacerbations, Resource Utilisation**

CRF Pages **151 - 180**

Unprocessed Forms : **Within this module the following occur which will generate attachments that need to be brought in-house.**

None

FOR OFFICE USE ONLY Module Comments:

Sent to Data Mngt	Review Complete Date: User:	First Entry Complete Date: User:
Second Entry Complete Date: User:	Validation Complete Date: User:	**Clintrial PID:**

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number		Visit Date (Day Month Year)	
207499/157		[redacted]			**Visit 8 Week 20**

PRESENTATION TO CLINIC

Note: ***Patients must wait for 4 hours after beta$_2$-agonist and / or anticholinergic administration before the pulmonary function tests are performed.***

Did the patient take a dose of beta$_2$ agonist in the past 24 hours?

☐ No

☐ Yes → Record date and time of the patient's last dose of beta$_2$ agonist: Day Month Yr 24hr:min

Did the patient take a dose of anticholinergic in the past 24 hours?

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: Day Month Yr 24hr:min

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes → Date and time of patient's last cigarette Day Month Yr 24hr:min

SMOKING STATUS

Does the patient currently smoke?

☐ No

☐ Yes → If 'Yes' please record the average number of cigarettes per day :

INFLUENZA VACCINATION

Has the patient had a vaccination for influenza since the last visit?

N.B. It is not necessary to record vaccinations on the Concomitant Medication or Medical Procedures page.

☐ No

☐ Yes → *If 'Yes', record date of vaccination :* Day Month Yr

Protocol		Patient Number			Visit 8 Week 20
207499/157		[redacted]			

RESOLUTION OF COPD EXACERBATIONS

Have any COPD Exacerbations resolved since the last visit?

☐ No

☐ Yes ⟶ *If 'Yes', please record details in the COPD Exacerbation section at the back of this module.*

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes ⟶ *If 'Yes' please record details in the COPD Exacerbation section at the back of this module.*

Level 1 (Mild-self treated): Acute worsening of COPD that is self-managed by the patient at home by increasing the dose of relief salbutamol medication by > 2 occasions/24 hour period on two or more consecutive days compared with their baseline (baseline = mean of last 10 days of run-in period) or use of other additional bronchodilator medication

Level 2 (Moderate- physician, investigator treated): Acute worsening of symptoms (cough, sputum production, breathlessness) requiring treatment with oral corticosteroids prescribed by a physician or primary care doctor, or as a result of hospital out-patient visit (including Emergency Room).

Exacerbations requiring oral corticosteroids will be treated with a standardised course of prednisolone or prednisone tablets 30mg/day for 10 days, or methylprednisolone tablets 24mg/day for 10 days.

Level 3 (Severe - attendance at hospital): Acute worsening of COPD that requires the patient to be admitted to hospital for treatment.

If a patient experienced a COPD exacerbation that was treated with corticosteroids, please withdraw the patient and complete the Study Continuation/Withdrawal page at the back of this book. 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, including an increase in usual COPD medications, must be recorded in the COPD Medications or Procedures pages.

00000

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number			Visit 8 Week 20
207499/157		[redacted]			

RESOURCE UTILISATION

If the patient has received any COPD exacerbation-related medical care since the last visit, record details on the Resource Utilisation pages of the COPD Exacerbation section at the back of this module.

DIARY CARD REVIEW

Review the diary card in the presence of the patient. Question any increased symptoms for possible COPD exacerbations. Place diary in the plastic wallet at the back of this module and re-issue another diary card.

ADVERSE EXPERIENCES

Please complete the Adverse Experiences 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 Experiences 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.

00000

SmithKline Beecham
Pharmaceuticals

Protocol **207499/157**		**Patient Number** [redacted]			**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. bd)

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
140					

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance ≥ 80% and ≤120%?

☐ No → *If 'No' please remind the patient of the importance of taking study medication according to the protocol.*

☐ Yes

00000

SmithKline Beecham
Pharmaceuticals

Protocol **207499/157**		**Patient Number** [redacted]			**Visit 8 Week 20**

INVESTIGATOR INSTRUCTIONS

The following procedures (Vital Signs and Pulmonary Function Tests) must be performed greater than 4 hours after the patient's last salbutamol administration.

VITAL SIGNS

Time of assessment : ☐☐ 24hr:min

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
☐☐☐/☐☐☐	☐☐☐

Are there any **clinically significant worsenings** since the previous visit?

☐ No

☐ Yes ⟶ *If 'Yes' please record the findings and/or diagnosis in the Adverse Experiences section at the back of this module.*

Protocol		Patient Number			Visit 8 Week 20
207499/157		[redacted]			

PRE-SALBUTAMOL PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed at least 4 hours after the last dose of inhaled beta$_2$-agonist or anticholinergic agent.

Measure the patient's pulmonary function up to eight times to obtain three acceptable readings using the spirometer provided by SB. ***(Note: Please follow instructions in the Spirometry Manual).*** *For each set of three FEV_1 measurements, one FEV_1 must be within 10% of the highest. Please record the results of the effort with the highest FEV_1 below.*

Measurement	Time	FEV_1 (L)	FVC (L)	FEF_{25-75} (L/sec)	PEF (L/min)
1	☐☐ 24hr:min	☐.☐☐	☐.☐☐	☐.☐☐	☐☐☐

Place the spirometry reports in the plasic wallet at the back of this module.

POST-SALBUTAMOL PULMONARY FUNCTION TESTS

Provide the patient with a salbutamol MDI and spacer. Administer 400 mcg (4 puffs) of salbutamol via MDI with a spacer. Remind the patient to use this inhaler (with or without the spacer), rather than any salbutamol inhaler they may have at home, for "as required" rescue-medication use during the study.

Record the time of salbutamol inhalation ☐☐ 24hr:min

Wait 30 minutes

Measure the patient's pulmonary function up to eight times to obtain three acceptable readings using the spirometer provided by SB. ***(Note: Please follow instructions in the Spirometry Manual).*** *For each set of three FEV_1 measurements, one FEV_1 must be within 10% of the highest. Please record the results of the effort with the highest FEV_1 below.*

Measurement	Time	FEV_1 (L)	FVC (L)	FEF_{25-75} (L/sec)	PEF (L/min)
1	☐☐ 24hr:min	☐.☐☐	☐.☐☐	☐.☐☐	☐☐☐

Place spirometry reports in the plastic wallets at the back of this module.

PULMONARY REHABILITATION PROGRAM

Has the patient entered a Pulmonary Rehabilitation Program since the last visit?

☐ No

☐ Yes

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number			Visit 8 Week 20
207499/157		[redacted]			

LABORATORY TESTS

Please take blood samples for haematology and blood chemistry (including serum beta-HCG for women of child-bearing potential) and a urine sample for urinalysis. Please refer to the instructions on the Quest shipping form and manual.

Blood Sample Date ☐☐ ☐☐☐ ☐☐
Day Month Yr

Attach a label from the 'Routine' laboratory requisition form used at this visit in the space below.

Attach label here

Are there any **clinically significant worsenings** since the last assessment?

☐ No

☐ Yes ⟶ *If 'Yes' please record the findings and/or diagnosis in the Adverse Experiences section at the back of this module.*

STUDY MEDICATION ALLOCATION - RAMOS CALL

Following completion of all preceding assessments, complete the RAMOS worksheet appropriate for this visit and contact RAMOS to obtain the container numbers for this visit.

*Please enter the 5-digit **randomisation number** assigned by RAMOS* ☐☐☐☐☐

*Please enter the 6-digit **container number** as it appears on the study medication label **(Container 1)**.* ☐☐☐☐☐☐

*Please enter the 6-digit **container number** as it appears on the study medication label **(Container 2)**.* ☐☐☐☐☐☐

STUDY MEDICATION LABEL

Attach the tear-off labels from the study medication containers 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

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

00000

SmithKline Beecham
Pharmaceuticals

Protocol **207499/157**		**Patient Number** [redacted]			**Visit 8 Week 20**

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 8

Is the patient continuing in the study?

☐ No

☐ Yes

*If the patient is **not** continuing in the study, is the patient willing to return for essential assessments?*

If 'No', please complete the assessments for Visit 8 and the additional assessments for patients withdrawing at Visit 8 and the Study Continuation/Withdrawal page at the back of this book.

If 'Yes', please complete the assessments for Visit 8, the assessments for patients withdrawing at Visit 8 and the Study Continuation/Withdrawal page at the back of this book. Ask the patient to return in 56 +/-6 days time for essential assessments only.

*If the patient **is** continuing in the study, please:*	(tick if done)
	☑
• *Issue the patient a new diary card and remind the patient to complete the diary each morning until the next visit.*	☐
• *Ask the patient to return for the next visit in 56 +/- 6 days for a morning visit.*	☐
• ***Remind the patient:***	
i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after their breakfast.*	☐
ii ***not** to take the morning dose of study medication at home on the day of the next clinic visit.*	☐
iii *to refrain from using salbutamol or anticholinergic agents during the **4 hours** immediately preceding 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, the study salbutamol inhaler and spacer, and the diary card.*	☐
vi *to continue to take the anticholinergic medication, if prescribed, at a constant dose, and salbutamol when needed to control symptoms.*	☐
vii *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 occurrence.*	☐

00000

SmithKline Beecham
Pharmaceuticals

Protocol 207499/157		Patient Number [redacted]			Withdrawal at Visit 8 Week 20

ASSESSMENTS FOR PATIENTS WITHDRAWING AT VISIT 8

Complete the assessments below only for patients who are withdrawing from the study at this visit.

ST. GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND EQ-5D

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

INVESTIGATOR GLOBAL EVALUATION OF IMPROVEMENT

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

PATIENT GLOBAL EVALUATION OF IMPROVEMENT

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

Protocol **207499/157**		**Patient Number** [redacted]			**Withdrawal at Visit 8 Week 20**

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 Experiences section at the back of this module.*

VITAL SIGNS - ORTHOSTATIC CHANGE

Time of assessment : ☐☐ 24hr:min

1st Measurement: After 5 Minutes Supine		**2nd Measurement: 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)
☐☐☐/☐☐☐	☐☐☐	☐☐☐/☐☐☐	☐☐☐

Have there been any clinically significant worsenings since the last assessment?

☐ No

☐ Yes⟶ *If 'Yes', please record the findings in the Adverse Experiences section at the back of this module.*

Protocol		Patient Number			Withdrawal at Visit 8 Week 20
207499/157		[redacted]			

12 LEAD ELECTROCARDIOGRAM

Time of assessment : ☐☐ 24hr:min **The ECG should be performed after the patient has been semi-supine for 5 minutes**

Date ECG Performed (Day Month Year)	Atrial Rate (beats/min)	Ventricular Rate (beats/min)	PR (msec)	QRS (msec)	☐ Uncorrected QT ☐ Corrected QT (msec)	Axis
☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐ + ☐ - ☐☐☐

Interpretation

☐ **(F74301) Within normal limits**

☐ **Abnormal** ⟶ ***Mark appropriate boxes below***

Rhythm
- ☐ (F73360) Sinus arrhythmia
- ☐ (F73310) Sinus bradycardia
- ☐ (F73380) Sinus tachycardia
- ☐ (F73440) Wandering atrial pacemaker
- ☐ (F73450) Premature atrial contractions
- ☐ (F73510) Paroxysmal atrial tachycardia
- ☐ (F73530) Chronic ectopic atrial tachycardia
- ☐ (F73550) Multifocal atrial tachycardia
- ☐ (F73560) Atrial flutter
- ☐ (F73570) Atrial fibrillation
- ☐ (F73610) Junctional (AV nodal) premature contractions
- ☐ (F73650) Junctional (AV nodal) tachycardia
- ☐ (F73150) Supraventricular tachycardia
- ☐ (F73860) Accelerated idioventricular rhythm
- ☐ (F73710) Premature Ventricular Contractions (NOS)
- ☐ (F73720) Unifocal PVC's
- ☐ (F73730) Multifocal PVC's
- ☐ (F73711) Ventricular couplets
- ☐ (F73750) Bigeminy
- ☐ (F73870) Ventricular tachycardia
- ☐ (F73880) Ventricular fibrillation
- ☐ (F73340) Sick sinus syndrome
- ☐ (F73190) Pacemaker rhythm

P-Wave Morphology
- ☐ (F74214) Left atrial hypertrophy, P mitrale
- ☐ (F74213) Right atrial hypertrophy, P pulmonale

Conduction
- ☐ (F73930) First degree AV block
- ☐ (F73950) Second degree AV block, Type 1
- ☐ (F73960) Second degree AV block, Type 11
- ☐ (F73970) Third degree AV block
- ☐ (F74090) Wolff-Parkinson-White syndrome

Axis
- ☐ (F74120) Right Axis deviation
- ☐ (F74130) Left Axis deviation

QRS
- ☐ (F74010) Right bundle branch block
- ☐ (F74020) Left bundle branch block
- ☐ (F74030) Left anterior hemiblock
- ☐ (F74040) Left posterior hemiblock
- ☐ (F74002) Intraventricular conduction delay
- ☐ (F74212) Left ventricular hypertrophy
- ☐ (F74211) Right ventricular hypertrophy
- ☐ (F74308) Q-wave > 0.04 sec
- ☐ (F74222) R-wave amplitude increased
- ☐ (F74225) R-wave amplitude decreased
- ☐ (F74313) Prolonged QT-interval
- ☐ (F74318) Poor R-wave progression
- ☐ (M54750) Myocardial infarction, old
  - ☐ (M54751) Anterior ☐ (M54754) Inferior
  - ☐ (M54752) Lateral ☐ (M54755) Septal
  - ☐ (M54753) Posterior

ST-T
- ☐ (F74291) Nonspecific ST-T changes
- ☐ (F74294) ST segment depression > 1 mm
- ☐ (F74295) ST segment elevation > 1 mm
- ☐ (F74350) T-wave flat
- ☐ (F74351) T-wave inversion
- ☐ (F74352) T-wave peaked
- ☐ (F74340) U-wave
- ☐ (F74360) Digitalis effect
- ☐ (F74260) Myocardial ischemia
  - ☐ (F74261) Anterior ☐ (F74264) Inferior
  - ☐ (F74262) Lateral ☐ (F74265) Septal
  - ☐ (F74263) Posterior
- ☐ (M54720) Myocardial infarction, acute
  - ☐ (M54721) Anterior ☐ (M54724) Inferior
  - ☐ (M54722) Lateral ☐ (M54725) Septal
  - ☐ (M54723) Posterior

Other interpretations not listed _

Were there any clinically important changes observed since the last assessment?

[1] ☐ No

[2] ☐ Yes ⟶ *If 'Yes', enter details on the Adverse Experiences page at the back of this module.*

Place the ECG trace in the plastic wallet a the back of this module

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number			Withdrawal at Visit 8 Week 20
207499/157		[redacted]			

(AT SELECTED CENTRES ONLY) RESIDUAL VOLUME BY BODY PLETHYSMOGRAPHY (PRE- AND POST-SALBUTAMOL)

Time of pre-salbutamol RV assessment: ☐☐ 24hr:min

Time of post-salbutamol RV assessment: ☐☐ 24hr:min

Pre-Salbutamol

$RV_{Box} = TLC_{Box} – max(|SVC|, |FVC|)$

$RV_{(Box)}$ = ☐.☐☐ (L)

Post-Salbutamol

$RV_{Box} = TLC_{Box} – max(|SVC|, |FVC|)$

$RV_{(Box)}$ = ☐.☐☐ (L)

Please attach plethysmography source data to the back of this page.

FAECAL OCCULT BLOOD TEST

The faecal occult blood test should be performed on three consecutive bowel movements between withdrawal and the next scheduled visit or the Follow-Up visit depending on whether the patient is willing, or not, to return for essential assessments. Patients are not to take samples during or up-to 3-days after a menstrual period or while having bleeding haemorrhoids or blood in the urine. Patients are not to take aspirin or other non-steroidal anti-inflammatory drugs for 7 days prior to and during the test period and they are to avoid Vitamin C in excess of 250mg 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.

Did the patient follow these instructions?

☐ No ⟶ *If 'No', please specify:* _

☐ Yes

Test	Date of Collection Day Mth Yr	Result of faecal occult blood test
1	☐☐ ☐☐☐ ☐☐	[NEG] ☐ Negative [POS] ☐ Positive
2	☐☐ ☐☐☐ ☐☐	[NEG] ☐ Negative [POS] ☐ Positive
3	☐☐ ☐☐☐ ☐☐	[NEG] ☐ Negative [POS] ☐ Positive

Are these findings clinically significant ?

☐ No

☐ Yes ⟶ *If 'Yes' please record the findings and/or diagnosis in the Adverse Experiences section at the back of this module.*

00000

SmithKline Beecham
Pharmaceuticals

Protocol		**Patient Number**			**Withdrawal at Visit 8 Week 20**
207499/157		[redacted]			

LABORATORY TESTS

Please take blood samples for CD4/CD8 ratio and C Reactive Protein. Please refer to the instructions on the Quest shipping form and manual.

Blood Sample Date ☐☐ ☐☐ ☐☐
Day Month Yr

Attach a label from the 'Routine' laboratory requisition form used at this visit in the space below.

Attach label here

Are there any **clinically significant worsenings** since the last assessment?

☐ No

☐ Yes ⟶ *If 'Yes' please record the findings and/or diagnosis in the Adverse Experiences section at the back of this module.*

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 study procedures should be reported as a serious event

IF AN 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

g_ae_instr_01

SmithKline Beecham Pharmaceuticals

Protocol	Centre Number	Patient Number			Adverse Experiences
207499/157		[redacted]			

ADVERSE EXPERIENCES (Non-serious)

g_ae_01

*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 last visit?" 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).

☐ Please mark this box if no adverse experiences occurred since the last module

Adverse Experience *(please print clearly)*		
For SB		
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 SAE section and follow instructions given there***	[1] ☐ Resolved [2] ☐ Ongoing [3] ☐ Died	[1] ☐ Resolved [2] ☐ Ongoing [3] ☐ Died
Experience Course	[1] ☐ Intermittent → No. of episodes ☐ [2] ☐ Constant	[1] ☐ Intermittent → No. of episodes ☐ [2] ☐ Constant
Intensity (maximum)	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Action Taken with Respect to Investigational Drug	[1] ☐ None [2] ☐ Dose reduced [3] ☐ Dose increased [4] ☐ Drug interrupted/restarted [5] ☐ Drug stopped	[1] ☐ None [2] ☐ Dose reduced [3] ☐ Dose increased [4] ☐ Drug interrupted/restarted [5] ☐ Drug stopped
Relationship to Investigational Drug	[1] ☐ Not related [2] ☐ Unlikely [3] ☐ Suspected (reasonable possibility) [4] ☐ Probable	[1] ☐ Not related [2] ☐ Unlikely [3] ☐ Suspected (reasonable possibility) [4] ☐ Probable
Corrective Therapy *If 'Yes', record details in the Concomitant Medication section and/ or Medical Procedures section if appropriate*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			Adverse Experiences
207499/157		[redacted]			

ADVERSE EXPERIENCES (Non-serious) - Continued

g_ae_01

*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 last visit?"*
*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).

Adverse Experience *(please print clearly)*		
For SB		
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 SAE section and follow instructions given there***	[1] Resolved [2] Ongoing [3] Died	[1] Resolved [2] Ongoing [3] Died
Experience Course	[1] Intermittent → No. of episodes [2] Constant	[1] Intermittent → No. of episodes [2] Constant
Intensity (maximum)	[1] Mild [2] Moderate [3] Severe	[1] Mild [2] Moderate [3] Severe
Action Taken with Respect to Investigational Drug	[1] None [2] Dose reduced [3] Dose increased [4] Drug interrupted/restarted [5] Drug stopped	[1] None [2] Dose reduced [3] Dose increased [4] Drug interrupted/restarted [5] Drug stopped
Relationship to Investigational Drug	[1] Not related [2] Unlikely [3] Suspected (reasonable possibility) [4] Probable	[1] Not related [2] Unlikely [3] Suspected (reasonable possibility) [4] Probable
Corrective Therapy *If 'Yes', record details in the Concomitant Medication section and/ or Medical Procedures section if appropriate*	Yes No	Yes No
Was patient withdrawn due to this specific AE?	Yes No	Yes No

SmithKline Beecham
Pharmaceuticals

Protocol	**Centre Number**	**Patient Number**			**Adverse Experiences**
207499/157		[redacted]			

ADVERSE EXPERIENCES (Non-serious) - Continued

g_ae_01

*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 last visit?"*
*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).

Adverse Experience *(please print clearly)*		
For SB		
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 SAE section and follow instructions given there***	[1] Resolved [2] Ongoing [3] Died	[1] Resolved [2] Ongoing [3] Died
Experience Course	[1] Intermittent → No. of episodes [2] Constant	[1] Intermittent → No. of episodes [2] Constant
Intensity (maximum)	[1] Mild [2] Moderate [3] Severe	[1] Mild [2] Moderate [3] Severe
Action Taken with Respect to Investigational Drug	[1] None [2] Dose reduced [3] Dose increased [4] Drug interrupted/restarted [5] Drug stopped	[1] None [2] Dose reduced [3] Dose increased [4] Drug interrupted/restarted [5] Drug stopped
Relationship to Investigational Drug	[1] Not related [2] Unlikely [3] Suspected (reasonable possibility) [4] Probable	[1] Not related [2] Unlikely [3] Suspected (reasonable possibility) [4] Probable
Corrective Therapy *If 'Yes', record details in the Concomitant Medication section and/ or Medical Procedures section if appropriate*	Yes No	Yes No
Was patient withdrawn due to this specific AE?	Yes No	Yes No

Protocol	Centre Number	Patient Number			Concomitant Medication
207499/157		[redacted]			

CONCOMITANT MEDICATION

Record any changes in concomitant medication taken since the last 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. At the patient's final study visit, record the end date for prn study rescue medication (salbutamol) use, using the date the study inhaler was returned.

☐ No concomitant medication changes since the last module

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded in the Adverse Experiences 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** (eg 500mg)	**Frequency** (eg bd, 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	
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							

** For Route, see general instructions for acceptable abbreviations.*

Protocol	**Centre Number**	**Patient Number**			**Concomitant Medication**
207499/157		[redacted]			

CONCOMITANT MEDICATION (Cont.)

Do not record any medication taken for COPD exacerbations in this section. Record all COPD exacerbation medication in the COPD Exacerbation section. At the patient's final study visit, record the end date for prn study rescue medication (salbutamol) use, using the date the study inhaler was returned.

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded in the Adverse Experiences 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** (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	
For SB							
For SB							
For SB							
For SB							
For SB							
For SB							
For SB							
For SB							
For SB							
For SB							

** For Route, see general instructions for acceptable abbreviations.*

g_conmed_01

Protocol	Centre Number	Patient Number			Medical Procedures
207499/157		[redacted]			

MEDICAL PROCEDURES

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 last module?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below using standard medical terminology*

All indications for procedures should be recorded on the Adverse Experiences Form.

Procedure	Indication	Procedure Start Date Day Mth Yr	Procedure End Date Day Mth Yr
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			COPD Exacerbations (AE)
207499/157		[redacted]			

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 last 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***

Has the patient suffered any COPD Exacerbations since the last module ?

☐ No

☐ Yes → *If 'Yes', please complete page below*

Adverse Event	COPD EXACERBATION
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, STOP: delete details of this exacerbation and go to SAE COPD Exacerbation pages.***	[1] ☐ Resolved [2] ☐ Ongoing [3] ☐ Died
Event Course	[1] ☐ Intermittent → No. of episodes ☐ [2] ☐ Constant
Intensity (maximum) *See definitions page for Adverse Experiences form.*	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Action Taken with Respect to Investigational Drug	[1] ☐ None [2] ☐ Dose reduced [3] ☐ Dose increased [4] ☐ Drug interrupted/restarted [5] ☐ Drug stopped
Relationship to Investigational Drug	[1] ☐ Not related [2] ☐ Unlikely [3] ☐ Suspected (reasonable possibility) [4] ☐ Probable
Corrective Therapy *If 'Yes', record details on the COPD Medications or Procedures page*	☐ Yes ☐ No
Was patient withdrawn due to this specific event?	☐ Yes ☐ No

DEFINITIONS OF LEVELS OF EXACERBATION OF COPD

Level 1 (Mild-self treated): Acute worsening of COPD that is self-managed by the patient at home by increasing the dose of relief salbutamol medication by > 2 occasions/24 hour period on two or more consecutive days compared with their baseline (baseline = mean of last 10 days of run-in period) or use of other additional bronchodilator medication

Level 2 (Moderate- physician, investigator treated): Acute worsening of symptoms (cough, sputum production, breathlessness) requiring treatment with oral corticosteroids prescribed by a physician or primary care doctor, or as a result of hospital out-patient visit (including Emergency Room).

Exacerbations requiring oral corticosteroids will be treated with a standardised course of prednisolone or prednisone tablets 30mg/day for 10 days, or methylprednisolone tablets 24mg/day for 10 days.

Level 3 (Severe - attendance at hospital): Acute worsening of COPD that requires the patient to be admitted to hospital for treatment.

Protocol	Centre Number	Patient Number			COPD Exacerbations (AE)
207499/157		[redacted]			

FURTHER DETAILS OF COPD EXACERBATIONS

COPD exacerbation onset date : Day Month Yr

Level of exacerbation (see definitions on facing page):

[1] ☐ Level 1
[2] ☐ Level 2
[3] ☐ Level 3

Pumonary function test result (FEV_1) (if done):

☐.☐☐ L

Did the patient suffer from any of the following during the exacerbation:

[1] ☐ Chest pain
[2] ☐ Upper Respiratory Tract Infection
[3] ☐ Confusion
[4] ☐ Change in alertness
[5] ☐ Pneumonia
[6] ☐ Oedema
[7] ☐ Ankle swelling

ARTERIAL BLOOD GASES (only for COPD exacerbations)

Where feasible, an arterial blood gas sample is to be taken for analysis

COPD exacerbation onset date : Day Month Yr

PO_2 (mmHg)	**PCO_2** (mmHg)	**pH**	**Resting SaO_2** (%)
☐☐☐	☐☐	☐.☐☐	☐☐☐

RESOURCE UTILISATION

Please complete the Resource Utilisation pages for this exacerbation.

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			COPD Exacerbations (AE)
207499/157		[redacted]			

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 last 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 Event	COPD EXACERBATION
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, STOP: delete details of this exacerbation and go to SAE COPD Exacerbation pages.***	[1] ☐ Resolved [2] ☐ Ongoing [3] ☐ Died
Event Course	[1] ☐ Intermittent → No. of episodes ☐ [2] ☐ Constant
Intensity (maximum) *See definitions page for Adverse Experiences form.*	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Action Taken with Respect to Investigational Drug	[1] ☐ None [2] ☐ Dose reduced [3] ☐ Dose increased [4] ☐ Drug interrupted/restarted [5] ☐ Drug stopped
Relationship to Investigational Drug	[1] ☐ Not related [2] ☐ Unlikely [3] ☐ Suspected (reasonable possibility) [4] ☐ Probable
Corrective Therapy *If 'Yes', record details on the COPD Medications or Procedures page*	☐ Yes ☐ No
Was patient withdrawn due to this specific event?	☐ Yes ☐ No

DEFINITIONS OF LEVELS OF EXACERBATION OF COPD

Level 1 (Mild-self treated): Acute worsening of COPD that is self-managed by the patient at home by increasing the dose of relief salbutamol medication by > 2 occasions/24 hour period on two or more consecutive days compared with their baseline (baseline = mean of last 10 days of run-in period) or use of other additional bronchodilator medication

Level 2 (Moderate- physician, investigator treated): Acute worsening of symptoms (cough, sputum production, breathlessness) requiring treatment with oral corticosteroids prescribed by a physician or primary care doctor, or as a result of hospital out-patient visit (including Emergency Room).

Exacerbations requiring oral corticosteroids will be treated with a standardised course of prednisolone or prednisone tablets 30mg/day for 10 days, or methylprednisolone tablets 24mg/day for 10 days.

Level 3 (Severe - attendance at hospital): Acute worsening of COPD that requires the patient to be admitted to hospital for treatment.

Protocol	Centre Number	Patient Number			COPD Exacerbations (AE)
207499/157		[redacted]			

FURTHER DETAILS OF COPD EXACERBATIONS

COPD exacerbation onset date : Day Month Yr

Level of exacerbation (see definitions on facing page):

[1] ☐ Level 1
[2] ☐ Level 2
[3] ☐ Level 3

Pumonary function test result (FEV_1) (if done):

☐.☐☐ L

Did the patient suffer from any of the following during the exacerbation:

[1] ☐ Chest pain
[2] ☐ Upper Respiratory Tract Infection
[3] ☐ Confusion
[4] ☐ Change in alertness
[5] ☐ Pneumonia
[6] ☐ Oedema
[7] ☐ Ankle swelling

ARTERIAL BLOOD GASES (only for COPD exacerbations)

Where feasible, an arterial blood gas sample is to be taken for analysis

COPD exacerbation onset date : Day Month Yr

PO_2 (mmHg)	**PCO_2** (mmHg)	**pH**	**Resting SaO_2** (%)
☐☐☐	☐☐	☐.☐☐	☐☐☐

RESOURCE UTILISATION

Please complete the Resource Utilisation pages for this exacerbation.

SmithKline Beecham Pharmaceuticals

Protocol	Centre Number	Patient Number		SB Receipt Date (Day Month Year)	COPD Exacerbations (SAE)
207499/157		[redacted]			

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation

Person Reporting SAE _____ *(Please print clearly)*

AEGIS Number _____ . _____

Serious Adverse Experience	**COPD Exacerbation**
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*	[1] ☐ Resolved [2] ☐ Ongoing [3] ☐ Died
Experience Course	[1] ☐ Intermittent → No. of episodes ☐ [2] ☐ Constant
Intensity *(maximum)*	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Action Taken with Respect to Investigational Drug	[1] ☐ None [2] ☐ Dose reduced [3] ☐ Dose increased [4] ☐ Drug interrupted/ restarted [5] ☐ Drug stopped
Relationship to Investigational Drug	[1] ☐ Not related [2] ☐ Unlikely [3] ☐ Suspected (reasonable possibility) [4] ☐ Probable
Corrective Therapy *If 'Yes', record details in the COPD Concomitant Medication section*	☐ Yes ☐ No
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No

→ *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

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 _____

00000

SmithKline Beecham
Pharmaceuticals

Protocol	**Centre Number**	**Patient Number**		**SB Receipt Date** Day Month Year	**COPD Exacerbations (SAE)**
207499/157		[redacted]			

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation

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 Number (please do NOT enter the container number): ☐☐☐☐☐

Investigator's Signature: _____ Date ☐☐ ☐☐☐ ☐☐
(confirming that the above data are accurate and complete) Day Month Year

Please PRINT Name _____

SB Medical Monitor's Signature: _____ Date ☐☐ ☐☐☐ ☐☐
Day Month Year

Please PRINT Name _____

DEFINITIONS OF LEVELS OF EXACERBATION OF COPD

Level 1 (Mild-self treated): Acute worsening of COPD that is self-managed by the patient at home by increasing the dose of relief salbutamol medication by > 2 occasions/24 hour period on two or more consecutive days compared with their baseline (baseline = mean of last 10 days of run-in period) or use of other additional bronchodilator medication

Level 2 (Moderate- physician, investigator treated): Acute worsening of symptoms (cough, sputum production, breathlessness) requiring treatment with oral corticosteroids prescribed by a physician or primary care doctor, or as a result of hospital out-patient visit (including Emergency Room).

Exacerbations requiring oral corticosteroids will be treated with a standardised course of prednisolone or prednisone tablets 30mg/day for 10 days, or methylprednisolone tablets 24mg/day for 10 days.

Level 3 (Severe - attendance at hospital): Acute worsening of COPD that requires the patient to be admitted to hospital for treatment.

00000

SmithKline Beecham
Pharmaceuticals

Protocol	**Centre Number**	**Patient Number**		**SB Receipt Date** Day Month Year	**COPD Exacerbations (SAE)**
207499/157		[redacted]			

FURTHER DETAILS OF SERIOUS COPD EXACERBATIONS

COPD exacerbation onset date : Day Month Yr

Level of exacerbation (see definitions on facing page):

[1] ☐ Level 1
[2] ☐ Level 2
[3] ☐ Level 3

Pumonary function test result (FEV_1) (if done):

☐.☐☐ L

Did the patient suffer from any of the following during the exacerbation:

[1] ☐ Chest pain
[2] ☐ Upper Respiratory Tract Infection
[3] ☐ Confusion
[4] ☐ Change in alertness
[5] ☐ Pneumonia
[6] ☐ Oedema
[7] ☐ Ankle swelling

ARTERIAL BLOOD GASES (only for serious COPD exacerbations)

Where feasible, an arterial blood gas sample is to be taken for analysis

COPD exacerbation onset date : Day Month Yr

PO_2 (mmHg)	**PCO_2** (mmHg)	**pH**	**Resting SaO_2** (%)
☐☐☐	☐☐	☐.☐☐	☐☐☐

RESOURCE UTILISATION

Please complete the Resource Utilisation pages for this exacerbation.

Protocol	Centre Number	Patient Number			COPD Exacerbations (ConMed)
207499/157		[redacted]			

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)	**Freq.** (eg bd, prn)	**Route***	**Medical Illness/ Diag.**	**Start Date** *(be as precise as possible)* Day Mth Yr	**End Date** *(or if Continuing mark box)* Day Mth Yr		COPD Exacerbation Onset Date
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								

** For Route, see General Instructions for acceptable abbreviations.*

Protocol	Centre Number	Patient Number			COPD Exacerbations (ConMed)
207499/157		[redacted]			

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 Day Mth Yr	Procedure End Date Day Mth Yr	COPD Exacerbation Onset Date
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				

Protocol	Centre Number	Patient Number			Resource Utilisation For COPD Exacerbations
207499/157		[redacted]			

RESOURCE UTILISATION FOR COPD EXACERBATIONS

Has the patient had any medical care for COPD Exacerbations that have occurred since the previous module?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below*

Has the patient had any **Physician contact** (COPD care excluding scheduled protocol visits) since the previous module?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below*

Date of Contact Day Mth Yr	Telephone	Home Visit		Office/ Practice	Out-patients	Reason for contact	COPD Exacerbation Onset Date Day Mth Yr
		Day	Night				

Has the patient had any **Emergency Room (ER)/Urgent Care Visits/Procedures (i.e., lung surgery)** since the previous module?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below*

Date of Contact Day Mth Yr	**Reason for contact**	**Patient Admitted from ER?**		COPD Exacerbation Onset Date Day Mth Yr
		Yes	**No**	

Protocol	Centre Number	Patient Number			Resource Utilisation For COPD Exacerbations
207499/157		[redacted]			

RESOURCE UTILISATION FOR COPD EXACERBATIONS - (cont)

Has the patient had any **Hospitalisations** since the previous module?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below* ***(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	COPD Exacerbation Onset Date Day Mth Yr

Has the patient had any **Intensive Care Unit (ICU) stays** ***(did the patient stay in the ICU during any of the above hospitalisations?)*** since the previous module?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below*

Date Admitted to ICU Day Mth Yr	Date Discharged from ICU Day Mth Yr	Reason for ICU Admission	COPD Exacerbation Onset Date Day Mth Yr

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			
207499/157		[redacted]			

2 0 7 4 9 9 1 5 7

MOD6

Please do not split modules

Module 6 : **Visit 9, Adverse Experiences, Concomitant Medications, Medical Procedures, COPD Exacerbations, Resource Utilisation**

CRF Pages **181 - 210**

Unprocessed Forms : **Within this module the following occur which will generate attachments that need to be brought in-house.**

None

FOR OFFICE USE ONLY Module Comments:

Sent to Data Mngt	Review Complete Date: User:	First Entry Complete Date: User:
Second Entry Complete Date: User:	Validation Complete Date: User:	**Clintrial PID:**

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number		Visit Date (Day Month Year)	
207499/157		[redacted]			**Visit 9 Week 28**

PRESENTATION TO CLINIC

Note: ***Patients must wait for 4 hours after beta$_2$-agonist and / or anticholinergic administration before the pulmonary function tests are performed.***

Did the patient take a dose of beta$_2$ agonist in the past 24 hours?

☐ No

☐ Yes → Record date and time of the patient's last dose of beta$_2$ agonist: Day Month Yr 24hr:min

Did the patient take a dose of anticholinergic in the past 24 hours?

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: Day Month Yr 24hr:min

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes → Date and time of patient's last cigarette Day Month Yr 24hr:min

SMOKING STATUS

Does the patient currently smoke?

☐ No

☐ Yes → If 'Yes' please record the average number of cigarettes per day :

INFLUENZA VACCINATION

Has the patient had a vaccination for influenza since the last visit?

N.B. It is not necessary to record vaccinations on the Concomitant Medication or Medical Procedures page.

☐ No

☐ Yes → *If 'Yes', record date of vaccination :* Day Month Yr

Protocol		Patient Number			Visit 9 Week 28
207499/157		[redacted]			

ST. GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND EQ-5D

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

INVESTIGATOR GLOBAL EVALUATION OF IMPROVEMENT

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

PATIENT GLOBAL EVALUATION OF IMPROVEMENT

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

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number			Visit 9 Week 28
207499/157		[redacted]			

RESOLUTION OF COPD EXACERBATIONS

Have any COPD Exacerbations resolved since the last visit?

☐ No

☐ Yes ⟶ *If 'Yes', please record details in the COPD Exacerbation section at the back of this module.*

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes ⟶ *If 'Yes' please record details in the COPD Exacerbation section at the back of this module.*

Level 1 (Mild-self treated): Acute worsening of COPD that is self-managed by the patient at home by increasing the dose of relief salbutamol medication by > 2 occasions/24 hour period on two or more consecutive days compared with their baseline (baseline = mean of last 10 days of run-in period) or use of other additional bronchodilator medication

Level 2 (Moderate- physician, investigator treated): Acute worsening of symptoms (cough, sputum production, breathlessness) requiring treatment with oral corticosteroids prescribed by a physician or primary care doctor, or as a result of hospital out-patient visit (including Emergency Room).

Exacerbations requiring oral corticosteroids will be treated with a standardised course of prednisolone or prednisone tablets 30mg/day for 10 days, or methylprednisolone tablets 24mg/day for 10 days.

Level 3 (Severe - attendance at hospital): Acute worsening of COPD that requires the patient to be admitted to hospital for treatment.

If a patient experienced a COPD exacerbation that was treated with corticosteroids, please withdraw the patient and complete the Study Continuation/Withdrawal page at the back of this book. 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, including an increase in usual COPD medications, must be recorded in the COPD Medications or Procedures pages.

00000

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number			Visit 9 Week 28
207499/157		[redacted]			

RESOURCE UTILISATION

If the patient has received any COPD exacerbation-related medical care since the last visit, record details on the Resource Utilisation pages of the COPD Exacerbation section at the back of this module.

DIARY CARD REVIEW

Review the diary card in the presence of the patient. Question any increased symptoms for possible COPD exacerbations. Place diary in the plastic wallet at the back of this module and re-issue another diary card.

ADVERSE EXPERIENCES

Please complete the Adverse Experiences 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 Experiences 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		Patient Number			Visit 9 Week 28
207499/157		[redacted]			

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. bd)

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
140	☐☐	☐☐	☐☐	☐☐	☐☐☐

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance ≥ 80% and ≤120%?

☐ No → *If 'No' please remind the patient of the importance of taking study medication according to the protocol.*

☐ Yes

Protocol		Patient Number			Visit 9 Week 28
207499/157		[redacted]			

INVESTIGATOR INSTRUCTIONS

The following procedures (Vital Signs, ECG and Pulmonary Function Tests) must be performed greater than 4 hours after the patient's last salbutamol administration.

VITAL SIGNS

Time of assessment : ☐☐ 24hr:min

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
☐☐☐/☐☐☐	☐☐☐

Are there any **clinically significant worsenings** since the previous visit?

☐ No

☐ Yes ⟶ *If 'Yes' please record the findings and/or diagnosis in the Adverse Experiences section at the back of this module.*

VITAL SIGNS - ORTHOSTATIC CHANGE

Time of assessment : ☐☐ 24hr:min

1st Measurement: After 5 Minutes Supine		2nd Measurement: 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)
☐☐☐/☐☐☐	☐☐☐	☐☐☐/☐☐☐	☐☐☐

Have there been any clinically significant worsenings since the last assessment?

☐ No

☐ Yes⟶ *If 'Yes', please record the findings in the Adverse Experiences section at the back of this module.*

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number			Visit 9 Week 28
207499/157		[redacted]			

12 LEAD ELECTROCARDIOGRAM

Time of assessment : ☐☐ 24hr:min **The ECG should be performed after the patient has been semi-supine for 5 minutes**

Date ECG Performed (Day Month Year)	Atrial Rate (beats/min)	Ventricular Rate (beats/min)	PR (msec)	QRS (msec)	☐ Uncorrected QT ☐ Corrected QT (msec)	Axis
☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐ + ☐ - ☐☐☐

Interpretation

☐ **(F74301) Within normal limits**

☐ **Abnormal** ⟶ ***Mark appropriate boxes below***

Rhythm
- ☐ (F73360) Sinus arrhythmia
- ☐ (F73310) Sinus bradycardia
- ☐ (F73380) Sinus tachycardia
- ☐ (F73440) Wandering atrial pacemaker
- ☐ (F73450) Premature atrial contractions
- ☐ (F73510) Paroxysmal atrial tachycardia
- ☐ (F73530) Chronic ectopic atrial tachycardia
- ☐ (F73550) Multifocal atrial tachycardia
- ☐ (F73560) Atrial flutter
- ☐ (F73570) Atrial fibrillation
- ☐ (F73610) Junctional (AV nodal) premature contractions
- ☐ (F73650) Junctional (AV nodal) tachycardia
- ☐ (F73150) Supraventricular tachycardia
- ☐ (F73860) Accelerated idioventricular rhythm
- ☐ (F73710) Premature Ventricular Contractions (NOS)
- ☐ (F73720) Unifocal PVC's
- ☐ (F73730) Multifocal PVC's
- ☐ (F73711) Ventricular couplets
- ☐ (F73750) Bigeminy
- ☐ (F73870) Ventricular tachycardia
- ☐ (F73880) Ventricular fibrillation
- ☐ (F73340) Sick sinus syndrome
- ☐ (F73190) Pacemaker rhythm

P-Wave Morphology
- ☐ (F74214) Left atrial hypertrophy, P mitrale
- ☐ (F74213) Right atrial hypertrophy, P pulmonale

Conduction
- ☐ (F73930) First degree AV block
- ☐ (F73950) Second degree AV block, Type 1
- ☐ (F73960) Second degree AV block, Type 11
- ☐ (F73970) Third degree AV block
- ☐ (F74090) Wolff-Parkinson-White syndrome

Axis
- ☐ (F74120) Right Axis deviation
- ☐ (F74130) Left Axis deviation

QRS
- ☐ (F74010) Right bundle branch block
- ☐ (F74020) Left bundle branch block
- ☐ (F74030) Left anterior hemiblock
- ☐ (F74040) Left posterior hemiblock
- ☐ (F74002) Intraventricular conduction delay
- ☐ (F74212) Left ventricular hypertrophy
- ☐ (F74211) Right ventricular hypertrophy
- ☐ (F74308) Q-wave > 0.04 sec
- ☐ (F74222) R-wave amplitude increased
- ☐ (F74225) R-wave amplitude decreased
- ☐ (F74313) Prolonged QT-interval
- ☐ (F74318) Poor R-wave progression
- ☐ (M54750) Myocardial infarction, old
  - ☐ (M54751) Anterior ☐ (M54754) Inferior
  - ☐ (M54752) Lateral ☐ (M54755) Septal
  - ☐ (M54753) Posterior

ST-T
- ☐ (F74291) Nonspecific ST-T changes
- ☐ (F74294) ST segment depression > 1 mm
- ☐ (F74295) ST segment elevation > 1 mm
- ☐ (F74350) T-wave flat
- ☐ (F74351) T-wave inversion
- ☐ (F74352) T-wave peaked
- ☐ (F74340) U-wave
- ☐ (F74360) Digitalis effect
- ☐ (F74260) Myocardial ischemia
  - ☐ (F74261) Anterior ☐ (F74264) Inferior
  - ☐ (F74262) Lateral ☐ (F74265) Septal
  - ☐ (F74263) Posterior
- ☐ (M54720) Myocardial infarction, acute
  - ☐ (M54721) Anterior ☐ (M54724) Inferior
  - ☐ (M54722) Lateral ☐ (M54725) Septal
  - ☐ (M54723) Posterior

Other interpretations not listed _

Were there any clinically important changes observed since the last assessment?

[1] ☐ No

[2] ☐ Yes ⟶ *If 'Yes', enter details on the Adverse Experiences page at the back of this module.*

Place the ECG trace in the plastic wallet a the back of this module

Protocol		Patient Number			Visit 9 Week 28
207499/157		[redacted]			

PRE-SALBUTAMOL PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed at least 4 hours after the last dose of inhaled beta$_2$-agonist or anticholinergic agent.

Measure the patient's pulmonary function up to eight times to obtain three acceptable readings using the spirometer provided by SB. ***(Note: Please follow instructions in the Spirometry Manual).*** *For each set of three FEV_1 measurements, one FEV_1 must be within 10% of the highest. Please record the results of the effort with the highest FEV_1 below.*

Measurement	Time	FEV_1 (L)	FVC (L)	FEF_{25-75} (L/sec)	PEF (L/min)
1	24hr:min	.	.	.	

Place the spirometry reports in the plasic wallet at the back of this module.

POST-SALBUTAMOL PULMONARY FUNCTION TESTS

Provide the patient with a salbutamol MDI and spacer. Administer 400 mcg (4 puffs) of salbutamol via MDI with a spacer. Remind the patient to use this inhaler (with or without the spacer), rather than any salbutamol inhaler they may have at home, for "as required" rescue-medication use during the study.

Record the time of salbutamol inhalation 24hr:min

Wait 30 minutes

Measure the patient's pulmonary function up to eight times to obtain three acceptable readings using the spirometer provided by SB. ***(Note: Please follow instructions in the Spirometry Manual).*** *For each set of three FEV_1 measurements, one FEV_1 must be within 10% of the highest. Please record the results of the effort with the highest FEV_1 below.*

Measurement	Time	FEV_1 (L)	FVC (L)	FEF_{25-75} (L/sec)	PEF (L/min)
1	24hr:min	.	.	.	

Place spirometry reports in the plastic wallets at the back of this module.

Protocol		Patient Number			Visit 9 Week 28
207499/157		[redacted]			

(AT SELECTED CENTRES ONLY) RESIDUAL VOLUME BY BODY PLETHYSMOGRAPHY (PRE- AND POST-SALBUTAMOL)

Time of pre-salbutamol RV assessment: ☐☐ 24hr:min

Time of post-salbutamol RV assessment: ☐☐ 24hr:min

Pre-Salbutamol

$RV_{Box} = TLC_{Box} – max(|SVC|, |FVC|)$

$RV_{(Box)}$ = ☐.☐☐ (L)

Post-Salbutamol

$RV_{Box} = TLC_{Box} – max(|SVC|, |FVC|)$

$RV_{(Box)}$ = ☐.☐☐ (L)

Please attach plethysmography source data to the back of this page.

PULMONARY REHABILITATION PROGRAM

Has the patient entered a Pulmonary Rehabilitation Program since the last visit?

☐ No

☐ Yes

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number			Visit 9 Week 28
207499/157		[redacted]			

LABORATORY TESTS

Please take blood samples for haematology and blood chemistry (including serum beta-HCG for women of child-bearing potential) and a urine sample for urinalysis. Please refer to the instructions on the Quest shipping form and manual.

Blood Sample Date ☐☐ ☐☐☐ ☐☐
Day Month Yr

Attach a label from the 'Routine' laboratory requisition form used at this visit in the space below.

Attach label here

Are there any **clinically significant worsenings** since the last assessment?

☐ No

☐ Yes ⟶ *If 'Yes' please record the findings and/or diagnosis in the Adverse Experiences section at the back of this module.*

STUDY MEDICATION ALLOCATION - RAMOS CALL

Following completion of all preceding assessments, complete the RAMOS worksheet appropriate for this visit and contact RAMOS to obtain the container numbers for this visit.

*Please enter the 5-digit **randomisation number** assigned by RAMOS* ☐☐☐☐☐

*Please enter the 6-digit **container number** as it appears on the study medication label **(Container 1)**.* ☐☐☐☐☐☐

*Please enter the 6-digit **container number** as it appears on the study medication label **(Container 2)**.* ☐☐☐☐☐☐

STUDY MEDICATION LABEL

Attach the tear-off labels from the study medication containers 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

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

00000

SmithKline Beecham
Pharmaceuticals

Protocol **207499/157**		**Patient Number** [redacted]			**Visit 9 Week 28**

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 9

Is the patient continuing in the study?

☐ No

☐ Yes

*If the patient is **not** continuing in the study, is the patient willing to return for essential assessments?*

If 'No', please complete the assessments for Visit 9 and the additional assessments for patients withdrawing at Visit 9 and the Study Continuation/Withdrawal page at the back of this book.

If 'Yes', please complete the assessments for Visit 9, the assessments for patients withdrawing at Visit 9 and the Study Continuation/Withdrawal page at the back of this book. Ask the patient to return in 56 +/-6 days time for essential assessments only.

*If the patient **is** continuing in the study, please:*	(tick if done)
	☑
• *Issue the patient a new diary card and remind the patient to complete the diary each morning until the next visit.*	☐
• *Ask the patient to return for the next visit in 56 +/- 6 days for a morning visit.*	☐
• ***Remind the patient:***	
i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after their breakfast.*	☐
ii ***not** to take the morning dose of study medication at home on the day of the next clinic visit.*	☐
iii *to refrain from using salbutamol or anticholinergic agents during the **4 hours** immediately preceding 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, the study salbutamol inhaler and spacer, and the diary card.*	☐
vi *to continue to take the anticholinergic medication, if prescribed, at a constant dose, and salbutamol when needed to control symptoms.*	☐
vii *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 occurrence.*	☐

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number		Visit Date (Day Month Year)	Withdrawal at Visit 9 Week 28
207499/157		[redacted]			

ASSESSMENTS FOR PATIENTS WITHDRAWING AT VISIT 9

Complete the assessments below only for patients who are withdrawing from the study at this visit.

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 Experiences section at the back of this module.*

FAECAL OCCULT BLOOD TEST

The faecal occult blood test should be performed on three consecutive bowel movements between withdrawal and the next scheduled visit or the Follow-Up visit depending on whether the patient is willing, or not, to return for essential assessments. Patients are not to take samples during or up-to 3-days after a menstrual period or while having bleeding haemorrhoids or blood in the urine. Patients are not to take aspirin or other non-steroidal anti-inflammatory drugs for 7 days prior to and during the test period and they are to avoid Vitamin C in excess of 250mg 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.

Did the patient follow these instructions?

☐ No ⟶ *If 'No', please specify:* _

☐ Yes

Test	Date of Collection Day Mth Yr	Result of faecal occult blood test
1		[NEG] ☐ Negative [POS] ☐ Positive
2		[NEG] ☐ Negative [POS] ☐ Positive
3		[NEG] ☐ Negative [POS] ☐ Positive

Are these findings clinically significant ?

☐ No

☐ Yes ⟶ *If 'Yes' please record the findings and/or diagnosis in the Adverse Experiences section at the back of this module.*

00000

SmithKline Beecham
Pharmaceuticals

Protocol		**Patient Number**			**Withdrawal at Visit 9 Week 28**
207499/157		[redacted]			

LABORATORY TESTS

Please take blood samples for CD4/CD8 ratio and C Reactive Protein. Please refer to the instructions on the Quest shipping form and manual.

Blood Sample Date ☐☐ ☐☐ ☐☐
Day Month Yr

Attach a label from the 'Routine' laboratory requisition form used at this visit in the space below.

Attach label here

Are there any **clinically significant worsenings** since the last assessment?

☐ No

☐ Yes ⟶ *If 'Yes' please record the findings and/or diagnosis in the Adverse Experiences section at the back of this module.*

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 study procedures should be reported as a serious event

IF AN 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

g_ae_instr_01

SmithKline Beecham Pharmaceuticals

Protocol	Centre Number	Patient Number			Adverse Experiences
207499/157		[redacted]			

ADVERSE EXPERIENCES (Non-serious)

g_ae_01

*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 last visit?" 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).

☐ Please mark this box if no adverse experiences occurred since the last module

Adverse Experience *(please print clearly)*		
For SB		
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 SAE section and follow instructions given there***	[1] ☐ Resolved [2] ☐ Ongoing [3] ☐ Died	[1] ☐ Resolved [2] ☐ Ongoing [3] ☐ Died
Experience Course	[1] ☐ Intermittent → No. of episodes ☐ [2] ☐ Constant	[1] ☐ Intermittent → No. of episodes ☐ [2] ☐ Constant
Intensity (maximum)	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Action Taken with Respect to Investigational Drug	[1] ☐ None [2] ☐ Dose reduced [3] ☐ Dose increased [4] ☐ Drug interrupted/restarted [5] ☐ Drug stopped	[1] ☐ None [2] ☐ Dose reduced [3] ☐ Dose increased [4] ☐ Drug interrupted/restarted [5] ☐ Drug stopped
Relationship to Investigational Drug	[1] ☐ Not related [2] ☐ Unlikely [3] ☐ Suspected (reasonable possibility) [4] ☐ Probable	[1] ☐ Not related [2] ☐ Unlikely [3] ☐ Suspected (reasonable possibility) [4] ☐ Probable
Corrective Therapy *If 'Yes', record details in the Concomitant Medication section and/ or Medical Procedures section if appropriate*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			Adverse Experiences
207499/157		[redacted]			

ADVERSE EXPERIENCES (Non-serious) - Continued

g_ae_01

*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 last visit?"*
*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).

Adverse Experience *(please print clearly)*		
For SB		
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 SAE section and follow instructions given there***	[1] Resolved [2] Ongoing [3] Died	[1] Resolved [2] Ongoing [3] Died
Experience Course	[1] Intermittent → No. of episodes [2] Constant	[1] Intermittent → No. of episodes [2] Constant
Intensity (maximum)	[1] Mild [2] Moderate [3] Severe	[1] Mild [2] Moderate [3] Severe
Action Taken with Respect to Investigational Drug	[1] None [2] Dose reduced [3] Dose increased [4] Drug interrupted/restarted [5] Drug stopped	[1] None [2] Dose reduced [3] Dose increased [4] Drug interrupted/restarted [5] Drug stopped
Relationship to Investigational Drug	[1] Not related [2] Unlikely [3] Suspected (reasonable possibility) [4] Probable	[1] Not related [2] Unlikely [3] Suspected (reasonable possibility) [4] Probable
Corrective Therapy *If 'Yes', record details in the Concomitant Medication section and/ or Medical Procedures section if appropriate*	Yes No	Yes No
Was patient withdrawn due to this specific AE?	Yes No	Yes No

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			Adverse Experiences
207499/157		[redacted]			

ADVERSE EXPERIENCES (Non-serious) - Continued

g_ae_01

*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 last visit?"*
*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).

Adverse Experience *(please print clearly)*		
For SB		
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 SAE section and follow instructions given there***	[1] Resolved [2] Ongoing [3] Died	[1] Resolved [2] Ongoing [3] Died
Experience Course	[1] Intermittent → No. of episodes [2] Constant	[1] Intermittent → No. of episodes [2] Constant
Intensity (maximum)	[1] Mild [2] Moderate [3] Severe	[1] Mild [2] Moderate [3] Severe
Action Taken with Respect to Investigational Drug	[1] None [2] Dose reduced [3] Dose increased [4] Drug interrupted/restarted [5] Drug stopped	[1] None [2] Dose reduced [3] Dose increased [4] Drug interrupted/restarted [5] Drug stopped
Relationship to Investigational Drug	[1] Not related [2] Unlikely [3] Suspected (reasonable possibility) [4] Probable	[1] Not related [2] Unlikely [3] Suspected (reasonable possibility) [4] Probable
Corrective Therapy *If 'Yes', record details in the Concomitant Medication section and/ or Medical Procedures section if appropriate*	Yes No	Yes No
Was patient withdrawn due to this specific AE?	Yes No	Yes No

CONCOMITANT MEDICATION
excluding treatment for COPD Exacerbations
(These are recorded in the COPD Exacerbations section)

Protocol	**Centre Number**	**Patient Number**			**Concomitant Medication**
207499/157		[redacted]			

CONCOMITANT MEDICATION

Record any changes in concomitant medication taken since the last 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. At the patient's final study visit, record the end date for prn study rescue medication (salbutamol) use, using the date the study inhaler was returned.

☐ No concomitant medication changes since the last module

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded in the Adverse Experiences 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** (eg 500mg)	**Frequency** (eg bd, 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	
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							

** For Route, see general instructions for acceptable abbreviations.*

Protocol	**Centre Number**	**Patient Number**			**Concomitant Medication**
207499/157		[redacted]			

CONCOMITANT MEDICATION (Cont.)

Do not record any medication taken for COPD exacerbations in this section. Record all COPD exacerbation medication in the COPD Exacerbation section. At the patient's final study visit, record the end date for prn study rescue medication (salbutamol) use, using the date the study inhaler was returned.

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded in the Adverse Experiences 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** (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	
For SB							
For SB							
For SB							
For SB							
For SB							
For SB							
For SB							
For SB							
For SB							
For SB							

** For Route, see general instructions for acceptable abbreviations.*

g_conmed_01

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			Medical Procedures
207499/157		[redacted]			

MEDICAL PROCEDURES

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 last module?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below using standard medical terminology*

All indications for procedures should be recorded on the Adverse Experiences Form.

Procedure	Indication	Procedure Start Date Day Mth Yr	Procedure End Date Day Mth Yr
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			

SmithKline Beecham Pharmaceuticals

Protocol	Centre Number	Patient Number			COPD Exacerbations (AE)
207499/157		[redacted]			

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 last 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***

Has the patient suffered any COPD Exacerbations since the last module ?

☐ No

☐ Yes → *If 'Yes', please complete page below*

Adverse Event	COPD EXACERBATION
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, STOP: delete details of this exacerbation and go to SAE COPD Exacerbation pages.***	[1] ☐ Resolved [2] ☐ Ongoing [3] ☐ Died
Event Course	[1] ☐ Intermittent → No. of episodes ☐ [2] ☐ Constant
Intensity (maximum) *See definitions page for Adverse Experiences form.*	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Action Taken with Respect to Investigational Drug	[1] ☐ None [2] ☐ Dose reduced [3] ☐ Dose increased [4] ☐ Drug interrupted/restarted [5] ☐ Drug stopped
Relationship to Investigational Drug	[1] ☐ Not related [2] ☐ Unlikely [3] ☐ Suspected (reasonable possibility) [4] ☐ Probable
Corrective Therapy *If 'Yes', record details on the COPD Medications or Procedures page*	☐ Yes ☐ No
Was patient withdrawn due to this specific event?	☐ Yes ☐ No

DEFINITIONS OF LEVELS OF EXACERBATION OF COPD

Level 1 (Mild-self treated): Acute worsening of COPD that is self-managed by the patient at home by increasing the dose of relief salbutamol medication by > 2 occasions/24 hour period on two or more consecutive days compared with their baseline (baseline = mean of last 10 days of run-in period) or use of other additional bronchodilator medication

Level 2 (Moderate- physician, investigator treated): Acute worsening of symptoms (cough, sputum production, breathlessness) requiring treatment with oral corticosteroids prescribed by a physician or primary care doctor, or as a result of hospital out-patient visit (including Emergency Room).

Exacerbations requiring oral corticosteroids will be treated with a standardised course of prednisolone or prednisone tablets 30mg/day for 10 days, or methylprednisolone tablets 24mg/day for 10 days.

Level 3 (Severe - attendance at hospital): Acute worsening of COPD that requires the patient to be admitted to hospital for treatment.

Protocol	Centre Number	Patient Number			COPD Exacerbations (AE)
207499/157					

FURTHER DETAILS OF COPD EXACERBATIONS

COPD exacerbation onset date : Day Month Yr

Level of exacerbation (see definitions on facing page):

[1] ☐ Level 1
[2] ☐ Level 2
[3] ☐ Level 3

Pumonary function test result (FEV_1) (if done):

☐.☐☐ L

Did the patient suffer from any of the following during the exacerbation:

[1] ☐ Chest pain
[2] ☐ Upper Respiratory Tract Infection
[3] ☐ Confusion
[4] ☐ Change in alertness
[5] ☐ Pneumonia
[6] ☐ Oedema
[7] ☐ Ankle swelling

ARTERIAL BLOOD GASES (only for COPD exacerbations)

Where feasible, an arterial blood gas sample is to be taken for analysis

COPD exacerbation onset date : Day Month Yr

PO_2 (mmHg)	**PCO_2** (mmHg)	**pH**	**Resting SaO_2** (%)
☐☐☐	☐☐	☐.☐☐	☐☐☐

RESOURCE UTILISATION

Please complete the Resource Utilisation pages for this exacerbation.

SmithKline Beecham Pharmaceuticals

Protocol	Centre Number	Patient Number			COPD Exacerbations (AE)
207499/157		[redacted]			

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 last 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 Event	COPD EXACERBATION
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, STOP: delete details of this exacerbation and go to SAE COPD Exacerbation pages.***	[1] ☐ Resolved [2] ☐ Ongoing [3] ☐ Died
Event Course	[1] ☐ Intermittent → No. of episodes ☐ [2] ☐ Constant
Intensity (maximum) *See definitions page for Adverse Experiences form.*	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Action Taken with Respect to Investigational Drug	[1] ☐ None [2] ☐ Dose reduced [3] ☐ Dose increased [4] ☐ Drug interrupted/restarted [5] ☐ Drug stopped
Relationship to Investigational Drug	[1] ☐ Not related [2] ☐ Unlikely [3] ☐ Suspected (reasonable possibility) [4] ☐ Probable
Corrective Therapy *If 'Yes', record details on the COPD Medications or Procedures page*	☐ Yes ☐ No
Was patient withdrawn due to this specific event?	☐ Yes ☐ No

DEFINITIONS OF LEVELS OF EXACERBATION OF COPD

Level 1 (Mild-self treated): Acute worsening of COPD that is self-managed by the patient at home by increasing the dose of relief salbutamol medication by > 2 occasions/24 hour period on two or more consecutive days compared with their baseline (baseline = mean of last 10 days of run-in period) or use of other additional bronchodilator medication

Level 2 (Moderate- physician, investigator treated): Acute worsening of symptoms (cough, sputum production, breathlessness) requiring treatment with oral corticosteroids prescribed by a physician or primary care doctor, or as a result of hospital out-patient visit (including Emergency Room).

Exacerbations requiring oral corticosteroids will be treated with a standardised course of prednisolone or prednisone tablets 30mg/day for 10 days, or methylprednisolone tablets 24mg/day for 10 days.

Level 3 (Severe - attendance at hospital): Acute worsening of COPD that requires the patient to be admitted to hospital for treatment.

Protocol	Centre Number	Patient Number			COPD Exacerbations (AE)
207499/157					

FURTHER DETAILS OF COPD EXACERBATIONS

COPD exacerbation onset date : Day Month Yr

Level of exacerbation (see definitions on facing page):

[1] ☐ Level 1
[2] ☐ Level 2
[3] ☐ Level 3

Pumonary function test result (FEV_1) (if done):

☐.☐☐ L

Did the patient suffer from any of the following during the exacerbation:

[1] ☐ Chest pain
[2] ☐ Upper Respiratory Tract Infection
[3] ☐ Confusion
[4] ☐ Change in alertness
[5] ☐ Pneumonia
[6] ☐ Oedema
[7] ☐ Ankle swelling

ARTERIAL BLOOD GASES (only for COPD exacerbations)

Where feasible, an arterial blood gas sample is to be taken for analysis

COPD exacerbation onset date : Day Month Yr

PO_2 (mmHg)	**PCO_2** (mmHg)	**pH**	**Resting SaO_2** (%)
☐☐☐	☐☐	☐.☐☐	☐☐☐

RESOURCE UTILISATION

Please complete the Resource Utilisation pages for this exacerbation.

SmithKline Beecham Pharmaceuticals

Protocol	Centre Number	Patient Number		SB Receipt Date (Day Month Year)	COPD Exacerbations (SAE)
207499/157		[redacted]			

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation

Person Reporting SAE _____ *(Please print clearly)*

AEGIS Number _____ . _____

Serious Adverse Experience	**COPD Exacerbation**
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*	[1] ☐ Resolved [2] ☐ Ongoing [3] ☐ Died
Experience Course	[1] ☐ Intermittent → No. of episodes ☐ [2] ☐ Constant
Intensity *(maximum)*	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Action Taken with Respect to Investigational Drug	[1] ☐ None [2] ☐ Dose reduced [3] ☐ Dose increased [4] ☐ Drug interrupted/ restarted [5] ☐ Drug stopped
Relationship to Investigational Drug	[1] ☐ Not related [2] ☐ Unlikely [3] ☐ Suspected (reasonable possibility) [4] ☐ Probable
Corrective Therapy *If 'Yes', record details in the COPD Concomitant Medication section*	☐ Yes ☐ No
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No

→ *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

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 _____

00000

SmithKline Beecham
Pharmaceuticals

Protocol	**Centre Number**	**Patient Number**		**SB Receipt Date** Day Month Year	**COPD Exacerbations (SAE)**
207499/157		[redacted]			

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation

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 Number (please do NOT enter the container number): ☐☐☐☐☐

Investigator's Signature: _____ Date ☐☐ ☐☐☐ ☐☐☐☐
(confirming that the above data are accurate and complete) Day Month Year

Please PRINT Name _____

SB Medical Monitor's Signature: _____ Date ☐☐ ☐☐☐ ☐☐☐☐
Day Month Year

Please PRINT Name _____

DEFINITIONS OF LEVELS OF EXACERBATION OF COPD

Level 1 (Mild-self treated): Acute worsening of COPD that is self-managed by the patient at home by increasing the dose of relief salbutamol medication by > 2 occasions/24 hour period on two or more consecutive days compared with their baseline (baseline = mean of last 10 days of run-in period) or use of other additional bronchodilator medication

Level 2 (Moderate- physician, investigator treated): Acute worsening of symptoms (cough, sputum production, breathlessness) requiring treatment with oral corticosteroids prescribed by a physician or primary care doctor, or as a result of hospital out-patient visit (including Emergency Room).

Exacerbations requiring oral corticosteroids will be treated with a standardised course of prednisolone or prednisone tablets 30mg/day for 10 days, or methylprednisolone tablets 24mg/day for 10 days.

Level 3 (Severe - attendance at hospital): Acute worsening of COPD that requires the patient to be admitted to hospital for treatment.

00000

SmithKline Beecham
Pharmaceuticals

Protocol	**Centre Number**	**Patient Number**		**SB Receipt Date** Day Month Year	**COPD Exacerbations (SAE)**
207499/157		[redacted]			

FURTHER DETAILS OF SERIOUS COPD EXACERBATIONS

COPD exacerbation onset date : Day Month Yr

Level of exacerbation (see definitions on facing page):

[1] ☐ Level 1
[2] ☐ Level 2
[3] ☐ Level 3

Pumonary function test result (FEV_1) (if done):

☐.☐☐ L

Did the patient suffer from any of the following during the exacerbation:

[1] ☐ Chest pain
[2] ☐ Upper Respiratory Tract Infection
[3] ☐ Confusion
[4] ☐ Change in alertness
[5] ☐ Pneumonia
[6] ☐ Oedema
[7] ☐ Ankle swelling

ARTERIAL BLOOD GASES (only for serious COPD exacerbations)

Where feasible, an arterial blood gas sample is to be taken for analysis

COPD exacerbation onset date : Day Month Yr

PO_2 (mmHg)	**PCO_2** (mmHg)	**pH**	**Resting SaO_2** (%)
☐☐☐	☐☐	☐.☐☐	☐☐☐

RESOURCE UTILISATION

Please complete the Resource Utilisation pages for this exacerbation.

Protocol	**Centre Number**	**Patient Number**			**COPD Exacerbations (ConMed)**
207499/157		[redacted]			

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)	**Freq.** (eg bd, prn)	**Route***	**Medical Illness/ Diag.**	**Start Date** *(be as precise as possible)* Day Mth Yr	**End Date** *(or if Continuing mark box)* Day Mth Yr		COPD Exacerbation Onset Date
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								

** For Route, see General Instructions for acceptable abbreviations.*

Protocol	**Centre Number**	**Patient Number**			**COPD Exacerbations (ConMed)**
207499/157		[redacted]			

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** Day Mth Yr	**Procedure End Date** Day Mth Yr	COPD Exacerbation Onset Date
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				

Protocol	Centre Number	Patient Number			Resource Utilisation For COPD Exacerbations
207499/157		[redacted]			

RESOURCE UTILISATION FOR COPD EXACERBATIONS

Has the patient had any medical care for COPD Exacerbations that have occurred since the previous module?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below*

Has the patient had any **Physician contact** (COPD care excluding scheduled protocol visits) since the previous module?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below*

Date of Contact Day Mth Yr	Telephone	Home Visit		Office/ Practice	Out-patients	Reason for contact	COPD Exacerbation Onset Date Day Mth Yr
		Day	Night				

Has the patient had any **Emergency Room (ER)/Urgent Care Visits/Procedures (i.e., lung surgery)** since the previous module?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below*

Date of Contact Day Mth Yr	**Reason for contact**	**Patient Admitted from ER?**		COPD Exacerbation Onset Date Day Mth Yr
		Yes	**No**	

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			Resource Utilisation For COPD Exacerbations
207499/157		[redacted]			

RESOURCE UTILISATION FOR COPD EXACERBATIONS - (cont)

Has the patient had any **Hospitalisations** since the previous module?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below* ***(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	COPD Exacerbation Onset Date Day Mth Yr

Has the patient had any **Intensive Care Unit (ICU) stays** ***(did the patient stay in the ICU during any of the above hospitalisations?)*** since the previous module?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below*

Date Admitted to ICU Day Mth Yr	Date Discharged from ICU Day Mth Yr	Reason for ICU Admission	COPD Exacerbation Onset Date Day Mth Yr

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			
207499/157		[redacted]			

2 0 7 4 9 9 1 5 7

MOD7

Please do not split modules

Module 7 : **Visit 10, Adverse Experiences, Concomitant Medications, Medical Procedures, COPD Exacerbations, Resource Utilisation**

CRF Pages **211 - 240**

Unprocessed Forms : **Within this module the following occur which will generate attachments that need to be brought in-house.**

None

FOR OFFICE USE ONLY Module Comments:

Sent to Data Mngt	Review Complete Date: User:	First Entry Complete Date: User:
Second Entry Complete Date: User:	Validation Complete Date: User:	**Clintrial PID:**

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number		Visit Date (Day Month Year)	
207499/157		[redacted]			**Visit 10 Week 36**

PRESENTATION TO CLINIC

Note: ***Patients must wait for 4 hours after beta$_2$-agonist and / or anticholinergic administration before the pulmonary function tests are performed.***

Did the patient take a dose of beta$_2$ agonist in the past 24 hours?

☐ No

☐ Yes → Record date and time of the patient's last dose of beta$_2$ agonist: Day Month Yr 24hr:min

Did the patient take a dose of anticholinergic in the past 24 hours?

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: Day Month Yr 24hr:min

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes → Date and time of patient's last cigarette Day Month Yr 24hr:min

SMOKING STATUS

Does the patient currently smoke?

☐ No

☐ Yes → If 'Yes' please record the average number of cigarettes per day :

INFLUENZA VACCINATION

Has the patient had a vaccination for influenza since the last visit?

N.B. It is not necessary to record vaccinations on the Concomitant Medication or Medical Procedures page.

☐ No

☐ Yes → *If 'Yes', record date of vaccination :* Day Month Yr

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number			Visit 10 Week 36
207499/157		[redacted]			

RESOLUTION OF COPD EXACERBATIONS

Have any COPD Exacerbations resolved since the last visit?

☐ No

☐ Yes ⟶ *If 'Yes', please record details in the COPD Exacerbation section at the back of this module.*

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes ⟶ *If 'Yes' please record details in the COPD Exacerbation section at the back of this module.*

Level 1 (Mild-self treated): Acute worsening of COPD that is self-managed by the patient at home by increasing the dose of relief salbutamol medication by > 2 occasions/24 hour period on two or more consecutive days compared with their baseline (baseline = mean of last 10 days of run-in period) or use of other additional bronchodilator medication

Level 2 (Moderate- physician, investigator treated): Acute worsening of symptoms (cough, sputum production, breathlessness) requiring treatment with oral corticosteroids prescribed by a physician or primary care doctor, or as a result of hospital out-patient visit (including Emergency Room).

Exacerbations requiring oral corticosteroids will be treated with a standardised course of prednisolone or prednisone tablets 30mg/day for 10 days, or methylprednisolone tablets 24mg/day for 10 days.

Level 3 (Severe - attendance at hospital): Acute worsening of COPD that requires the patient to be admitted to hospital for treatment.

If a patient experienced a COPD exacerbation that was treated with corticosteroids, please withdraw the patient and complete the Study Continuation/Withdrawal page at the back of this book. 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, including an increase in usual COPD medications, must be recorded in the COPD Medications or Procedures pages.

00000

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number			Visit 10 Week 36
207499/157		[redacted]			

RESOURCE UTILISATION

If the patient has received any COPD exacerbation-related medical care since the last visit, record details on the Resource Utilisation pages of the COPD Exacerbation section at the back of this module.

DIARY CARD REVIEW

Review the diary card in the presence of the patient. Question any increased symptoms for possible COPD exacerbations. Place diary in the plastic wallet at the back of this module and re-issue another diary card.

ADVERSE EXPERIENCES

Please complete the Adverse Experiences 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 Experiences 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.

SmithKline Beecham
Pharmaceuticals

Protocol **207499/157**		**Patient Number** [redacted]			**Visit 10 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. bd)

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
140	☐☐	☐☐	☐☐	☐☐	☐☐☐

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance ≥ 80% and ≤120%?

☐ No → *If 'No' please remind the patient of the importance of taking study medication according to the protocol.*

☐ Yes

00000

SmithKline Beecham
Pharmaceuticals

Protocol		**Patient Number**			**Visit 10**
207499/157		[redacted]			**Week 36**

INVESTIGATOR INSTRUCTIONS

The following procedures (Vital Signs and Pulmonary Function Tests) must be performed greater than 4 hours after the patient's last salbutamol administration.

VITAL SIGNS

Time of assessment : ☐☐ 24hr:min

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
☐☐☐/☐☐☐	☐☐☐

Are there any **clinically significant worsenings** since the previous visit?

☐ No

☐ Yes ⟶ *If 'Yes' please record the findings and/or diagnosis in the Adverse Experiences section at the back of this module.*

Protocol		Patient Number			Visit 10 Week 36
207499/157		[redacted]			

PRE-SALBUTAMOL PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed at least 4 hours after the last dose of inhaled beta$_2$-agonist or anticholinergic agent.

Measure the patient's pulmonary function up to eight times to obtain three acceptable readings using the spirometer provided by SB. ***(Note: Please follow instructions in the Spirometry Manual).*** *For each set of three FEV_1 measurements, one FEV_1 must be within 10% of the highest. Please record the results of the effort with the highest FEV_1 below.*

Measurement	Time	FEV_1 (L)	FVC (L)	FEF_{25-75} (L/sec)	PEF (L/min)
1	☐☐ 24hr:min	☐.☐☐	☐.☐☐	☐.☐☐	☐☐☐

Place the spirometry reports in the plasic wallet at the back of this module.

POST-SALBUTAMOL PULMONARY FUNCTION TESTS

Provide the patient with a salbutamol MDI and spacer. Administer 400 mcg (4 puffs) of salbutamol via MDI with a spacer. Remind the patient to use this inhaler (with or without the spacer), rather than any salbutamol inhaler they may have at home, for "as required" rescue-medication use during the study.

Record the time of salbutamol inhalation ☐☐ 24hr:min

Wait 30 minutes

Measure the patient's pulmonary function up to eight times to obtain three acceptable readings using the spirometer provided by SB. ***(Note: Please follow instructions in the Spirometry Manual).*** *For each set of three FEV_1 measurements, one FEV_1 must be within 10% of the highest. Please record the results of the effort with the highest FEV_1 below.*

Measurement	Time	FEV_1 (L)	FVC (L)	FEF_{25-75} (L/sec)	PEF (L/min)
1	☐☐ 24hr:min	☐.☐☐	☐.☐☐	☐.☐☐	☐☐☐

Place spirometry reports in the plastic wallets at the back of this module.

PULMONARY REHABILITATION PROGRAM

Has the patient entered a Pulmonary Rehabilitation Program since the last visit?

☐ No

☐ Yes

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number			Visit 10 Week 36
207499/157		[redacted]			

LABORATORY TESTS

Please take blood samples for haematology and blood chemistry (including serum beta-HCG for women of child-bearing potential) and a urine sample for urinalysis. Please refer to the instructions on the Quest shipping form and manual.

Blood Sample Date ☐☐ ☐☐☐ ☐☐
Day Month Yr

Attach a label from the 'Routine' laboratory requisition form used at this visit in the space below.

Attach label here

Are there any **clinically significant worsenings** since the last assessment?

☐ No

☐ Yes ⟶ *If 'Yes' please record the findings and/or diagnosis in the Adverse Experiences section at the back of this module.*

STUDY MEDICATION ALLOCATION - RAMOS CALL

Following completion of all preceding assessments, complete the RAMOS worksheet appropriate for this visit and contact RAMOS to obtain the container numbers for this visit.

*Please enter the 5-digit **randomisation number** assigned by RAMOS* ☐☐☐☐☐

*Please enter the 6-digit **container number** as it appears on the study medication label **(Container 1)**.* ☐☐☐☐☐☐

*Please enter the 6-digit **container number** as it appears on the study medication label **(Container 2)**.* ☐☐☐☐☐☐

STUDY MEDICATION LABEL

Attach the tear-off labels from the study medication containers 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

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

00000

SmithKline Beecham
Pharmaceuticals

Protocol 207499/157		**Patient Number** [redacted]			**Visit 10 Week 36**

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 10

Is the patient continuing in the study?

☐ No

☐ Yes

*If the patient is **not** continuing in the study, is the patient willing to return for essential assessments?*

If 'No', please complete the assessments for Visit 10 and the additional assessments for patients withdrawing at Visit 10 and the Study Continuation/Withdrawal page at the back of this book.

If 'Yes', please complete the assessments for Visit 10, the assessments for patients withdrawing at Visit 10 and the Study Continuation/Withdrawal page at the back of this book. Ask the patient to return in 56 +/-6 days time for essential assessments only.

*If the patient **is** continuing in the study, please:* (tick if done)

- *Issue the patient a new diary card and remind the patient to complete the diary each morning until the next visit.* ☐
- *Ask the patient to return for the next visit in 56 +/- 6 days for a morning visit.* ☐
- ***Remind the patient:***

i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after their breakfast.* ☐

ii ***not** to take the morning dose of study medication at home on the day of the next clinic visit.* ☐

iii *to refrain from using salbutamol or anticholinergic agents during the **4 hours** immediately preceding 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, the study salbutamol inhaler and spacer, and the diary card.* ☐

vi *to continue to take the anticholinergic medication, if prescribed, at a constant dose, and salbutamol when needed to control symptoms.* ☐

vii *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 occurrence.* ☐

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number		Visit Date (Day / Month / Year)	Withdrawal at Visit 10 Week 36
207499/157		[redacted]			

ASSESSMENTS FOR PATIENTS WITHDRAWING AT VISIT 10

Complete the assessments below only for patients who are withdrawing from the study at this visit.

ST. GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND EQ-5D

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

INVESTIGATOR GLOBAL EVALUATION OF IMPROVEMENT

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

PATIENT GLOBAL EVALUATION OF IMPROVEMENT

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

Protocol 207499/157		Patient Number [redacted]			Withdrawal at Visit 10 Week 36

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 Experiences section at the back of this module.*

VITAL SIGNS - ORTHOSTATIC CHANGE

Time of assessment : ☐☐ 24hr:min

1st Measurement: After 5 Minutes Supine		**2nd Measurement: 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)
☐☐☐/☐☐☐	☐☐☐	☐☐☐/☐☐☐	☐☐☐

Have there been any clinically significant worsenings since the last assessment?

☐ No

☐ Yes⟶ *If 'Yes', please record the findings in the Adverse Experiences section at the back of this module.*

SmithKline Beecham
Pharmaceuticals

Protocol **207499/157**		**Patient Number** [redacted]			**Withdrawal at Visit 10 Week 36**

12 LEAD ELECTROCARDIOGRAM

Time of assessment : ☐☐ 24hr:min **The ECG should be performed after the patient has been semi-supine for 5 minutes**

Date ECG Performed (Day Month Year)	**Atrial Rate** (beats/min)	**Ventricular Rate** (beats/min)	**PR** (msec)	**QRS** (msec)	☐ **Uncorrected QT** ☐ **Corrected QT** (msec)	**Axis**
☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐ + ☐ - ☐☐☐

Interpretation

☐ **(F74301) Within normal limits**

☐ **Abnormal** ⟶ ***Mark appropriate boxes below***

Rhythm
- ☐ (F73360) Sinus arrhythmia
- ☐ (F73310) Sinus bradycardia
- ☐ (F73380) Sinus tachycardia
- ☐ (F73440) Wandering atrial pacemaker
- ☐ (F73450) Premature atrial contractions
- ☐ (F73510) Paroxysmal atrial tachycardia
- ☐ (F73530) Chronic ectopic atrial tachycardia
- ☐ (F73550) Multifocal atrial tachycardia
- ☐ (F73560) Atrial flutter
- ☐ (F73570) Atrial fibrillation
- ☐ (F73610) Junctional (AV nodal) premature contractions
- ☐ (F73650) Junctional (AV nodal) tachycardia
- ☐ (F73150) Supraventricular tachycardia
- ☐ (F73860) Accelerated idioventricular rhythm
- ☐ (F73710) Premature Ventricular Contractions (NOS)
- ☐ (F73720) Unifocal PVC's
- ☐ (F73730) Multifocal PVC's
- ☐ (F73711) Ventricular couplets
- ☐ (F73750) Bigeminy
- ☐ (F73870) Ventricular tachycardia
- ☐ (F73880) Ventricular fibrillation
- ☐ (F73340) Sick sinus syndrome
- ☐ (F73190) Pacemaker rhythm

P-Wave Morphology
- ☐ (F74214) Left atrial hypertrophy, P mitrale
- ☐ (F74213) Right atrial hypertrophy, P pulmonale

Conduction
- ☐ (F73930) First degree AV block
- ☐ (F73950) Second degree AV block, Type 1
- ☐ (F73960) Second degree AV block, Type 11
- ☐ (F73970) Third degree AV block
- ☐ (F74090) Wolff-Parkinson-White syndrome

Axis
- ☐ (F74120) Right Axis deviation
- ☐ (F74130) Left Axis deviation

QRS
- ☐ (F74010) Right bundle branch block
- ☐ (F74020) Left bundle branch block
- ☐ (F74030) Left anterior hemiblock
- ☐ (F74040) Left posterior hemiblock
- ☐ (F74002) Intraventricular conduction delay
- ☐ (F74212) Left ventricular hypertrophy
- ☐ (F74211) Right ventricular hypertrophy
- ☐ (F74308) Q-wave > 0.04 sec
- ☐ (F74222) R-wave amplitude increased
- ☐ (F74225) R-wave amplitude decreased
- ☐ (F74313) Prolonged QT-interval
- ☐ (F74318) Poor R-wave progression
- ☐ (M54750) Myocardial infarction, old
  - ☐ (M54751) Anterior ☐ (M54754) Inferior
  - ☐ (M54752) Lateral ☐ (M54755) Septal
  - ☐ (M54753) Posterior

ST-T
- ☐ (F74291) Nonspecific ST-T changes
- ☐ (F74294) ST segment depression > 1 mm
- ☐ (F74295) ST segment elevation > 1 mm
- ☐ (F74350) T-wave flat
- ☐ (F74351) T-wave inversion
- ☐ (F74352) T-wave peaked
- ☐ (F74340) U-wave
- ☐ (F74360) Digitalis effect
- ☐ (F74260) Myocardial ischemia
  - ☐ (F74261) Anterior ☐ (F74264) Inferior
  - ☐ (F74262) Lateral ☐ (F74265) Septal
  - ☐ (F74263) Posterior
- ☐ (M54720) Myocardial infarction, acute
  - ☐ (M54721) Anterior ☐ (M54724) Inferior
  - ☐ (M54722) Lateral ☐ (M54725) Septal
  - ☐ (M54723) Posterior

Other interpretations not listed _

Were there any clinically important changes observed since the last assessment?

[1] ☐ No

[2] ☐ Yes ⟶ *If 'Yes', enter details on the Adverse Experiences page at the back of this module.*

Place the ECG trace in the plastic wallet a the back of this module

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number			Withdrawal at Visit 10 Week 36
207499/157		[redacted]			

(AT SELECTED CENTRES ONLY) RESIDUAL VOLUME BY BODY PLETHYSMOGRAPHY (PRE- AND POST-SALBUTAMOL)

Time of pre-salbutamol RV assessment: ☐☐ 24hr:min

Time of post-salbutamol RV assessment: ☐☐ 24hr:min

Pre-Salbutamol

$RV_{Box} = TLC_{Box} – max(|SVC|, |FVC|)$

$RV_{(Box)}$ = ☐.☐☐ (L)

Post-Salbutamol

$RV_{Box} = TLC_{Box} – max(|SVC|, |FVC|)$

$RV_{(Box)}$ = ☐.☐☐ (L)

Please attach plethysmography source data to the back of this page.

FAECAL OCCULT BLOOD TEST

The faecal occult blood test should be performed on three consecutive bowel movements between withdrawal and the next scheduled visit or the Follow-Up visit depending on whether the patient is willing, or not, to return for essential assessments. Patients are not to take samples during or up-to 3-days after a menstrual period or while having bleeding haemorrhoids or blood in the urine. Patients are not to take aspirin or other non-steroidal anti-inflammatory drugs for 7 days prior to and during the test period and they are to avoid Vitamin C in excess of 250mg 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.

Did the patient follow these instructions?

☐ No ⟶ *If 'No', please specify:* _

☐ Yes

Test	Date of Collection Day Mth Yr	Result of faecal occult blood test
1	☐☐ ☐☐ ☐☐	[NEG] ☐ Negative [POS] ☐ Positive
2	☐☐ ☐☐ ☐☐	[NEG] ☐ Negative [POS] ☐ Positive
3	☐☐ ☐☐ ☐☐	[NEG] ☐ Negative [POS] ☐ Positive

Are these findings clinically significant ?

☐ No

☐ Yes ⟶ *If 'Yes' please record the findings and/or diagnosis in the Adverse Experiences section at the back of this module.*

00000

SmithKline Beecham
Pharmaceuticals

Protocol		**Patient Number**			**Withdrawal at Visit 10 Week 36**
207499/157		[redacted]			

LABORATORY TESTS

Please take blood samples for CD4/CD8 ratio and C Reactive Protein. Please refer to the instructions on the Quest shipping form and manual.

Blood Sample Date ☐☐ ☐☐ ☐☐
Day Month Yr

Attach a label from the 'Routine' laboratory requisition form used at this visit in the space below.

Attach label here

Are there any **clinically significant worsenings** since the last assessment?

☐ No

☐ Yes ⟶ *If 'Yes' please record the findings and/or diagnosis in the Adverse Experiences section at the back of this module.*

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 study procedures should be reported as a serious event

IF AN 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

g_ae_instr_01

SmithKline Beecham Pharmaceuticals

Protocol	Centre Number	Patient Number			Adverse Experiences
207499/157		[redacted]			

ADVERSE EXPERIENCES (Non-serious)

g_ae_01

*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 last visit?" 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).

☐ Please mark this box if no adverse experiences occurred since the last module

Adverse Experience *(please print clearly)*		
For SB		
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 SAE section and follow instructions given there***	[1] ☐ Resolved [2] ☐ Ongoing [3] ☐ Died	[1] ☐ Resolved [2] ☐ Ongoing [3] ☐ Died
Experience Course	[1] ☐ Intermittent → No. of episodes ☐ [2] ☐ Constant	[1] ☐ Intermittent → No. of episodes ☐ [2] ☐ Constant
Intensity (maximum)	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Action Taken with Respect to Investigational Drug	[1] ☐ None [2] ☐ Dose reduced [3] ☐ Dose increased [4] ☐ Drug interrupted/restarted [5] ☐ Drug stopped	[1] ☐ None [2] ☐ Dose reduced [3] ☐ Dose increased [4] ☐ Drug interrupted/restarted [5] ☐ Drug stopped
Relationship to Investigational Drug	[1] ☐ Not related [2] ☐ Unlikely [3] ☐ Suspected (reasonable possibility) [4] ☐ Probable	[1] ☐ Not related [2] ☐ Unlikely [3] ☐ Suspected (reasonable possibility) [4] ☐ Probable
Corrective Therapy *If 'Yes', record details in the Concomitant Medication section and/ or Medical Procedures section if appropriate*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No

SmithKline Beecham
Pharmaceuticals

Protocol **207499/157**	**Centre Number**	**Patient Number**			**Adverse Experiences**

ADVERSE EXPERIENCES (Non-serious) - Continued

g_ae_01

*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 last visit?" 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).

Adverse Experience *(please print clearly)*		
For SB		
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 SAE section and follow instructions given there***	[1] Resolved [2] Ongoing [3] Died	[1] Resolved [2] Ongoing [3] Died
Experience Course	[1] Intermittent → No. of episodes [2] Constant	[1] Intermittent → No. of episodes [2] Constant
Intensity (maximum)	[1] Mild [2] Moderate [3] Severe	[1] Mild [2] Moderate [3] Severe
Action Taken with Respect to Investigational Drug	[1] None [2] Dose reduced [3] Dose increased [4] Drug interrupted/restarted [5] Drug stopped	[1] None [2] Dose reduced [3] Dose increased [4] Drug interrupted/restarted [5] Drug stopped
Relationship to Investigational Drug	[1] Not related [2] Unlikely [3] Suspected (reasonable possibility) [4] Probable	[1] Not related [2] Unlikely [3] Suspected (reasonable possibility) [4] Probable
Corrective Therapy *If 'Yes', record details in the Concomitant Medication section and/ or Medical Procedures section if appropriate*	Yes No	Yes No
Was patient withdrawn due to this specific AE?	Yes No	Yes No

SmithKline Beecham
Pharmaceuticals

Protocol	**Centre Number**	**Patient Number**			**Adverse Experiences**
207499/157		[redacted]			

ADVERSE EXPERIENCES (Non-serious) - Continued

g_ae_01

*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 last visit?"*
*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).

Adverse Experience *(please print clearly)*		
For SB		
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 SAE section and follow instructions given there***	[1] Resolved [2] Ongoing [3] Died	[1] Resolved [2] Ongoing [3] Died
Experience Course	[1] Intermittent → No. of episodes [2] Constant	[1] Intermittent → No. of episodes [2] Constant
Intensity (maximum)	[1] Mild [2] Moderate [3] Severe	[1] Mild [2] Moderate [3] Severe
Action Taken with Respect to Investigational Drug	[1] None [2] Dose reduced [3] Dose increased [4] Drug interrupted/restarted [5] Drug stopped	[1] None [2] Dose reduced [3] Dose increased [4] Drug interrupted/restarted [5] Drug stopped
Relationship to Investigational Drug	[1] Not related [2] Unlikely [3] Suspected (reasonable possibility) [4] Probable	[1] Not related [2] Unlikely [3] Suspected (reasonable possibility) [4] Probable
Corrective Therapy *If 'Yes', record details in the Concomitant Medication section and/ or Medical Procedures section if appropriate*	Yes No	Yes No
Was patient withdrawn due to this specific AE?	Yes No	Yes No

Protocol	**Centre Number**	**Patient Number**			**Concomitant Medication**
207499/157		[redacted]			

CONCOMITANT MEDICATION

Record any changes in concomitant medication taken since the last 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. At the patient's final study visit, record the end date for prn study rescue medication (salbutamol) use, using the date the study inhaler was returned.

☐ No concomitant medication changes since the last module

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded in the Adverse Experiences 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** (eg 500mg)	**Frequency** (eg bd, 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	
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							

** For Route, see general instructions for acceptable abbreviations.*

Protocol	**Centre Number**	**Patient Number**			**Concomitant Medication**
207499/157		[redacted]			

CONCOMITANT MEDICATION (Cont.)

Do not record any medication taken for COPD exacerbations in this section. Record all COPD exacerbation medication in the COPD Exacerbation section. At the patient's final study visit, record the end date for prn study rescue medication (salbutamol) use, using the date the study inhaler was returned.

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded in the Adverse Experiences 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** (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	
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							

** For Route, see general instructions for acceptable abbreviations.*

g_conmed_01

Protocol	Centre Number	Patient Number			Medical Procedures
207499/157		[redacted]			

MEDICAL PROCEDURES

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 last module?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below using standard medical terminology*

All indications for procedures should be recorded on the Adverse Experiences Form.

Procedure	Indication	Procedure Start Date Day Mth Yr	Procedure End Date Day Mth Yr
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			COPD Exacerbations (AE)
207499/157		[redacted]			

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 last 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***

Has the patient suffered any COPD Exacerbations since the last module ?

☐ No

☐ Yes → *If 'Yes', please complete page below*

Adverse Event	COPD EXACERBATION
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, STOP: delete details of this exacerbation and go to SAE COPD Exacerbation pages.***	[1] ☐ Resolved [2] ☐ Ongoing [3] ☐ Died
Event Course	[1] ☐ Intermittent → No. of episodes ☐ [2] ☐ Constant
Intensity (maximum) *See definitions page for Adverse Experiences form.*	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Action Taken with Respect to Investigational Drug	[1] ☐ None [2] ☐ Dose reduced [3] ☐ Dose increased [4] ☐ Drug interrupted/restarted [5] ☐ Drug stopped
Relationship to Investigational Drug	[1] ☐ Not related [2] ☐ Unlikely [3] ☐ Suspected (reasonable possibility) [4] ☐ Probable
Corrective Therapy *If 'Yes', record details on the COPD Medications or Procedures page*	☐ Yes ☐ No
Was patient withdrawn due to this specific event?	☐ Yes ☐ No

DEFINITIONS OF LEVELS OF EXACERBATION OF COPD

Level 1 (Mild-self treated): Acute worsening of COPD that is self-managed by the patient at home by increasing the dose of relief salbutamol medication by > 2 occasions/24 hour period on two or more consecutive days compared with their baseline (baseline = mean of last 10 days of run-in period) or use of other additional bronchodilator medication

Level 2 (Moderate- physician, investigator treated): Acute worsening of symptoms (cough, sputum production, breathlessness) requiring treatment with oral corticosteroids prescribed by a physician or primary care doctor, or as a result of hospital out-patient visit (including Emergency Room).

Exacerbations requiring oral corticosteroids will be treated with a standardised course of prednisolone or prednisone tablets 30mg/day for 10 days, or methylprednisolone tablets 24mg/day for 10 days.

Level 3 (Severe - attendance at hospital): Acute worsening of COPD that requires the patient to be admitted to hospital for treatment.

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			COPD Exacerbations (AE)
207499/157					

FURTHER DETAILS OF COPD EXACERBATIONS

COPD exacerbation onset date : Day Month Yr

Level of exacerbation (see definitions on facing page):

[1] ☐ Level 1
[2] ☐ Level 2
[3] ☐ Level 3

Pumonary function test result (FEV_1) (if done):

☐.☐☐ L

Did the patient suffer from any of the following during the exacerbation:

[1] ☐ Chest pain
[2] ☐ Upper Respiratory Tract Infection
[3] ☐ Confusion
[4] ☐ Change in alertness
[5] ☐ Pneumonia
[6] ☐ Oedema
[7] ☐ Ankle swelling

ARTERIAL BLOOD GASES (only for COPD exacerbations)

Where feasible, an arterial blood gas sample is to be taken for analysis

COPD exacerbation onset date : Day Month Yr

PO_2 (mmHg)	**PCO_2** (mmHg)	**pH**	**Resting SaO_2** (%)
☐☐☐	☐☐	☐.☐☐	☐☐☐

RESOURCE UTILISATION

Please complete the Resource Utilisation pages for this exacerbation.

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			COPD Exacerbations (AE)
207499/157		[redacted]			

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 last 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 Event	COPD EXACERBATION
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, STOP: delete details of this exacerbation and go to SAE COPD Exacerbation pages.***	[1] ☐ Resolved [2] ☐ Ongoing [3] ☐ Died
Event Course	[1] ☐ Intermittent → No. of episodes ☐ [2] ☐ Constant
Intensity (maximum) *See definitions page for Adverse Experiences form.*	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Action Taken with Respect to Investigational Drug	[1] ☐ None [2] ☐ Dose reduced [3] ☐ Dose increased [4] ☐ Drug interrupted/restarted [5] ☐ Drug stopped
Relationship to Investigational Drug	[1] ☐ Not related [2] ☐ Unlikely [3] ☐ Suspected (reasonable possibility) [4] ☐ Probable
Corrective Therapy *If 'Yes', record details on the COPD Medications or Procedures page*	☐ Yes ☐ No
Was patient withdrawn due to this specific event?	☐ Yes ☐ No

DEFINITIONS OF LEVELS OF EXACERBATION OF COPD

Level 1 (Mild-self treated): Acute worsening of COPD that is self-managed by the patient at home by increasing the dose of relief salbutamol medication by > 2 occasions/24 hour period on two or more consecutive days compared with their baseline (baseline = mean of last 10 days of run-in period) or use of other additional bronchodilator medication

Level 2 (Moderate- physician, investigator treated): Acute worsening of symptoms (cough, sputum production, breathlessness) requiring treatment with oral corticosteroids prescribed by a physician or primary care doctor, or as a result of hospital out-patient visit (including Emergency Room).

Exacerbations requiring oral corticosteroids will be treated with a standardised course of prednisolone or prednisone tablets 30mg/day for 10 days, or methylprednisolone tablets 24mg/day for 10 days.

Level 3 (Severe - attendance at hospital): Acute worsening of COPD that requires the patient to be admitted to hospital for treatment.

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			COPD Exacerbations (AE)
207499/157					

FURTHER DETAILS OF COPD EXACERBATIONS

COPD exacerbation onset date : Day Month Yr

Level of exacerbation (see definitions on facing page):

[1] ☐ Level 1
[2] ☐ Level 2
[3] ☐ Level 3

Pumonary function test result (FEV_1) (if done):

☐.☐☐ L

Did the patient suffer from any of the following during the exacerbation:

[1] ☐ Chest pain
[2] ☐ Upper Respiratory Tract Infection
[3] ☐ Confusion
[4] ☐ Change in alertness
[5] ☐ Pneumonia
[6] ☐ Oedema
[7] ☐ Ankle swelling

ARTERIAL BLOOD GASES (only for COPD exacerbations)

Where feasible, an arterial blood gas sample is to be taken for analysis

COPD exacerbation onset date : Day Month Yr

PO_2 (mmHg)	**PCO_2** (mmHg)	**pH**	**Resting SaO_2** (%)
☐☐☐	☐☐	☐.☐☐	☐☐☐

RESOURCE UTILISATION

Please complete the Resource Utilisation pages for this exacerbation.

SmithKline Beecham Pharmaceuticals

Protocol	Centre Number	Patient Number		SB Receipt Date (Day Month Year)	COPD Exacerbations (SAE)
207499/157		[redacted]			

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation

Person Reporting SAE _____ *(Please print clearly)*

AEGIS Number _____ . _____

Serious Adverse Experience	**COPD Exacerbation**
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*	[1] ☐ Resolved [2] ☐ Ongoing [3] ☐ Died
Experience Course	[1] ☐ Intermittent → No. of episodes ☐ [2] ☐ Constant
Intensity *(maximum)*	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Action Taken with Respect to Investigational Drug	[1] ☐ None [2] ☐ Dose reduced [3] ☐ Dose increased [4] ☐ Drug interrupted/ restarted [5] ☐ Drug stopped
Relationship to Investigational Drug	[1] ☐ Not related [2] ☐ Unlikely [3] ☐ Suspected (reasonable possibility) [4] ☐ Probable
Corrective Therapy *If 'Yes', record details in the COPD Concomitant Medication section*	☐ Yes ☐ No
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No

→ *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

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 _____

00000

SmithKline Beecham
Pharmaceuticals

Protocol	**Centre Number**	**Patient Number**		**SB Receipt Date** Day Month Year	**COPD Exacerbations (SAE)**
207499/157		[redacted]			

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation

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 Number (please do NOT enter the container number): ☐☐☐☐☐

Investigator's Signature: _____ Date ☐☐ ☐☐☐ ☐☐☐☐
(confirming that the above data are accurate and complete) Day Month Year

Please PRINT Name _____

SB Medical Monitor's Signature: _____ Date ☐☐ ☐☐☐ ☐☐☐☐
Day Month Year

Please PRINT Name _____

DEFINITIONS OF LEVELS OF EXACERBATION OF COPD

Level 1 (Mild-self treated): Acute worsening of COPD that is self-managed by the patient at home by increasing the dose of relief salbutamol medication by > 2 occasions/24 hour period on two or more consecutive days compared with their baseline (baseline = mean of last 10 days of run-in period) or use of other additional bronchodilator medication

Level 2 (Moderate- physician, investigator treated): Acute worsening of symptoms (cough, sputum production, breathlessness) requiring treatment with oral corticosteroids prescribed by a physician or primary care doctor, or as a result of hospital out-patient visit (including Emergency Room).

Exacerbations requiring oral corticosteroids will be treated with a standardised course of prednisolone or prednisone tablets 30mg/day for 10 days, or methylprednisolone tablets 24mg/day for 10 days.

Level 3 (Severe - attendance at hospital): Acute worsening of COPD that requires the patient to be admitted to hospital for treatment.

00000

SmithKline Beecham
Pharmaceuticals

Protocol	**Centre Number**	**Patient Number**		**SB Receipt Date** Day Month Year	**COPD Exacerbations (SAE)**
207499/157		[redacted]			

FURTHER DETAILS OF SERIOUS COPD EXACERBATIONS

COPD exacerbation onset date : Day Month Yr

Level of exacerbation (see definitions on facing page):

[1] ☐ Level 1
[2] ☐ Level 2
[3] ☐ Level 3

Pumonary function test result (FEV_1) (if done):

☐.☐☐ L

Did the patient suffer from any of the following during the exacerbation:

[1] ☐ Chest pain
[2] ☐ Upper Respiratory Tract Infection
[3] ☐ Confusion
[4] ☐ Change in alertness
[5] ☐ Pneumonia
[6] ☐ Oedema
[7] ☐ Ankle swelling

ARTERIAL BLOOD GASES (only for serious COPD exacerbations)

Where feasible, an arterial blood gas sample is to be taken for analysis

COPD exacerbation onset date : Day Month Yr

PO_2 (mmHg)	**PCO_2** (mmHg)	**pH**	**Resting SaO_2** (%)
☐☐☐	☐☐	☐.☐☐	☐☐☐

RESOURCE UTILISATION

Please complete the Resource Utilisation pages for this exacerbation.

SmithKline Beecham
Pharmaceuticals

Protocol	**Centre Number**	**Patient Number**			**COPD Exacerbations (ConMed)**
207499/157		[redacted]			

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)	**Freq.** (eg bd, prn)	**Route***	**Medical Illness/ Diag.**	**Start Date** *(be as precise as possible)* Day Mth Yr	**End Date** *(or if Continuing mark box)* Day Mth Yr		COPD Exacerbation Onset Date
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								

** For Route, see General Instructions for acceptable abbreviations.*

SmithKline Beecham
Pharmaceuticals

Protocol	**Centre Number**	**Patient Number**			**COPD Exacerbations (ConMed)**
207499/157		[redacted]			

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** Day Mth Yr	**Procedure End Date** Day Mth Yr	COPD Exacerbation Onset Date
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				

Protocol	Centre Number	Patient Number			Resource Utilisation For COPD Exacerbations
207499/157		[redacted]			

RESOURCE UTILISATION FOR COPD EXACERBATIONS

Has the patient had any medical care for COPD Exacerbations that have occurred since the previous module?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below*

Has the patient had any **Physician contact** (COPD care excluding scheduled protocol visits) since the previous module?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below*

Date of Contact Day Mth Yr	Telephone	Home Visit		Office/ Practice	Out-patients	Reason for contact	COPD Exacerbation Onset Date Day Mth Yr
		Day	Night				

Has the patient had any **Emergency Room (ER)/Urgent Care Visits/Procedures (i.e., lung surgery)** since the previous module?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below*

Date of Contact Day Mth Yr	**Reason for contact**	**Patient Admitted from ER?**		COPD Exacerbation Onset Date Day Mth Yr
		Yes	**No**	

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			Resource Utilisation For COPD Exacerbations
207499/157		[redacted]			

RESOURCE UTILISATION FOR COPD EXACERBATIONS - (cont)

Has the patient had any **Hospitalisations** since the previous module?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below* ***(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	COPD Exacerbation Onset Date Day Mth Yr

Has the patient had any **Intensive Care Unit (ICU) stays** ***(did the patient stay in the ICU during any of the above hospitalisations?)*** since the previous module?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below*

Date Admitted to ICU Day Mth Yr	Date Discharged from ICU Day Mth Yr	Reason for ICU Admission	COPD Exacerbation Onset Date Day Mth Yr

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			
207499/157					

2 0 7 4 9 9 1 5 7

CONC3

Please do not split modules

Module: **Study Continuation / Withdrawal**

CRF Pages **241**

Unprocessed Forms : **Within this module the following occur which will generate attachments that need to be brought in-house.**

None

FOR OFFICE USE ONLY Module Comments:

Sent to Data Mngt	Review Complete Date: User:	First Entry Complete Date: User:
Second Entry Complete Date: User:	Validation Complete Date: User:	**Clintrial PID:**

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			Study Continuation/ Withdrawal
207499/157		[redacted]			

STUDY CONTINUATION/WITHDRAWAL

Is the patient continuing in the study? ***(For patients who have withdrawn from study medication but are continuing with essential assessment visits, please mark 'No' and the primary reason for withdrawal)***

☐ Yes ⟶ *If 'Yes', please sign in the appropriate space below and continue to Book 4 for the next visit.*

☐ No ⟶ If 'No', please mark the **primary** cause of withdrawal. *(Mark one box only).*

[1] ☐ Adverse Experience *(please complete Adverse Experiences page)*

[2] ☐ Insufficient therapeutic effect

[3] ☐ Protocol deviation (including non-compliance)

[4] ☐ Lost to follow-up

[7] ☐ Other - *specify*: _

g_cont_wthd_01

INVESTIGATOR SIGNATURE

I certify that I have reviewed the data on this case report form, including laboratory data and that in the Baseline Signs and Symptoms, Adverse Experiences and Serious Adverse Experiences sections (if appropriate) and that all information is complete and accurate.

Investigator's Signature _

Date ☐☐ ☐☐☐ ☐☐
Day Month Yr

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			
207499/157		[redacted]			

2 0 7 4 9 9 1 5 7

SAE3

Please do not split modules

Module : **Serious Adverse Experiences**

CRF Pages **242 - 243**

Unprocessed Forms : **Within this module the following occur which will generate attachments that need to be brought in-house.**

None

FOR OFFICE USE ONLY Module Comments:

Sent to Data Mngt	Review Complete Date: User:	First Entry Complete Date: User:
Second Entry Complete Date: User:	Validation Complete Date: User:	**Clintrial PID:**

REPORTING SERIOUS ADVERSE EXPERIENCES (SAE)

INSTRUCTIONS

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

g_sae_instr_01

00000

SmithKline Beecham
Pharmaceuticals

Protocol	**Centre Number**	**Patient Number**		**SB Receipt Date** Day Month Year	**Serious Adverse Experiences**
207499/157		[redacted]			

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* →
[1] ☐ Resolved
[2] ☐ Ongoing
[3] ☐ Died

Experience Course
[1] ☐ Intermittent → No. of episodes ☐
[2] ☐ Constant

Intensity *(maximum)*
[1] ☐ Mild
[2] ☐ Moderate
[3] ☐ Severe

Action Taken with Respect to Investigational Drug
[1] ☐ None
[2] ☐ Dose reduced
[3] ☐ Dose increased
[4] ☐ Drug interrupted restarted
[5] ☐ 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
[1] ☐ Not related
[2] ☐ Unlikely
[3] ☐ Suspected (reasonable possibility)
[4] ☐ 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

g_sae_01

00000

SmithKline Beecham Pharmaceuticals

Protocol	Centre Number	Patient Number		SB Receipt Date (Day Month Year)	Serious Adverse Experiences
207499/157		[redacted]			

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 Number (please do NOT enter the container number): ☐☐☐☐☐

Investigator's Signature: _____ Date ☐☐ ☐☐ ☐☐
(confirming that the above data are accurate and complete) Day Month Year

Please PRINT Name _____

SB Medical Monitor's Signature: _____ Date ☐☐ ☐☐ ☐☐

Please PRINT Name _____ Day Month Year

g_sae_01

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			
207499/157		[redacted]			

2 0 7 4 9 9 1 5 7

RPLAB5

Please do not split modules

Module: **Repeat / unscheduled laboratory assessments**

CRF Pages: **244**

Unprocessed Forms: **Within this module, the following tests / procedures occur which may generate attachments.**

None

FOR OFFICE USE ONLY Module Comments:

Sent to Data Mngt	Review Complete Date: User:	First Entry Complete Date: User:
Second Entry Complete Date: User:	Validation Complete Date: User:	**Clintrial PID:**

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			Repeat / Unscheduled Lab Tests
207499/157		[redacted]			

REPEAT / UNSCHEDULED LABORATORY TESTS

Visit Number (or last scheduled visit number): ☐☐ Sample Date ☐☐ ☐☐ ☐☐
Day Month Yr

Please take blood samples for hematology and/or blood chemistry (including serum beta-HCG for women of child-bearing potential) and/or a urine sample for urinalysis. Please refer to the instructions on the Quest shipping form and manual.

Please attach Central Lab CRF label here

(Attach label when sample is sent to central lab.)

Laboratory reports will stay at the site as part of the patient's source documentation.

Request βhCG test on Quest requisition for women of child-bearing potential. If the pregnancy test is positive, please withdraw the patient and complete the Serious Adverse Experiences form and forward it to SB within 24 hours.

Are there any **clinically significant** worsenings since the last assessment?

☐ No

☐ Yes ⟶ *If 'Yes', please record the findings and/or diagnosis in the Adverse Experiences section.*

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			
207499/157		[redacted]			

2 0 7 4 9 9 1 5 7

RPLAB6

Please do not split modules

Module: **Repeat / unscheduled laboratory assessments**

CRF Pages: **245**

Unprocessed Forms: **Within this module, the following tests / procedures occur which may generate attachments.**

None

FOR OFFICE USE ONLY Module Comments:

Sent to Data Mngt	Review Complete Date: User:	First Entry Complete Date: User:
Second Entry Complete Date: User:	Validation Complete Date: User:	**Clintrial PID:**

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			Repeat / Unscheduled Lab Tests
207499/157		[redacted]			

REPEAT / UNSCHEDULED LABORATORY TESTS

Visit Number (or last scheduled visit number): ☐☐ Sample Date ☐☐ ☐☐☐ ☐☐ Day Month Yr

Please take blood samples for hematology and/or blood chemistry (including serum beta-HCG for women of child-bearing potential) and/or a urine sample for urinalysis. Please refer to the instructions on the Quest shipping form and manual.

Please attach Central Lab CRF label here

(Attach label when sample is sent to central lab.)

Laboratory reports will stay at the site as part of the patient's source documentation.

Request βhCG test on Quest requisition for women of child-bearing potential. If the pregnancy test is positive, please withdraw the patient and complete the Serious Adverse Experiences form and forward it to SB within 24 hours.

Are there any **clinically significant** worsenings since the last assessment?

☐ No

☐ Yes ⟶ *If 'Yes', please record the findings and/or diagnosis in the Adverse Experiences section.*

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number		Investigator
207499/157		[redacted]		_ _

CRF TRACKING/REVIEW FORM (TRF) (BOOK 3)

Please submit COMPLETE modules only. Do not submit whole blank modules.

- *Mark the **Unused** box for all remaining modules that will **not** be completed and sent in-house*
- *Ensure the Missing Pages field is completed if pages are missing from modules*
- *Ensure the Patient Numbers entered match the information on the CRF*
- *Complete one TRF per batch of modules to be sent in-house*
- *Ensure all sections of the TRF are legible*

Module	Module Description	Page Range	Modules		Missing pages (if applicable)
			Sent to DM	Unused	
DIA7	Visit 7 Patient diary	1 - 6	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
MOD5	Visit 8, AE, CM, Med Pro, COPD, RU	151 - 180	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
PFT7	Visit 8 PFT printout	n/a	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
DIA8	Visit 8 Patient diary	1 - 6	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
MOD6	Visit 9, AE, CM, Med Pro, COPD, RU	181 - 210	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
ECG4	Visit 9 ECG Trace	n/a	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
PFT8	Visit 9 PFT printout	n/a	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
DIA9	Visit 9 Patient diary	1 - 6	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
SGRQ2	Visit 9 SGRQ	SG1-SG5	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
EQ5D2	Visit 9 EQ-5D	EQ1-EQ2	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
MOD7	V10, AE, CM, Med Pro, COPD, RU	211 - 240	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
PFT9	Visit 10 PFT printout	n/a	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
CONC3	Continuation/Withdrawal	241	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
SAE3	Serious Adverse Experiences	242 - 243	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
RPLAB5	Repeat Labs	244	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
RPLAB6	Repeat Labs	245	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
FORMD	Form D	n/a	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _

If multiple modules are submitted together, please ensure they are sorted according to the order above

Site Monitor's Name _ *(Print clearly)*

Site Monitor's Signature _ **Date Submitted** ☐☐ ☐☐☐ ☐☐
Day Month Yr

g_trf_01

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number		Investigator
207499/157		[redacted]		_ _

CRF TRACKING/REVIEW FORM (TRF) (BOOK 3)

Site Monitor's comments (eg. protocol violations or deviations)

_ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _

00000

SmithKline Beecham
Pharmaceuticals

Protocol		**Patient Number**			**Visit 11**
207499/157		[redacted]			**Week 44**

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 11

Is the patient continuing in the study?

☐ No ⟶ *Go to '1' below.*

☐ Yes ⟶ *Go to '2' below.*

*1. If the patient is **not** continuing in the study, is the patient willing to return for essential assessments?*

Please complete the assessments for Visit 11, the additional assessments for patients withdrawing at Visit 11 and the Study Conclusion page at the back of this book. Please schedule a safety follow-up visit in 7 days (+/- 3 days).

Please complete the assessments for Visit 11, the additional assessments for patients withdrawing at Visit 11 and the Study Conclusion page at the back of this book. Ask the patient to return for a safety follow-up visit in 7 days (+/- 3 days) and then for their next scheduled visit 49 (+/- 6 days) later for essential assessments only.

*2. If the patient **is** continuing in the study, please:*	(tick if done)
	☑
• *Issue the patient a new diary card and remind the patient to complete the diary each morning until the next visit.*	☐
• *Ask the patient to return for the next visit in 56 +/- 6 days at the same time of day.*	☐
• ***Remind the patient:***	
i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after their breakfast.*	☐
ii ***not** to take their dose of study medication for at least 8 hours prior to their next study visit appointment.*	☐
iii *to refrain from using salbutamol or anticholinergic agents during the **4 hours** immediately preceding 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, the study salbutamol inhaler and spacer, and the diary card.*	☐
vi *to continue to take the anticholinergic medication, if prescribed, at a constant dose, and salbutamol when needed to control symptoms.*	☐
vii *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 occurrence.*	☐

Protocol		Patient Number			Visit 12 Week 52
207499/157		[redacted]			

FAECAL OCCULT BLOOD TEST

The faecal occult blood test should be performed on three consecutive bowel movements closely spaced in time between Visits 12 and Safety Follow-up. Patients were not to collect samples during or until 3 days after a menstrual period or while they had bleeding hemorrhoids or blood in the urine. They were not to take aspirin or other non-steroidal anti-inflammatory drugs for 7 days prior to and during the test period, and they were 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.

Did the patient follow these instructions?

☐ No ⟶ *If 'No', please specify:* _

☐ Yes

Test	Date of Collection Day Mth Yr	Result of faecal occult blood test
1	☐☐ ☐☐ ☐☐	[NEG] ☐ Negative [POS] ☐ Positive
2	☐☐ ☐☐ ☐☐	[NEG] ☐ Negative [POS] ☐ Positive
3	☐☐ ☐☐ ☐☐	[NEG] ☐ Negative [POS] ☐ Positive

Are these findings clinically significant ?

☐ No

☐ Yes ⟶ *If 'Yes' please record the findings and/or diagnosis in the Adverse Experiences section at the back of this module.*

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 12

- *Please complete the Study Conclusion page at the back of this book.*
- *Ask the patient to return for the Safety Follow-Up Visit in 7+/-3 days. The patient may resume their previous COPD medications.*
- *Please issue the faecal occult blood test kit and ask the patient to follow the instructions provided on the kit and to bring it with them to the Follow-Up Visit.*

Protocol	Centre Number	Patient Number
207499/157		[redacted]

CONFIDENTIAL

SmithKline Beecham
Pharmaceuticals

PROTOCOL 207499/157

BOOK 4 : VISIT 11 TO STUDY CONCLUSION

A RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL GROUP STUDY TO EVALUATE THE EFFICACY, SAFETY AND TOLERABILITY OF ORAL CILOMILAST (15 MG BD) WHEN GIVEN AS MAINTENANCE TREATMENT FOR 12 MONTHS TO SUBJECTS 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 and centre number on all pages 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 | *= 1st January 2001*
Day Month Year

TIME

Unless specified otherwise, please use the 24 hour clock

e.g. | 1 5 | 3 0 | *= 3.30 p.m*
24hr:min

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*

SCHEDULE OF ASSESSMENTS

Visit	1	2	3	4	5	6	7	8	9	10	11	12		13
	Screen		Base-line									End of DB	Early With-drawal	Follow -up
Time relative to baseline (weeks)[1]	-4	-2	0	+2	+4	+8	+12	+20	+28	+36	+44	+52		+53
Signed written informed consent	x													
Medical & surgical history	x													
Pulmonary symptoms	x													
Postero-anterior chest X-ray[2]	x													
Medication history including influenza vaccination[3]	x													
Health Status Assessments: SGRQ and EQ-5D			x						x			x	x	
Patient global assessment			x						x			x	x	
Investigator global assessment			x						x			x	x	
Physical examination [4]	x		x									x	x	x[5]
Smoking status	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Exacerbation assessment	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Resource utilisation				x	x	x	x	x	x	x	x	x	x	x
Diary Card Review		x	x	x	x	x	x	x	x	x	x	x	x	
Baseline signs and symptoms [6]	x	x	x											
Adverse experiences [6]				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
Study medication compliance		x	x	x	x	x	x	x	x	x	x	x	x	
Resting 12-lead ECG	x		x				x		x			x	x	x[5]
Vital signs (BP, HR)[7]	x[7]	x	x[7]	x	x	x	x[7]	x	x[7]	x	x	x[7]	x[7]	x
PFTs pre and post salbutamol: Pre-dose [8]	x		x		x	x	x	x	x	x	x	x	x	x
PFTs: salbutamol reversibility [9]	x		x											
PFTs: ipratropium reversibility		x												
Residual Volume (body box) pre-/ post-salbutamol Selected sites only			x						x			x	x	
Laboratory tests	x		x[10]		x	x	x	x	x	x	x	x[10]	x[10]	x[5]
Faecal occult blood test [11]	x	x										x	x	
Dispense single-blind med	x[12]	x[13]												
Dispense double-blind med			x[14]	x[13]	x[15]	x[15]	x[15]	x[15]	x[15]	x[15]	x[15]			
Study conclusion record														x[16]

1 All visit dates must be scheduled at the visit interval listed here using the Baseline visit as Day 0.
2 Chest X-ray to be taken at entry to the run-in period or in the 3 months prior to entry to the run-in period
3 Details of 'flu vaccinations will be recorded at every visit
4 Includes respiratory examination.
5 Only if abnormalities are present at Visit 12/Early Withdrawal.
6 Does not include COPD exacerbations
7 Orthostatic vital signs to be measured at Visits 1, 3, 7, 9, and 12
8 Includes FEV_1, FVC, FEF_{25-75} and PEF measured by spirometry by the same study personnel at each visit before dose of study medication is taken.
9 Includes FEV_1, FVC, FEF_{25-75} and PEF measured by spirometry by the same study personnel at each visit 30 minutes after administration of 400 mcg of salbutamol via MDI with or without a spacer, and before dose of study medication is taken.
10 Includes Blood CD4+/CD8+ ratio and serum C Reactive Protein
11 In addition to the usual laboratory tests, three faecal occult blood tests will be performed between Visits 1 and 3, at the end of the treatment period and at Early Withdrawal
12 Register the patient with RAMOS.
13 The container of study medication issued at the previous visit will be re-issued at this visit
14 Call RAMOS to randomise the patient and to obtain study medication assignment and container number.
15 Call RAMOS to obtain study medication container number(s)
16 Or earlier if the subject withdraws from the study prior to Visit 12.

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			
207499/157		[redacted]			

2 0 7 4 9 9 1 5 7

MOD8

Please do not split modules

Module 8 : **Visit 11, Adverse Experiences, Concomitant Medications, Medical Procedures, COPD Exacerbations, Resource Utilisation**

CRF Pages **246 - 275**

Unprocessed Forms : **Within this module the following occur which will generate attachments that need to be brought in-house.**

None

FOR OFFICE USE ONLY Module Comments:

Sent to Data Mngt	Review Complete Date: User:	First Entry Complete Date: User:
Second Entry Complete Date: User:	Validation Complete Date: User:	**Clintrial PID:**

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number		Visit Date (Day Month Year)	
207499/157		[redacted]			**Visit 11 Week 44**

PRESENTATION TO CLINIC

Note: ***Patients must wait for 4 hours after beta$_2$-agonist and / or anticholinergic administration before the pulmonary function tests are performed.***

Did the patient take a dose of beta$_2$ agonist in the past 24 hours?

☐ No

☐ Yes → Record date and time of the patient's last dose of beta$_2$ agonist: Day Month Yr 24hr:min

Did the patient take a dose of anticholinergic in the past 24 hours?

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: Day Month Yr 24hr:min

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes → Date and time of patient's last cigarette Day Month Yr 24hr:min

SMOKING STATUS

Does the patient currently smoke?

☐ No

☐ Yes → If 'Yes' please record the average number of cigarettes per day :

INFLUENZA VACCINATION

Has the patient had a vaccination for influenza since the last visit?

N.B. It is not necessary to record vaccinations on the Concomitant Medication or Medical Procedures page.

☐ No

☐ Yes → *If 'Yes', record date of vaccination :* Day Month Yr

00000

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number			Visit 11 Week 44
207499/157		[redacted]			

RESOLUTION OF COPD EXACERBATIONS

Have any COPD Exacerbations resolved since the last visit?

☐ No

☐ Yes ⟶ *If 'Yes', please record details in the COPD Exacerbation section at the back of this module.*

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes ⟶ *If 'Yes' please record details in the COPD Exacerbation section at the back of this module.*

Level 1 (Mild-self treated): Acute worsening of COPD that is self-managed by the patient at home by increasing the dose of relief salbutamol medication by > 2 occasions/24 hour period on two or more consecutive days compared with their baseline (baseline = mean of last 10 days of run-in period) or use of other additional bronchodilator medication

Level 2 (Moderate- physician, investigator treated): Acute worsening of symptoms (cough, sputum production, breathlessness) requiring treatment with oral corticosteroids prescribed by a physician or primary care doctor, or as a result of hospital out-patient visit (including Emergency Room).

Exacerbations requiring oral corticosteroids will be treated with a standardised course of prednisolone or prednisone tablets 30mg/day for 10 days, or methylprednisolone tablets 24mg/day for 10 days.

Level 3 (Severe - attendance at hospital): Acute worsening of COPD that requires the patient to be admitted to hospital for treatment.

If a patient experienced a COPD exacerbation that was treated with corticosteroids, please withdraw the patient and complete the Study Conclusion page at the back of this book. 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, including an increase in usual COPD medications, must be recorded in the COPD Medications or Procedures pages.

00000

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number			Visit 11 Week 44
207499/157		[redacted]			

RESOURCE UTILISATION

If the patient has received any COPD exacerbation-related medical care since the last visit, record details on the Resource Utilisation pages of the COPD Exacerbation section at the back of this module.

DIARY CARD REVIEW

Review the diary card in the presence of the patient. Question any increased symptoms for possible COPD exacerbations. Place diary in the plastic wallet at the back of this module and re-issue another diary card.

ADVERSE EXPERIENCES

Please complete the Adverse Experiences 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 Experiences 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.

SmithKline Beecham
Pharmaceuticals

Protocol		**Patient Number**			**Visit 11**
207499/157		[redacted]			**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. bd)

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
140	☐☐	☐☐	☐☐	☐☐	☐☐☐

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance ≥ 80% and ≤120%?

☐ No → *If 'No' please remind the patient of the importance of taking study medication according to the protocol.*

☐ Yes

00000

SmithKline Beecham
Pharmaceuticals

Protocol		**Patient Number**			**Visit 11**
207499/157		[redacted]			**Week 44**

INVESTIGATOR INSTRUCTIONS

The following procedures (Vital Signs and Pulmonary Function Tests) must be performed greater than 4 hours after the patient's last salbutamol administration.

VITAL SIGNS

Time of assessment : ☐☐ 24hr:min

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
☐☐☐/☐☐☐	☐☐☐

Are there any **clinically significant worsenings** since the previous visit?

☐ No

☐ Yes ⟶ *If 'Yes' please record the findings and/or diagnosis in the Adverse Experiences section at the back of this module.*

Protocol		Patient Number			Visit 11 Week 44
207499/157		[redacted]			

PRE-SALBUTAMOL PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed at least 4 hours after the last dose of inhaled beta$_2$-agonist or anticholinergic agent.

Measure the patient's pulmonary function up to eight times to obtain three acceptable readings using the spirometer provided by SB. ***(Note: Please follow instructions in the Spirometry Manual).*** *For each set of three FEV_1 measurements, one FEV_1 must be within 10% of the highest. Please record the results of the effort with the highest FEV_1 below.*

Measurement	Time	FEV_1 (L)	FVC (L)	FEF_{25-75} (L/sec)	PEF (L/min)
1	☐☐:☐☐ 24hr:min	☐.☐☐	☐.☐☐	☐.☐☐	☐☐☐

Place the spirometry reports in the plasic wallet at the back of this module.

POST-SALBUTAMOL PULMONARY FUNCTION TESTS

Provide the patient with a salbutamol MDI and spacer. Administer 400 mcg (4 puffs) of salbutamol via MDI with a spacer. Remind the patient to use this inhaler (with or without the spacer), rather than any salbutamol inhaler they may have at home, for "as required" rescue-medication use during the study.

Record the time of salbutamol inhalation ☐☐:☐☐ 24hr:min

Wait 30 minutes

Measure the patient's pulmonary function up to eight times to obtain three acceptable readings using the spirometer provided by SB. ***(Note: Please follow instructions in the Spirometry Manual).*** *For each set of three FEV_1 measurements, one FEV_1 must be within 10% of the highest. Please record the results of the effort with the highest FEV_1 below.*

Measurement	Time	FEV_1 (L)	FVC (L)	FEF_{25-75} (L/sec)	PEF (L/min)
1	☐☐:☐☐ 24hr:min	☐.☐☐	☐.☐☐	☐.☐☐	☐☐☐

Place spirometry reports in the plastic wallets at the back of this module.

PULMONARY REHABILITATION PROGRAM

Has the patient entered a Pulmonary Rehabilitation Program since the last visit?

☐ No

☐ Yes

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number			Visit 11 Week 44
207499/157		[redacted]			

LABORATORY TESTS

Please take blood samples for haematology and blood chemistry (including serum beta-HCG for women of child-bearing potential) and a urine sample for urinalysis. Please refer to the instructions on the Quest shipping form and manual.

Blood Sample Date ☐☐ ☐☐☐ ☐☐
Day Month Yr

Attach a label from the 'Routine' laboratory requisition form used at this visit in the space below.

Attach label here

Are there any **clinically significant worsenings** since the last assessment?

☐ No

☐ Yes ⟶ *If 'Yes' please record the findings and/or diagnosis in the Adverse Experiences section at the back of this module.*

STUDY MEDICATION ALLOCATION - RAMOS CALL

Following completion of all preceding assessments, complete the RAMOS worksheet appropriate for this visit and contact RAMOS to obtain the container numbers for this visit.

*Please enter the 5-digit **randomisation number** assigned by RAMOS* ☐☐☐☐☐

*Please enter the 6-digit **container number** as it appears on the study medication label **(Container 1)**.* ☐☐☐☐☐☐

*Please enter the 6-digit **container number** as it appears on the study medication label **(Container 2)**.* ☐☐☐☐☐☐

STUDY MEDICATION LABEL

Attach the tear-off labels from the study medication containers 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

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

00000

SmithKline Beecham
Pharmaceuticals

Protocol **207499/157**		**Patient Number** [redacted]			**Visit 11 Week 44**

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 11

Is the patient continuing in the study?

☐ No

☐ Yes

*If the patient is **not** continuing in the study, is the patient willing to return for essential assessments?*

If 'No', please complete the assessments for Visit 11 and the additional assessments for patients withdrawing at Visit 11 and the Study Conclusion page at the back of this book.

If 'Yes', please complete the assessments for Visit 11 and the additional assessments for patients withdrawing at Visit 11 and ask the patient to return for essential assessments only in 56 +/- 6 days time.

*If the patient **is** continuing in the study, please:*	(tick if done)
	☑
• *Issue the patient a new diary card and remind the patient to complete the diary each morning until the next visit.*	☐
• *Ask the patient to return for the next visit in 56 +/- 6 days for a morning visit.*	☐
• ***Remind the patient:***	
i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after their breakfast.*	☐
ii ***not** to take the morning dose of study medication at home on the day of the next clinic visit.*	☐
iii *to refrain from using salbutamol or anticholinergic agents during the **4 hours** immediately preceding 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, the study salbutamol inhaler and spacer, and the diary card.*	☐
vi *to continue to take the anticholinergic medication, if prescribed, at a constant dose, and salbutamol when needed to control symptoms.*	☐
vii *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 occurrence.*	☐

00000

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number			Withdrawal at Visit 11 Week 44
207499/157		[redacted]			

ASSESSMENTS FOR PATIENTS WITHDRAWING AT VISIT 11

Complete the assessments below only for patients who are withdrawing from the study.

ST. GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND EQ-5D

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

INVESTIGATOR GLOBAL EVALUATION OF IMPROVEMENT

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

PATIENT GLOBAL EVALUATION OF IMPROVEMENT

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

00000

SmithKline Beecham
Pharmaceuticals

Protocol **207499/157**		**Patient Number** [redacted]			**Withdrawal at Visit 11 Week 44**

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 Experiences section at the back of this module.*

VITAL SIGNS - ORTHOSTATIC CHANGE

Time of assessment : ☐☐ 24hr:min

1st Measurement: After 5 Minutes Supine		**2nd Measurement: 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)
☐☐☐/☐☐☐	☐☐☐	☐☐☐/☐☐☐	☐☐☐

Have there been any clinically significant worsenings since the last assessment?

☐ No

☐ Yes⟶ *If 'Yes', please record the findings in the Adverse Experiences section at the back of this module.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number			Withdrawal at Visit 11 Week 44
207499/157		[redacted]			

12 LEAD ELECTROCARDIOGRAM

Time of assessment : ☐☐ 24hr:min **The ECG should be performed after the patient has been semi-supine for 5 minutes**

Date ECG Performed (Day Month Year)	Atrial Rate (beats/min)	Ventricular Rate (beats/min)	PR (msec)	QRS (msec)	☐ Uncorrected QT ☐ Corrected QT (msec)	Axis
☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐ + ☐ - ☐☐☐

Interpretation

☐ **(F74301) Within normal limits**

☐ **Abnormal** ⟶ ***Mark appropriate boxes below***

Rhythm
- ☐ (F73360) Sinus arrhythmia
- ☐ (F73310) Sinus bradycardia
- ☐ (F73380) Sinus tachycardia
- ☐ (F73440) Wandering atrial pacemaker
- ☐ (F73450) Premature atrial contractions
- ☐ (F73510) Paroxysmal atrial tachycardia
- ☐ (F73530) Chronic ectopic atrial tachycardia
- ☐ (F73550) Multifocal atrial tachycardia
- ☐ (F73560) Atrial flutter
- ☐ (F73570) Atrial fibrillation
- ☐ (F73610) Junctional (AV nodal) premature contractions
- ☐ (F73650) Junctional (AV nodal) tachycardia
- ☐ (F73150) Supraventricular tachycardia
- ☐ (F73860) Accelerated idioventricular rhythm
- ☐ (F73710) Premature Ventricular Contractions (NOS)
- ☐ (F73720) Unifocal PVC's
- ☐ (F73730) Multifocal PVC's
- ☐ (F73711) Ventricular couplets
- ☐ (F73750) Bigeminy
- ☐ (F73870) Ventricular tachycardia
- ☐ (F73880) Ventricular fibrillation
- ☐ (F73340) Sick sinus syndrome
- ☐ (F73190) Pacemaker rhythm

P-Wave Morphology
- ☐ (F74214) Left atrial hypertrophy, P mitrale
- ☐ (F74213) Right atrial hypertrophy, P pulmonale

Conduction
- ☐ (F73930) First degree AV block
- ☐ (F73950) Second degree AV block, Type 1
- ☐ (F73960) Second degree AV block, Type 11
- ☐ (F73970) Third degree AV block
- ☐ (F74090) Wolff-Parkinson-White syndrome

Axis
- ☐ (F74120) Right Axis deviation
- ☐ (F74130) Left Axis deviation

QRS
- ☐ (F74010) Right bundle branch block
- ☐ (F74020) Left bundle branch block
- ☐ (F74030) Left anterior hemiblock
- ☐ (F74040) Left posterior hemiblock
- ☐ (F74002) Intraventricular conduction delay
- ☐ (F74212) Left ventricular hypertrophy
- ☐ (F74211) Right ventricular hypertrophy
- ☐ (F74308) Q-wave > 0.04 sec
- ☐ (F74222) R-wave amplitude increased
- ☐ (F74225) R-wave amplitude decreased
- ☐ (F74313) Prolonged QT-interval
- ☐ (F74318) Poor R-wave progression
- ☐ (M54750) Myocardial infarction, old
  - ☐ (M54751) Anterior ☐ (M54754) Inferior
  - ☐ (M54752) Lateral ☐ (M54755) Septal
  - ☐ (M54753) Posterior

ST-T
- ☐ (F74291) Nonspecific ST-T changes
- ☐ (F74294) ST segment depression > 1 mm
- ☐ (F74295) ST segment elevation > 1 mm
- ☐ (F74350) T-wave flat
- ☐ (F74351) T-wave inversion
- ☐ (F74352) T-wave peaked
- ☐ (F74340) U-wave
- ☐ (F74360) Digitalis effect
- ☐ (F74260) Myocardial ischemia
  - ☐ (F74261) Anterior ☐ (F74264) Inferior
  - ☐ (F74262) Lateral ☐ (F74265) Septal
  - ☐ (F74263) Posterior
- ☐ (M54720) Myocardial infarction, acute
  - ☐ (M54721) Anterior ☐ (M54724) Inferior
  - ☐ (M54722) Lateral ☐ (M54725) Septal
  - ☐ (M54723) Posterior

Other interpretations not listed _

Were there any clinically important changes observed since the last assessment?

[1] ☐ No

[2] ☐ Yes ⟶ *If 'Yes', enter details on the Adverse Experiences page at the back of this module.*

Place the ECG trace in the plastic wallet a the back of this module

Protocol		Patient Number			Withdrawal at Visit 11 Week 44
207499/157		[redacted]			

(AT SELECTED CENTRES ONLY) RESIDUAL VOLUME BY BODY PLETHYSMOGRAPHY (PRE- AND POST-SALBUTAMOL)

Time of pre-salbutamol RV assessment: ☐☐ 24hr:min

Time of post-salbutamol RV assessment: ☐☐ 24hr:min

Pre-Salbutamol

$RV_{Box} = TLC_{Box} - \max(|SVC|, |FVC|)$

$RV_{(Box)}$ = ☐.☐☐ (L)

Post-Salbutamol

$RV_{Box} = TLC_{Box} - \max(|SVC|, |FVC|)$

$RV_{(Box)}$ = ☐.☐☐ (L)

Please attach plethysmography source data to the back of this page.

FAECAL OCCULT BLOOD TEST

The faecal occult blood test should be performed on three consecutive bowel movements between withdrawal and the next scheduled visit or the Follow-Up visit depending on whether the patient is willing, or not, to return for essential assessments. Patients are not to take samples during or up-to 3-days after a menstrual period or while having bleeding haemorrhoids or blood in the urine. Patients are not to take aspirin or other non-steroidal anti-inflammatory drugs for 7 days prior to and during the test period and they are to avoid Vitamin C in excess of 250mg 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.

Did the patient follow these instructions?

☐ No ⟶ *If 'No', please specify:* _____

☐ Yes

Test	Date of Collection Day Mth Yr	Result of faecal occult blood test
1	☐☐ ☐☐ ☐☐	[NEG] ☐ Negative [POS] ☐ Positive
2	☐☐ ☐☐ ☐☐	[NEG] ☐ Negative [POS] ☐ Positive
3	☐☐ ☐☐ ☐☐	[NEG] ☐ Negative [POS] ☐ Positive

Are these findings clinically significant ?

☐ No

☐ Yes ⟶ *If 'Yes' please record the findings and/or diagnosis in the Adverse Experiences section at the back of this module.*

00000

SmithKline Beecham
Pharmaceuticals

Protocol		**Patient Number**			**Withdrawal at Visit 11 Week 44**
207499/157		[redacted]			

LABORATORY TESTS

Please take blood samples for CD4/CD8 ratio and C Reactive Protein. Please refer to the instructions on the Quest shipping form and manual.

Blood Sample Date ☐☐ ☐☐ ☐☐
Day Month Yr

Attach a label from the 'Routine' laboratory requisition form used at this visit in the space below.

Attach label here

Are there any **clinically significant worsenings** since the last assessment?

☐ No

☐ Yes ⟶ *If 'Yes' please record the findings and/or diagnosis in the Adverse Experiences section at the back of this module.*

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 study procedures should be reported as a serious event

IF AN 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

g_ae_instr_01

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			Adverse Experiences
207499/157		[redacted]			

ADVERSE EXPERIENCES (Non-serious)

g_ae_01

*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 last visit?"*
*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).

☐ Please mark this box if no adverse experiences occurred since the last module

Adverse Experience *(please print clearly)*		
For SB		
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 SAE section and follow instructions given there***	[1] ☐ Resolved [2] ☐ Ongoing [3] ☐ Died	[1] ☐ Resolved [2] ☐ Ongoing [3] ☐ Died
Experience Course	[1] ☐ Intermittent → No. of episodes ☐ [2] ☐ Constant	[1] ☐ Intermittent → No. of episodes ☐ [2] ☐ Constant
Intensity (maximum)	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Action Taken with Respect to Investigational Drug	[1] ☐ None [2] ☐ Dose reduced [3] ☐ Dose increased [4] ☐ Drug interrupted/restarted [5] ☐ Drug stopped	[1] ☐ None [2] ☐ Dose reduced [3] ☐ Dose increased [4] ☐ Drug interrupted/restarted [5] ☐ Drug stopped
Relationship to Investigational Drug	[1] ☐ Not related [2] ☐ Unlikely [3] ☐ Suspected (reasonable possibility) [4] ☐ Probable	[1] ☐ Not related [2] ☐ Unlikely [3] ☐ Suspected (reasonable possibility) [4] ☐ Probable
Corrective Therapy *If 'Yes', record details in the Concomitant Medication section and/ or Medical Procedures section if appropriate*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No

SmithKline Beecham Pharmaceuticals

Protocol	Centre Number	Patient Number			Adverse Experiences
207499/157		[redacted]			

ADVERSE EXPERIENCES (Non-serious) - Continued

g_ae_01

*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 last visit?"*
*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).

Adverse Experience *(please print clearly)*		
For SB		
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 SAE section and follow instructions given there***	[1] Resolved [2] Ongoing [3] Died	[1] Resolved [2] Ongoing [3] Died
Experience Course	[1] Intermittent → No. of episodes [2] Constant	[1] Intermittent → No. of episodes [2] Constant
Intensity (maximum)	[1] Mild [2] Moderate [3] Severe	[1] Mild [2] Moderate [3] Severe
Action Taken with Respect to Investigational Drug	[1] None [2] Dose reduced [3] Dose increased [4] Drug interrupted/restarted [5] Drug stopped	[1] None [2] Dose reduced [3] Dose increased [4] Drug interrupted/restarted [5] Drug stopped
Relationship to Investigational Drug	[1] Not related [2] Unlikely [3] Suspected (reasonable possibility) [4] Probable	[1] Not related [2] Unlikely [3] Suspected (reasonable possibility) [4] Probable
Corrective Therapy *If 'Yes', record details in the Concomitant Medication section and/ or Medical Procedures section if appropriate*	Yes No	Yes No
Was patient withdrawn due to this specific AE?	Yes No	Yes No

SmithKline Beecham Pharmaceuticals

Protocol	Centre Number	Patient Number			Adverse Experiences
207499/157		[redacted]			

ADVERSE EXPERIENCES (Non-serious) - Continued

g_ae_01

*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 last visit?" 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).

Adverse Experience *(please print clearly)*		
For SB		
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 SAE section and follow instructions given there***	[1] Resolved [2] Ongoing [3] Died	[1] Resolved [2] Ongoing [3] Died
Experience Course	[1] Intermittent → No. of episodes [2] Constant	[1] Intermittent → No. of episodes [2] Constant
Intensity (maximum)	[1] Mild [2] Moderate [3] Severe	[1] Mild [2] Moderate [3] Severe
Action Taken with Respect to Investigational Drug	[1] None [2] Dose reduced [3] Dose increased [4] Drug interrupted/restarted [5] Drug stopped	[1] None [2] Dose reduced [3] Dose increased [4] Drug interrupted/restarted [5] Drug stopped
Relationship to Investigational Drug	[1] Not related [2] Unlikely [3] Suspected (reasonable possibility) [4] Probable	[1] Not related [2] Unlikely [3] Suspected (reasonable possibility) [4] Probable
Corrective Therapy *If 'Yes', record details in the Concomitant Medication section and/ or Medical Procedures section if appropriate*	Yes No	Yes No
Was patient withdrawn due to this specific AE?	Yes No	Yes No

Protocol	**Centre Number**	**Patient Number**			**Concomitant Medication**
207499/157		[redacted]			

CONCOMITANT MEDICATION

Record any changes in concomitant medication taken since the last 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. At the patient's final study visit, record the end date for prn study rescue medication (salbutamol) use, using the date the study inhaler was returned.

☐ No concomitant medication changes since the last module

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded in the Adverse Experiences 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** (eg 500mg)	**Frequency** (eg bd, 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	
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							

** For Route, see general instructions for acceptable abbreviations.*

Protocol	Centre Number	Patient Number			Concomitant Medication
207499/157		[redacted]			

CONCOMITANT MEDICATION (Cont.)

Do not record any medication taken for COPD exacerbations in this section. Record all COPD exacerbation medication in the COPD Exacerbation section. At the patient's final study visit, record the end date for prn study rescue medication (salbutamol) use, using the date the study inhaler was returned.

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded in the Adverse Experiences 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** (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	
For SB							
For SB							
For SB							
For SB							
For SB							
For SB							
For SB							
For SB							
For SB							
For SB							

** For Route, see general instructions for acceptable abbreviations.*

g_conmed_01

Protocol	Centre Number	Patient Number			Medical Procedures
207499/157		[redacted]			

MEDICAL PROCEDURES

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 last module?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below using standard medical terminology*

All indications for procedures should be recorded on the Adverse Experiences Form.

Procedure	Indication	Procedure Start Date Day Mth Yr	Procedure End Date Day Mth Yr
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			COPD Exacerbations (AE)
207499/157		[redacted]			

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 last 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***

Has the patient suffered any COPD Exacerbations since the last module ?

☐ No

☐ Yes → *If 'Yes', please complete page below*

Adverse Event	COPD EXACERBATION
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, STOP: delete details of this exacerbation and go to SAE COPD Exacerbation pages.***	[1] ☐ Resolved [2] ☐ Ongoing [3] ☐ Died
Event Course	[1] ☐ Intermittent → No. of episodes ☐ [2] ☐ Constant
Intensity (maximum) *See definitions page for Adverse Experiences form.*	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Action Taken with Respect to Investigational Drug	[1] ☐ None [2] ☐ Dose reduced [3] ☐ Dose increased [4] ☐ Drug interrupted/restarted [5] ☐ Drug stopped
Relationship to Investigational Drug	[1] ☐ Not related [2] ☐ Unlikely [3] ☐ Suspected (reasonable possibility) [4] ☐ Probable
Corrective Therapy *If 'Yes', record details on the COPD Medications or Procedures page*	☐ Yes ☐ No
Was patient withdrawn due to this specific event?	☐ Yes ☐ No

DEFINITIONS OF LEVELS OF EXACERBATION OF COPD

Level 1 (Mild-self treated): Acute worsening of COPD that is self-managed by the patient at home by increasing the dose of relief salbutamol medication by > 2 occasions/24 hour period on two or more consecutive days compared with their baseline (baseline = mean of last 10 days of run-in period) or use of other additional bronchodilator medication

Level 2 (Moderate- physician, investigator treated): Acute worsening of symptoms (cough, sputum production, breathlessness) requiring treatment with oral corticosteroids prescribed by a physician or primary care doctor, or as a result of hospital out-patient visit (including Emergency Room).

Exacerbations requiring oral corticosteroids will be treated with a standardised course of prednisolone or prednisone tablets 30mg/day for 10 days, or methylprednisolone tablets 24mg/day for 10 days.

Level 3 (Severe - attendance at hospital): Acute worsening of COPD that requires the patient to be admitted to hospital for treatment.

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			COPD Exacerbations (AE)
207499/157					

FURTHER DETAILS OF COPD EXACERBATIONS

COPD exacerbation onset date : Day Month Yr

Level of exacerbation (see definitions on facing page):

[1] ☐ Level 1
[2] ☐ Level 2
[3] ☐ Level 3

Pumonary function test result (FEV_1) (if done):

☐.☐☐ L

Did the patient suffer from any of the following during the exacerbation:

[1] ☐ Chest pain
[2] ☐ Upper Respiratory Tract Infection
[3] ☐ Confusion
[4] ☐ Change in alertness
[5] ☐ Pneumonia
[6] ☐ Oedema
[7] ☐ Ankle swelling

ARTERIAL BLOOD GASES (only for COPD exacerbations)

Where feasible, an arterial blood gas sample is to be taken for analysis

COPD exacerbation onset date : Day Month Yr

PO_2 (mmHg)	**PCO_2** (mmHg)	**pH**	**Resting SaO_2** (%)
☐☐☐	☐☐	☐.☐☐	☐☐☐

RESOURCE UTILISATION

Please complete the Resource Utilisation pages for this exacerbation.

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			COPD Exacerbations (AE)
207499/157		[redacted]			

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 last 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 Event	COPD EXACERBATION
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, STOP: delete details of this exacerbation and go to SAE COPD Exacerbation pages.***	[1] ☐ Resolved [2] ☐ Ongoing [3] ☐ Died
Event Course	[1] ☐ Intermittent → No. of episodes ☐ [2] ☐ Constant
Intensity (maximum) *See definitions page for Adverse Experiences form.*	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Action Taken with Respect to Investigational Drug	[1] ☐ None [2] ☐ Dose reduced [3] ☐ Dose increased [4] ☐ Drug interrupted/restarted [5] ☐ Drug stopped
Relationship to Investigational Drug	[1] ☐ Not related [2] ☐ Unlikely [3] ☐ Suspected (reasonable possibility) [4] ☐ Probable
Corrective Therapy *If 'Yes', record details on the COPD Medications or Procedures page*	☐ Yes ☐ No
Was patient withdrawn due to this specific event?	☐ Yes ☐ No

DEFINITIONS OF LEVELS OF EXACERBATION OF COPD

Level 1 (Mild-self treated): Acute worsening of COPD that is self-managed by the patient at home by increasing the dose of relief salbutamol medication by > 2 occasions/24 hour period on two or more consecutive days compared with their baseline (baseline = mean of last 10 days of run-in period) or use of other additional bronchodilator medication

Level 2 (Moderate- physician, investigator treated): Acute worsening of symptoms (cough, sputum production, breathlessness) requiring treatment with oral corticosteroids prescribed by a physician or primary care doctor, or as a result of hospital out-patient visit (including Emergency Room).

Exacerbations requiring oral corticosteroids will be treated with a standardised course of prednisolone or prednisone tablets 30mg/day for 10 days, or methylprednisolone tablets 24mg/day for 10 days.

Level 3 (Severe - attendance at hospital): Acute worsening of COPD that requires the patient to be admitted to hospital for treatment.

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			COPD Exacerbations (AE)
207499/157					

FURTHER DETAILS OF COPD EXACERBATIONS

COPD exacerbation onset date : Day Month Yr

Level of exacerbation (see definitions on facing page):

[1] ☐ Level 1
[2] ☐ Level 2
[3] ☐ Level 3

Pumonary function test result (FEV_1) (if done):

☐.☐☐ L

Did the patient suffer from any of the following during the exacerbation:

[1] ☐ Chest pain
[2] ☐ Upper Respiratory Tract Infection
[3] ☐ Confusion
[4] ☐ Change in alertness
[5] ☐ Pneumonia
[6] ☐ Oedema
[7] ☐ Ankle swelling

ARTERIAL BLOOD GASES (only for COPD exacerbations)

Where feasible, an arterial blood gas sample is to be taken for analysis

COPD exacerbation onset date : Day Month Yr

PO_2 (mmHg)	**PCO_2** (mmHg)	**pH**	**Resting SaO_2** (%)
☐☐☐	☐☐	☐.☐☐	☐☐☐

RESOURCE UTILISATION

Please complete the Resource Utilisation pages for this exacerbation.

SmithKline Beecham Pharmaceuticals

Protocol	Centre Number	Patient Number		SB Receipt Date (Day Month Year)	COPD Exacerbations (SAE)
207499/157		[redacted]			

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation

Person Reporting SAE _____ *(Please print clearly)*

AEGIS Number _____ . _____

Serious Adverse Experience	**COPD Exacerbation**
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*	[1] ☐ Resolved [2] ☐ Ongoing [3] ☐ Died
Experience Course	[1] ☐ Intermittent → No. of episodes ☐ [2] ☐ Constant
Intensity *(maximum)*	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Action Taken with Respect to Investigational Drug	[1] ☐ None [2] ☐ Dose reduced [3] ☐ Dose increased [4] ☐ Drug interrupted/ restarted [5] ☐ Drug stopped
Relationship to Investigational Drug	[1] ☐ Not related [2] ☐ Unlikely [3] ☐ Suspected (reasonable possibility) [4] ☐ Probable
Corrective Therapy *If 'Yes', record details in the COPD Concomitant Medication section*	☐ Yes ☐ No
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No

→ *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

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 _____

00000

SmithKline Beecham
Pharmaceuticals

Protocol	**Centre Number**	**Patient Number**		**SB Receipt Date** Day Month Year	**COPD Exacerbations (SAE)**
207499/157		[redacted]			

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation

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 Number (please do NOT enter the container number): ☐☐☐☐☐

Investigator's Signature: _____ Date ☐☐ ☐☐☐ ☐☐☐☐
(confirming that the above data are accurate and complete) Day Month Year

Please PRINT Name _____

SB Medical Monitor's Signature: _____ Date ☐☐ ☐☐☐ ☐☐☐☐
Day Month Year

Please PRINT Name _____

DEFINITIONS OF LEVELS OF EXACERBATION OF COPD

Level 1 (Mild-self treated): Acute worsening of COPD that is self-managed by the patient at home by increasing the dose of relief salbutamol medication by > 2 occasions/24 hour period on two or more consecutive days compared with their baseline (baseline = mean of last 10 days of run-in period) or use of other additional bronchodilator medication

Level 2 (Moderate- physician, investigator treated): Acute worsening of symptoms (cough, sputum production, breathlessness) requiring treatment with oral corticosteroids prescribed by a physician or primary care doctor, or as a result of hospital out-patient visit (including Emergency Room).

Exacerbations requiring oral corticosteroids will be treated with a standardised course of prednisolone or prednisone tablets 30mg/day for 10 days, or methylprednisolone tablets 24mg/day for 10 days.

Level 3 (Severe - attendance at hospital): Acute worsening of COPD that requires the patient to be admitted to hospital for treatment.

00000

SmithKline Beecham
Pharmaceuticals

Protocol	**Centre Number**	**Patient Number**		**SB Receipt Date** Day Month Year	**COPD Exacerbations (SAE)**
207499/157		[redacted]			

FURTHER DETAILS OF SERIOUS COPD EXACERBATIONS

COPD exacerbation onset date : Day Month Yr

Level of exacerbation (see definitions on facing page):

[1] ☐ Level 1
[2] ☐ Level 2
[3] ☐ Level 3

Pumonary function test result (FEV_1) (if done):

☐.☐☐ L

Did the patient suffer from any of the following during the exacerbation:

[1] ☐ Chest pain
[2] ☐ Upper Respiratory Tract Infection
[3] ☐ Confusion
[4] ☐ Change in alertness
[5] ☐ Pneumonia
[6] ☐ Oedema
[7] ☐ Ankle swelling

ARTERIAL BLOOD GASES (only for serious COPD exacerbations)

Where feasible, an arterial blood gas sample is to be taken for analysis

COPD exacerbation onset date : Day Month Yr

PO_2 (mmHg)	**PCO_2** (mmHg)	**pH**	**Resting SaO_2** (%)
☐☐☐	☐☐	☐.☐☐	☐☐☐

RESOURCE UTILISATION

Please complete the Resource Utilisation pages for this exacerbation.

SmithKline Beecham Pharmaceuticals

Protocol	Centre Number	Patient Number			COPD Exacerbations (ConMed)
207499/157		[redacted]			

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)	**Freq.** (eg bd, prn)	**Route***	**Medical Illness/ Diag.**	**Start Date** *(be as precise as possible)* Day Mth Yr	**End Date** *(or if Continuing mark box)* Day Mth Yr		COPD Exacerbation Onset Date
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								

** For Route, see General Instructions for acceptable abbreviations.*

SmithKline Beecham
Pharmaceuticals

Protocol	**Centre Number**	**Patient Number**			**COPD Exacerbations (ConMed)**
207499/157		[redacted]			

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** Day Mth Yr	**Procedure End Date** Day Mth Yr	COPD Exacerbation Onset Date
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				

SmithKline Beecham
Pharmaceuticals

Protocol	**Centre Number**	**Patient Number**			**Resource Utilisation For COPD Exacerbations**
207499/157		[redacted]			

RESOURCE UTILISATION FOR COPD EXACERBATIONS

Has the patient had any medical care for COPD Exacerbations that have occurred since the previous module?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below*

Has the patient had any **Physician contact** (COPD care excluding scheduled protocol visits) since the previous module?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below*

Date of Contact Day Mth Yr	Telephone	Home Visit		Office/ Practice	Out-patients	Reason for contact	COPD Exacerbation Onset Date Day Mth Yr
		Day	Night				

Has the patient had any **Emergency Room (ER)/Urgent Care Visits/Procedures (i.e., lung surgery)** since the previous module?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below*

Date of Contact Day Mth Yr	**Reason for contact**	**Patient Admitted from ER?**		COPD Exacerbation Onset Date Day Mth Yr
		Yes	**No**	

Protocol	Centre Number	Patient Number			Resource Utilisation For COPD Exacerbations
207499/157		[redacted]			

RESOURCE UTILISATION FOR COPD EXACERBATIONS - (cont)

Has the patient had any **Hospitalisations** since the previous module?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below* ***(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	COPD Exacerbation Onset Date Day Mth Yr

Has the patient had any **Intensive Care Unit (ICU) stays** ***(did the patient stay in the ICU during any of the above hospitalisations?)*** since the previous module?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below*

Date Admitted to ICU Day Mth Yr	Date Discharged from ICU Day Mth Yr	Reason for ICU Admission	COPD Exacerbation Onset Date Day Mth Yr

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			
207499/157		[redacted]			

2 0 7 4 9 9 1 5 7

MOD9

Please do not split modules

Module 9 : **Visit 12, Adverse Experiences, Concomitant Medications, Medical Procedures, COPD Exacerbations, Resource Utilisation**

CRF Pages **276 - 302**

Unprocessed Forms : **Within this module the following occur which will generate attachments that need to be brought in-house.**

None

FOR OFFICE USE ONLY Module Comments:

Sent to Data Mngt	Review Complete Date: User:	First Entry Complete Date: User:
Second Entry Complete Date: User:	Validation Complete Date: User:	**Clintrial PID:**

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number		Visit Date (Day Month Year)	
207499/157		[redacted]			**Visit 12 Week 52**

PRESENTATION TO CLINIC

Note: ***Patients must wait for 4 hours after beta$_2$-agonist and / or anticholinergic administration before the pulmonary function tests are performed.***

Did the patient take a dose of beta$_2$ agonist in the past 24 hours?

☐ No

☐ Yes → Record date and time of the patient's last dose of beta$_2$ agonist: Day Month Yr 24hr:min

Did the patient take a dose of anticholinergic in the past 24 hours?

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: Day Month Yr 24hr:min

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes → Date and time of patient's last cigarette Day Month Yr 24hr:min

SMOKING STATUS

Does the patient currently smoke?

☐ No

☐ Yes → If 'Yes' please record the average number of cigarettes per day :

INFLUENZA VACCINATION

Has the patient had a vaccination for influenza since the last visit?

N.B. It is not necessary to record vaccinations on the Concomitant Medication or Medical Procedures page.

☐ No

☐ Yes → *If 'Yes', record date of vaccination :* Day Month Yr

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number			Visit 12 Week 52
207499/157		[redacted]			

ST. GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND EQ-5D

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

INVESTIGATOR GLOBAL EVALUATION OF IMPROVEMENT

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

PATIENT GLOBAL EVALUATION OF IMPROVEMENT

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			Visit 12 Week 52
207499/157		[redacted]			

RESOLUTION OF COPD EXACERBATIONS

Have any COPD Exacerbations resolved since the last visit?

☐ No

☐ Yes ⟶ *If 'Yes', please record details in the COPD Exacerbation section at the back of this module.*

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes ⟶ *If 'Yes' please record details in the COPD Exacerbation section at the back of this module.*

Level 1 (Mild-self treated): Acute worsening of COPD that is self-managed by the patient at home by increasing the dose of relief salbutamol medication by > 2 occasions/24 hour period on two or more consecutive days compared with their baseline (baseline = mean of last 10 days of run-in period) or use of other additional bronchodilator medication

Level 2 (Moderate- physician, investigator treated): Acute worsening of symptoms (cough, sputum production, breathlessness) requiring treatment with oral corticosteroids prescribed by a physician or primary care doctor, or as a result of hospital out-patient visit (including Emergency Room).

Exacerbations requiring oral corticosteroids will be treated with a standardised course of prednisolone or prednisone tablets 30mg/day for 10 days, or methylprednisolone tablets 24mg/day for 10 days.

Level 3 (Severe - attendance at hospital): Acute worsening of COPD that requires the patient to be admitted to hospital for treatment.

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, including an increase in usual COPD medications, must be recorded in the COPD Medications or Procedures pages.

00000

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number			Visit 12 Week 52
207499/157		[redacted]			

RESOURCE UTILISATION

If the patient has received any COPD exacerbation-related medical care since the last visit, record details on the Resource Utilisation pages of the COPD Exacerbation section at the back of this module.

DIARY CARD REVIEW

Review the diary card in the presence of the patient. Question any increased symptoms for possible COPD exacerbations. Place diary in the plastic wallet at the back of this module.

ADVERSE EXPERIENCES

Please complete the Adverse Experiences 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 Experiences 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 Experiences section at the back of this module.*

Protocol		Patient Number			Visit 12 Week 52
207499/157		[redacted]			

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. bd)

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
140	☐☐	☐☐	☐☐	☐☐	☐☐☐

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance ≥ 80% and ≤120%?

☐ No

☐ Yes

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number			Visit 12 Week 52
207499/157		[redacted]			

INVESTIGATOR INSTRUCTIONS

The following procedures (Vital Signs, ECG and Pulmonary Function Tests) must be performed greater than 4 hours after the patient's last salbutamol administration.

VITAL SIGNS

Time of assessment : ☐☐ 24hr:min

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
☐☐☐/☐☐☐	☐☐☐

Are there any **clinically significant worsenings** since the previous visit?

☐ No

☐ Yes ⟶ *If 'Yes' please record the findings and/or diagnosis in the Adverse Experiences section at the back of this module.*

VITAL SIGNS - ORTHOSTATIC CHANGE

Time of assessment : ☐☐ 24hr:min

1st Measurement: After 5 Minutes Supine		2nd Measurement: 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)
☐☐☐/☐☐☐	☐☐☐	☐☐☐/☐☐☐	☐☐☐

Have there been any clinically significant worsenings since the last assessment?

☐ No

☐ Yes⟶ *If 'Yes', please record the findings in the Adverse Experiences section at the back of this module.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number			Visit 12 Week 52
207499/157		[redacted]			

12 LEAD ELECTROCARDIOGRAM

Time of assessment : ☐☐ 24hr:min **The ECG should be performed after the patient has been semi-supine for 5 minutes**

Date ECG Performed (Day Month Year)	Atrial Rate (beats/min)	Ventricular Rate (beats/min)	PR (msec)	QRS (msec)	☐ Uncorrected QT ☐ Corrected QT (msec)	Axis
☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐ + ☐ - ☐☐☐

Interpretation

☐ **(F74301) Within normal limits**

☐ **Abnormal** ⟶ ***Mark appropriate boxes below***

Rhythm
- ☐ (F73360) Sinus arrhythmia
- ☐ (F73310) Sinus bradycardia
- ☐ (F73380) Sinus tachycardia
- ☐ (F73440) Wandering atrial pacemaker
- ☐ (F73450) Premature atrial contractions
- ☐ (F73510) Paroxysmal atrial tachycardia
- ☐ (F73530) Chronic ectopic atrial tachycardia
- ☐ (F73550) Multifocal atrial tachycardia
- ☐ (F73560) Atrial flutter
- ☐ (F73570) Atrial fibrillation
- ☐ (F73610) Junctional (AV nodal) premature contractions
- ☐ (F73650) Junctional (AV nodal) tachycardia
- ☐ (F73150) Supraventricular tachycardia
- ☐ (F73860) Accelerated idioventricular rhythm
- ☐ (F73710) Premature Ventricular Contractions (NOS)
- ☐ (F73720) Unifocal PVC's
- ☐ (F73730) Multifocal PVC's
- ☐ (F73711) Ventricular couplets
- ☐ (F73750) Bigeminy
- ☐ (F73870) Ventricular tachycardia
- ☐ (F73880) Ventricular fibrillation
- ☐ (F73340) Sick sinus syndrome
- ☐ (F73190) Pacemaker rhythm

P-Wave Morphology
- ☐ (F74214) Left atrial hypertrophy, P mitrale
- ☐ (F74213) Right atrial hypertrophy, P pulmonale

Conduction
- ☐ (F73930) First degree AV block
- ☐ (F73950) Second degree AV block, Type 1
- ☐ (F73960) Second degree AV block, Type 11
- ☐ (F73970) Third degree AV block
- ☐ (F74090) Wolff-Parkinson-White syndrome

Axis
- ☐ (F74120) Right Axis deviation
- ☐ (F74130) Left Axis deviation

QRS
- ☐ (F74010) Right bundle branch block
- ☐ (F74020) Left bundle branch block
- ☐ (F74030) Left anterior hemiblock
- ☐ (F74040) Left posterior hemiblock
- ☐ (F74002) Intraventricular conduction delay
- ☐ (F74212) Left ventricular hypertrophy
- ☐ (F74211) Right ventricular hypertrophy
- ☐ (F74308) Q-wave > 0.04 sec
- ☐ (F74222) R-wave amplitude increased
- ☐ (F74225) R-wave amplitude decreased
- ☐ (F74313) Prolonged QT-interval
- ☐ (F74318) Poor R-wave progression
- ☐ (M54750) Myocardial infarction, old
  - ☐ (M54751) Anterior ☐ (M54754) Inferior
  - ☐ (M54752) Lateral ☐ (M54755) Septal
  - ☐ (M54753) Posterior

ST-T
- ☐ (F74291) Nonspecific ST-T changes
- ☐ (F74294) ST segment depression > 1 mm
- ☐ (F74295) ST segment elevation > 1 mm
- ☐ (F74350) T-wave flat
- ☐ (F74351) T-wave inversion
- ☐ (F74352) T-wave peaked
- ☐ (F74340) U-wave
- ☐ (F74360) Digitalis effect
- ☐ (F74260) Myocardial ischemia
  - ☐ (F74261) Anterior ☐ (F74264) Inferior
  - ☐ (F74262) Lateral ☐ (F74265) Septal
  - ☐ (F74263) Posterior
- ☐ (M54720) Myocardial infarction, acute
  - ☐ (M54721) Anterior ☐ (M54724) Inferior
  - ☐ (M54722) Lateral ☐ (M54725) Septal
  - ☐ (M54723) Posterior

Other interpretations not listed _

Were there any clinically important changes observed since the last assessment?

[1] ☐ No

[2] ☐ Yes ⟶ *If 'Yes', enter details on the Adverse Experiences page at the back of this module.*

Place the ECG trace in the plastic wallet a the back of this module

Protocol		Patient Number			Visit 12 Week 52
207499/157		[redacted]			

PRE-SALBUTAMOL PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed at least 4 hours after the last dose of inhaled beta$_2$-agonist or anticholinergic agent.

Measure the patient's pulmonary function up to eight times to obtain three acceptable readings using the spirometer provided by SB. ***(Note: Please follow instructions in the Spirometry Manual).*** *For each set of three FEV_1 measurements, one FEV_1 must be within 10% of the highest. Please record the results of the effort with the highest FEV_1 below.*

Measurement	Time	FEV_1 (L)	FVC (L)	FEF_{25-75} (L/sec)	PEF (L/min)
1	24hr:min	.	.	.	

Place the spirometry reports in the plasic wallet at the back of this module.

POST-SALBUTAMOL PULMONARY FUNCTION TESTS

Provide the patient with a salbutamol MDI and spacer. Administer 400 mcg (4 puffs) of salbutamol via MDI with a spacer.

Record the time of salbutamol inhalation 24hr:min

Wait 30 minutes

Measure the patient's pulmonary function up to eight times to obtain three acceptable readings using the spirometer provided by SB. ***(Note: Please follow instructions in the Spirometry Manual).*** *For each set of three FEV_1 measurements, one FEV_1 must be within 10% of the highest. Please record the results of the effort with the highest FEV_1 below.*

Measurement	Time	FEV_1 (L)	FVC (L)	FEF_{25-75} (L/sec)	PEF (L/min)
1	24hr:min	.	.	.	

Place spirometry reports in the plastic wallets at the back of this module.

(AT SELECTED CENTRES ONLY) RESIDUAL VOLUME BY BODY PLETHYSMOGRAPHY (PRE- AND POST-SALBUTAMOL)

Time of pre-salbutamol RV assessment: 24hr:min

Time of post-salbutamol RV assessment: 24hr:min

Pre-Salbutamol

$RV_{Box} = TLC_{Box} - \max(|SVC|, |FVC|)$

$RV_{(Box)} =$. (L)

Post-Salbutamol

$RV_{Box} = TLC_{Box} - \max(|SVC|, |FVC|)$

$RV_{(Box)} =$. (L)

Please attach plethysmography source data to the back of this page.

00000

SmithKline Beecham
Pharmaceuticals

Protocol		**Patient Number**			**Visit 12**
207499/157		[redacted]			**Week 52**

PULMONARY REHABILITATION PROGRAM

Has the patient entered a Pulmonary Rehabilitation Program 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,CD4/CD8 ratio, serum protein C) and a urine sample for urinalysis. Please refer to the instructions on the Quest shipping form and manual.

Blood Sample Date ☐☐ ☐☐☐ ☐☐
Day Month Yr

Attach a label from the 'Routine' laboratory requisition form used at this visit in the space below.

Attach label here

Are there any **clinically significant worsenings** since the last assessment?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experiences section at the back of this module.*

Protocol		Patient Number			Visit 12 Week 52
207499/157		[redacted]			

FAECAL OCCULT BLOOD TEST

The faecal occult blood test should be performed on three consecutive bowel movements closely spaced in time between Visits 11 and 12. Patients were not to collect samples during or until 3 days after a menstrual period or while they had bleeding hemorrhoids or blood in the urine. They were not to take aspirin or other non-steroidal anti-inflammatory drugs for 7 days prior to and during the test period, and they were 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.

Did the patient follow these instructions?

☐ No ⟶ *If 'No', please specify:* _

☐ Yes

Test	Date of Collection Day Mth Yr	Result of faecal occult blood test
1	☐☐ ☐☐☐ ☐☐	[NEG] ☐ Negative [POS] ☐ Positive
2	☐☐ ☐☐☐ ☐☐	[NEG] ☐ Negative [POS] ☐ Positive
3	☐☐ ☐☐☐ ☐☐	[NEG] ☐ Negative [POS] ☐ Positive

Are these findings clinically significant ?

☐ No

☐ Yes ⟶ *If 'Yes' please record the findings and/or diagnosis in the Adverse Experiences section at the back of this module.*

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 12

- *Please complete the Study Conclusion page at the back of this book.*
- *Ask the patient to return for the Safety Follow-Up Visit in 7+/-3 days. The patient may resume their previous COPD medications.*
- *Please issue the faecal occult blood test kit and ask the patient to follow the instructions provided on the kit and to bring it with them to the Follow-Up Visit.*

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 study procedures should be reported as a serious event

IF AN 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

g_ae_instr_01

SmithKline Beecham Pharmaceuticals

Protocol	Centre Number	Patient Number			Adverse Experiences
207499/157		[redacted]			

ADVERSE EXPERIENCES (Non-serious)

g_ae_01

*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 last visit?" 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).

☐ Please mark this box if no adverse experiences occurred since the last module

Adverse Experience *(please print clearly)*		
For SB		
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 SAE section and follow instructions given there***	[1] ☐ Resolved [2] ☐ Ongoing [3] ☐ Died	[1] ☐ Resolved [2] ☐ Ongoing [3] ☐ Died
Experience Course	[1] ☐ Intermittent → No. of episodes ☐ [2] ☐ Constant	[1] ☐ Intermittent → No. of episodes ☐ [2] ☐ Constant
Intensity (maximum)	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Action Taken with Respect to Investigational Drug	[1] ☐ None [2] ☐ Dose reduced [3] ☐ Dose increased [4] ☐ Drug interrupted/restarted [5] ☐ Drug stopped	[1] ☐ None [2] ☐ Dose reduced [3] ☐ Dose increased [4] ☐ Drug interrupted/restarted [5] ☐ Drug stopped
Relationship to Investigational Drug	[1] ☐ Not related [2] ☐ Unlikely [3] ☐ Suspected (reasonable possibility) [4] ☐ Probable	[1] ☐ Not related [2] ☐ Unlikely [3] ☐ Suspected (reasonable possibility) [4] ☐ Probable
Corrective Therapy *If 'Yes', record details in the Concomitant Medication section and/ or Medical Procedures section if appropriate*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No

SmithKline Beecham
Pharmaceuticals

Protocol	**Centre Number**	**Patient Number**			**Adverse Experiences**
207499/157		[redacted]			

ADVERSE EXPERIENCES (Non-serious) - Continued

g_ae_01

*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 last visit?"*
*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).

Adverse Experience *(please print clearly)*		
For SB		
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 SAE section and follow instructions given there***	[1] Resolved [2] Ongoing [3] Died	[1] Resolved [2] Ongoing [3] Died
Experience Course	[1] Intermittent → No. of episodes [2] Constant	[1] Intermittent → No. of episodes [2] Constant
Intensity (maximum)	[1] Mild [2] Moderate [3] Severe	[1] Mild [2] Moderate [3] Severe
Action Taken with Respect to Investigational Drug	[1] None [2] Dose reduced [3] Dose increased [4] Drug interrupted/restarted [5] Drug stopped	[1] None [2] Dose reduced [3] Dose increased [4] Drug interrupted/restarted [5] Drug stopped
Relationship to Investigational Drug	[1] Not related [2] Unlikely [3] Suspected (reasonable possibility) [4] Probable	[1] Not related [2] Unlikely [3] Suspected (reasonable possibility) [4] Probable
Corrective Therapy *If 'Yes', record details in the Concomitant Medication section and/ or Medical Procedures section if appropriate*	Yes No	Yes No
Was patient withdrawn due to this specific AE?	Yes No	Yes No

SmithKline Beecham
Pharmaceuticals

Protocol **207499/157**	**Centre Number**	**Patient Number**			**Adverse Experiences**

ADVERSE EXPERIENCES (Non-serious) - Continued

g_ae_01

*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 last visit?" 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).

Adverse Experience *(please print clearly)*		
For SB		
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 SAE section and follow instructions given there***	[1] Resolved [2] Ongoing [3] Died	[1] Resolved [2] Ongoing [3] Died
Experience Course	[1] Intermittent → No. of episodes [2] Constant	[1] Intermittent → No. of episodes [2] Constant
Intensity (maximum)	[1] Mild [2] Moderate [3] Severe	[1] Mild [2] Moderate [3] Severe
Action Taken with Respect to Investigational Drug	[1] None [2] Dose reduced [3] Dose increased [4] Drug interrupted/restarted [5] Drug stopped	[1] None [2] Dose reduced [3] Dose increased [4] Drug interrupted/restarted [5] Drug stopped
Relationship to Investigational Drug	[1] Not related [2] Unlikely [3] Suspected (reasonable possibility) [4] Probable	[1] Not related [2] Unlikely [3] Suspected (reasonable possibility) [4] Probable
Corrective Therapy *If 'Yes', record details in the Concomitant Medication section and/ or Medical Procedures section if appropriate*	Yes No	Yes No
Was patient withdrawn due to this specific AE?	Yes No	Yes No

Protocol	Centre Number	Patient Number			Concomitant Medication
207499/157		[redacted]			

CONCOMITANT MEDICATION

Record any changes in concomitant medication taken since the last 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. At the patient's final study visit, record the end date for prn study rescue medication (salbutamol) use, using the date the study inhaler was returned.

☐ No concomitant medication changes since the last module

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded in the Adverse Experiences 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** (eg 500mg)	**Frequency** (eg bd, 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	
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							

** For Route, see general instructions for acceptable abbreviations.*

00000

SmithKline Beecham
Pharmaceuticals

Protocol	**Centre Number**	**Patient Number**			**Concomitant Medication**
207499/157		[redacted]			

CONCOMITANT MEDICATION (Cont.)

Do not record any medication taken for COPD exacerbations in this section. Record all COPD exacerbation medication in the COPD Exacerbation section. At the patient's final study visit, record the end date for prn study rescue medication (salbutamol) use, using the date the study inhaler was returned.

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded in the Adverse Experiences 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** (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	
For SB							
For SB							
For SB							
For SB							
For SB							
For SB							
For SB							
For SB							
For SB							
For SB							

** For Route, see general instructions for acceptable abbreviations.*

g_conmed_01

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			Medical Procedures
207499/157		[redacted]			

MEDICAL PROCEDURES

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 last module?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below using standard medical terminology*

All indications for procedures should be recorded on the Adverse Experiences Form.

Procedure	Indication	Procedure Start Date Day Mth Yr	Procedure End Date Day Mth Yr
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			

SmithKline Beecham Pharmaceuticals

Protocol	Centre Number	Patient Number			COPD Exacerbations (AE)
207499/157		[redacted]			

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 last 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***

Has the patient suffered any COPD Exacerbations since the last module ?

☐ No

☐ Yes → *If 'Yes', please complete page below*

Adverse Event	COPD EXACERBATION
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, STOP: delete details of this exacerbation and go to SAE COPD Exacerbation pages.***	[1] ☐ Resolved [2] ☐ Ongoing [3] ☐ Died
Event Course	[1] ☐ Intermittent → No. of episodes ☐ [2] ☐ Constant
Intensity (maximum) *See definitions page for Adverse Experiences form.*	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Action Taken with Respect to Investigational Drug	[1] ☐ None [2] ☐ Dose reduced [3] ☐ Dose increased [4] ☐ Drug interrupted/restarted [5] ☐ Drug stopped
Relationship to Investigational Drug	[1] ☐ Not related [2] ☐ Unlikely [3] ☐ Suspected (reasonable possibility) [4] ☐ Probable
Corrective Therapy *If 'Yes', record details on the COPD Medications or Procedures page*	☐ Yes ☐ No
Was patient withdrawn due to this specific event?	☐ Yes ☐ No

DEFINITIONS OF LEVELS OF EXACERBATION OF COPD

Level 1 (Mild-self treated): Acute worsening of COPD that is self-managed by the patient at home by increasing the dose of relief salbutamol medication by > 2 occasions/24 hour period on two or more consecutive days compared with their baseline (baseline = mean of last 10 days of run-in period) or use of other additional bronchodilator medication

Level 2 (Moderate- physician, investigator treated): Acute worsening of symptoms (cough, sputum production, breathlessness) requiring treatment with oral corticosteroids prescribed by a physician or primary care doctor, or as a result of hospital out-patient visit (including Emergency Room).

Exacerbations requiring oral corticosteroids will be treated with a standardised course of prednisolone or prednisone tablets 30mg/day for 10 days, or methylprednisolone tablets 24mg/day for 10 days.

Level 3 (Severe - attendance at hospital): Acute worsening of COPD that requires the patient to be admitted to hospital for treatment.

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			COPD Exacerbations (AE)
207499/157					

FURTHER DETAILS OF COPD EXACERBATIONS

COPD exacerbation onset date : Day Month Yr

Level of exacerbation (see definitions on facing page):

[1] ☐ Level 1
[2] ☐ Level 2
[3] ☐ Level 3

Pumonary function test result (FEV_1) (if done):

☐.☐☐ L

Did the patient suffer from any of the following during the exacerbation:

[1] ☐ Chest pain
[2] ☐ Upper Respiratory Tract Infection
[3] ☐ Confusion
[4] ☐ Change in alertness
[5] ☐ Pneumonia
[6] ☐ Oedema
[7] ☐ Ankle swelling

ARTERIAL BLOOD GASES (only for COPD exacerbations)

Where feasible, an arterial blood gas sample is to be taken for analysis

COPD exacerbation onset date : Day Month Yr

PO_2 (mmHg)	**PCO_2** (mmHg)	**pH**	**Resting SaO_2** (%)
☐☐☐	☐☐	☐.☐☐	☐☐☐

RESOURCE UTILISATION

Please complete the Resource Utilisation pages for this exacerbation.

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			COPD Exacerbations (AE)
207499/157		[redacted]			

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 last 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 Event	COPD EXACERBATION
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, STOP: delete details of this exacerbation and go to SAE COPD Exacerbation pages.***	[1] ☐ Resolved [2] ☐ Ongoing [3] ☐ Died
Event Course	[1] ☐ Intermittent → No. of episodes ☐ [2] ☐ Constant
Intensity (maximum) *See definitions page for Adverse Experiences form.*	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Action Taken with Respect to Investigational Drug	[1] ☐ None [2] ☐ Dose reduced [3] ☐ Dose increased [4] ☐ Drug interrupted/restarted [5] ☐ Drug stopped
Relationship to Investigational Drug	[1] ☐ Not related [2] ☐ Unlikely [3] ☐ Suspected (reasonable possibility) [4] ☐ Probable
Corrective Therapy *If 'Yes', record details on the COPD Medications or Procedures page*	☐ Yes ☐ No
Was patient withdrawn due to this specific event?	☐ Yes ☐ No

DEFINITIONS OF LEVELS OF EXACERBATION OF COPD

Level 1 (Mild-self treated): Acute worsening of COPD that is self-managed by the patient at home by increasing the dose of relief salbutamol medication by > 2 occasions/24 hour period on two or more consecutive days compared with their baseline (baseline = mean of last 10 days of run-in period) or use of other additional bronchodilator medication

Level 2 (Moderate- physician, investigator treated): Acute worsening of symptoms (cough, sputum production, breathlessness) requiring treatment with oral corticosteroids prescribed by a physician or primary care doctor, or as a result of hospital out-patient visit (including Emergency Room).

Exacerbations requiring oral corticosteroids will be treated with a standardised course of prednisolone or prednisone tablets 30mg/day for 10 days, or methylprednisolone tablets 24mg/day for 10 days.

Level 3 (Severe - attendance at hospital): Acute worsening of COPD that requires the patient to be admitted to hospital for treatment.

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			COPD Exacerbations (AE)
207499/157					

FURTHER DETAILS OF COPD EXACERBATIONS

COPD exacerbation onset date : Day Month Yr

Level of exacerbation (see definitions on facing page):

[1] ☐ Level 1
[2] ☐ Level 2
[3] ☐ Level 3

Pumonary function test result (FEV_1) (if done):

☐.☐☐ L

Did the patient suffer from any of the following during the exacerbation:

[1] ☐ Chest pain
[2] ☐ Upper Respiratory Tract Infection
[3] ☐ Confusion
[4] ☐ Change in alertness
[5] ☐ Pneumonia
[6] ☐ Oedema
[7] ☐ Ankle swelling

ARTERIAL BLOOD GASES (only for COPD exacerbations)

Where feasible, an arterial blood gas sample is to be taken for analysis

COPD exacerbation onset date : Day Month Yr

PO_2 (mmHg)	**PCO_2** (mmHg)	**pH**	**Resting SaO_2** (%)
☐☐☐	☐☐	☐.☐☐	☐☐☐

RESOURCE UTILISATION

Please complete the Resource Utilisation pages for this exacerbation.

SmithKline Beecham Pharmaceuticals

Protocol	Centre Number	Patient Number		SB Receipt Date (Day Month Year)	COPD Exacerbations (SAE)
207499/157		[redacted]			

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation

Person Reporting SAE _____ *(Please print clearly)*

AEGIS Number _____ . _____

Serious Adverse Experience	**COPD Exacerbation**
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*	[1] ☐ Resolved [2] ☐ Ongoing [3] ☐ Died
Experience Course	[1] ☐ Intermittent → No. of episodes ☐ [2] ☐ Constant
Intensity *(maximum)*	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Action Taken with Respect to Investigational Drug	[1] ☐ None [2] ☐ Dose reduced [3] ☐ Dose increased [4] ☐ Drug interrupted/ restarted [5] ☐ Drug stopped
Relationship to Investigational Drug	[1] ☐ Not related [2] ☐ Unlikely [3] ☐ Suspected (reasonable possibility) [4] ☐ Probable
Corrective Therapy *If 'Yes', record details in the COPD Concomitant Medication section*	☐ Yes ☐ No
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No

→ *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

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 _____

00000

SmithKline Beecham
Pharmaceuticals

Protocol	**Centre Number**	**Patient Number**		**SB Receipt Date** Day Month Year	**COPD Exacerbations (SAE)**
207499/157		[redacted]			

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation

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 Number (please do NOT enter the container number): ☐☐☐☐☐

Investigator's Signature: _____ Date ☐☐ ☐☐ ☐☐☐☐
(confirming that the above data are accurate and complete) Day Month Year

Please PRINT Name _____

SB Medical Monitor's Signature: _____ Date ☐☐ ☐☐ ☐☐☐☐

Please PRINT Name _____ Day Month Year

DEFINITIONS OF LEVELS OF EXACERBATION OF COPD

Level 1 (Mild-self treated): Acute worsening of COPD that is self-managed by the patient at home by increasing the dose of relief salbutamol medication by > 2 occasions/24 hour period on two or more consecutive days compared with their baseline (baseline = mean of last 10 days of run-in period) or use of other additional bronchodilator medication

Level 2 (Moderate- physician, investigator treated): Acute worsening of symptoms (cough, sputum production, breathlessness) requiring treatment with oral corticosteroids prescribed by a physician or primary care doctor, or as a result of hospital out-patient visit (including Emergency Room).

Exacerbations requiring oral corticosteroids will be treated with a standardised course of prednisolone or prednisone tablets 30mg/day for 10 days, or methylprednisolone tablets 24mg/day for 10 days.

Level 3 (Severe - attendance at hospital): Acute worsening of COPD that requires the patient to be admitted to hospital for treatment.

00000

SmithKline Beecham
Pharmaceuticals

Protocol	**Centre Number**	**Patient Number**		**SB Receipt Date** Day Month Year	**COPD Exacerbations (SAE)**
207499/157		[redacted]			

FURTHER DETAILS OF SERIOUS COPD EXACERBATIONS

COPD exacerbation onset date : Day Month Yr

Level of exacerbation (see definitions on facing page):

[1] ☐ Level 1
[2] ☐ Level 2
[3] ☐ Level 3

Pumonary function test result (FEV_1) (if done):

☐.☐☐ L

Did the patient suffer from any of the following during the exacerbation:

[1] ☐ Chest pain
[2] ☐ Upper Respiratory Tract Infection
[3] ☐ Confusion
[4] ☐ Change in alertness
[5] ☐ Pneumonia
[6] ☐ Oedema
[7] ☐ Ankle swelling

ARTERIAL BLOOD GASES (only for serious COPD exacerbations)

Where feasible, an arterial blood gas sample is to be taken for analysis

COPD exacerbation onset date : Day Month Yr

PO_2 (mmHg)	**PCO_2** (mmHg)	**pH**	**Resting SaO_2** (%)
☐☐☐	☐☐	☐.☐☐	☐☐☐

RESOURCE UTILISATION

Please complete the Resource Utilisation pages for this exacerbation.

SmithKline Beecham
Pharmaceuticals

Protocol	**Centre Number**	**Patient Number**			**COPD Exacerbations (ConMed)**
207499/157		[redacted]			

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)	**Freq.** (eg bd, prn)	**Route***	**Medical Illness/ Diag.**	**Start Date** *(be as precise as possible)* Day Mth Yr	**End Date** *(or if Continuing mark box)* Day Mth Yr		COPD Exacerbation Onset Date
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								

** For Route, see General Instructions for acceptable abbreviations.*

Protocol	**Centre Number**	**Patient Number**			**COPD Exacerbations (ConMed)**
207499/157		[redacted]			

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** Day Mth Yr	**Procedure End Date** Day Mth Yr	COPD Exacerbation Onset Date
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				

SmithKline Beecham
Pharmaceuticals

Protocol	**Centre Number**	**Patient Number**			**Resource Utilisation For COPD Exacerbations**
207499/157		[redacted]			

RESOURCE UTILISATION FOR COPD EXACERBATIONS

Has the patient had any medical care for COPD Exacerbations that have occurred since the previous module?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below*

Has the patient had any **Physician contact** (COPD care excluding scheduled protocol visits) since the previous module?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below*

Date of Contact Day Mth Yr	Telephone	Home Visit		Office/ Practice	Out-patients	Reason for contact	COPD Exacerbation Onset Date Day Mth Yr
		Day	Night				

Has the patient had any **Emergency Room (ER)/Urgent Care Visits/Procedures (i.e., lung surgery)** since the previous module?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below*

Date of Contact Day Mth Yr	**Reason for contact**	**Patient Admitted from ER?**		COPD Exacerbation Onset Date Day Mth Yr
		Yes	**No**	

Protocol	Centre Number	Patient Number			Resource Utilisation For COPD Exacerbations
207499/157		[redacted]			

RESOURCE UTILISATION FOR COPD EXACERBATIONS - (cont)

Has the patient had any **Hospitalisations** since the previous module?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below* ***(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	COPD Exacerbation Onset Date Day Mth Yr

Has the patient had any **Intensive Care Unit (ICU) stays** ***(did the patient stay in the ICU during any of the above hospitalisations?)*** since the previous module?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below*

Date Admitted to ICU Day Mth Yr	Date Discharged from ICU Day Mth Yr	Reason for ICU Admission	COPD Exacerbation Onset Date Day Mth Yr

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			
207499/157					

2 0 7 4 9 9 1 5 7

CONC4

Please do not split modules

Module : **Study Conclusion**

CRF Pages **303**

Unprocessed Forms : **Within this module the following occur which will generate attachments that need to be brought in-house.**

None

FOR OFFICE USE ONLY Module Comments:

Sent to Data Mngt	Review Complete Date: User:	First Entry Complete Date: User:
Second Entry Complete Date: User:	Validation Complete Date: User:	**Clintrial PID:**

Protocol	Centre Number	Patient Number			Study Conclusion
207499/157		[redacted]			

STUDY CONCLUSION

Did the patient complete the study according to the protocol? ***(For patients who have withdrawn from study medication but are continuing with essential assessment visits, please mark 'No' and the primary reason for withdrawal)***

☐ Yes

☐ No → If 'No', please mark the **primary** cause of withdrawal. *(Mark one box only).*

[1] ☐ Adverse Experience *(please complete Adverse Experiences page)*

[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

g_stud_conc_01
Date of final dose ☐☐ ☐☐☐ ☐☐ Day Month Yr

INVESTIGATOR SIGNATURE

I certify that I have reviewed the data on this case report form, including laboratory data and that in the Baseline Signs and Symptoms, Adverse Experiences and Serious Adverse Experiences sections (if appropriate) and that all information is complete and accurate.

Investigator's Signature _____ Date ☐☐ ☐☐☐ ☐☐ Day Month Yr

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			
207499/157		[redacted]			

2 0 7 4 9 9 1 5 7

SAE4

Please do not split modules

Module : **Serious Adverse Experiences**

CRF Pages **304 - 305**

Unprocessed Forms : **Within this module the following occur which will generate attachments that need to be brought in-house.**

None

FOR OFFICE USE ONLY Module Comments:

Sent to Data Mngt	Review Complete Date: User:	First Entry Complete Date: User:
Second Entry Complete Date: User:	Validation Complete Date: User:	**Clintrial PID:**

REPORTING SERIOUS ADVERSE EXPERIENCES (SAE)

INSTRUCTIONS

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

g_sae_instr_01

SmithKline Beecham Pharmaceuticals

Protocol	Centre Number	Patient Number		SB Receipt Date (Day Month Year)	Serious Adverse Experiences
207499/157		[redacted]			

SERIOUS ADVERSE EXPERIENCE (SAE)

Person Reporting SAE *(Please print clearly)* _

AEGIS Number _ _ _ _ _ _ _ _ . _

Serious Adverse Experience *(Please print clearly)*

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*
[1] ☐ Resolved
[2] ☐ Ongoing
[3] ☐ Died

Experience Course
[1] ☐ Intermittent → No. of episodes ☐
[2] ☐ Constant

Intensity *(maximum)*
[1] ☐ Mild
[2] ☐ Moderate
[3] ☐ Severe

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

Action Taken with Respect to Investigational Drug
[1] ☐ None
[2] ☐ Dose reduced
[3] ☐ Dose increased
[4] ☐ Drug interrupted restarted
[5] ☐ 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
[1] ☐ Not related
[2] ☐ Unlikely
[3] ☐ Suspected (reasonable possibility)
[4] ☐ 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

g_sae_01

00000

SmithKline Beecham Pharmaceuticals

Protocol	Centre Number	Patient Number		SB Receipt Date (Day Month Year)	Serious Adverse Experiences
207499/157		[redacted]			

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 Number (please do NOT enter the container number): ☐☐☐☐☐

Investigator's Signature: _____ Date ☐☐ ☐☐ ☐☐
(confirming that the above data are accurate and complete) Day Month Year

Please PRINT Name _____

SB Medical Monitor's Signature: _____ Date ☐☐ ☐☐ ☐☐

Please PRINT Name _____ Day Month Year

g_sae_01

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			
207499/157					

2 0 7 4 9 9 1 5 7

RPLAB7

Please do not split modules

Module: **Repeat / unscheduled laboratory assessments**

CRF Pages: **306**

Unprocessed Forms: **Within this module, the following tests / procedures occur which may generate attachments.**

None

FOR OFFICE USE ONLY Module Comments:

Sent to Data Mngt	Review Complete Date: User:	First Entry Complete Date: User:
Second Entry Complete Date: User:	Validation Complete Date: User:	**Clintrial PID:**

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			Repeat / Unscheduled Lab Tests
207499/157		[redacted]			

REPEAT / UNSCHEDULED LABORATORY TESTS

Visit Number (or last scheduled visit number): ☐☐ Sample Date ☐☐ ☐☐ ☐☐
Day Month Yr

Please take blood samples for hematology and/or blood chemistry (including serum beta-HCG for women of child-bearing potential) and/or a urine sample for urinalysis. Please refer to the instructions on the Quest shipping form and manual.

Please attach Central Lab CRF label here

(Attach label when sample is sent to central lab.)

Laboratory reports will stay at the site as part of the patient's source documentation.

Request βhCG test on Quest requisition for women of child-bearing potential. If the pregnancy test is positive, please withdraw the patient and complete the Serious Adverse Experiences form and forward it to SB within 24 hours.

Are there any **clinically significant** worsenings since the last assessment?

☐ No

☐ Yes ⟶ *If 'Yes', please record the findings and/or diagnosis in the Adverse Experiences section.*

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			
207499/157		[redacted]			

2 0 7 4 9 9 1 5 7

RPLAB8

Please do not split modules

Module: **Repeat / unscheduled laboratory assessments**

CRF Pages: **307**

Unprocessed Forms: **Within this module, the following tests / procedures occur which may generate attachments.**

None

FOR OFFICE USE ONLY Module Comments:

Sent to Data Mngt	Review Complete Date: User:	First Entry Complete Date: User:
Second Entry Complete Date: User:	Validation Complete Date: User:	**Clintrial PID:**

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			Repeat / Unscheduled Lab Tests
207499/157		[redacted]			

REPEAT / UNSCHEDULED LABORATORY TESTS

Visit Number (or last scheduled visit number): ☐☐ Sample Date ☐☐ ☐☐☐ ☐☐ Day Month Yr

Please take blood samples for hematology and/or blood chemistry (including serum beta-HCG for women of child-bearing potential) and/or a urine sample for urinalysis. Please refer to the instructions on the Quest shipping form and manual.

Please attach Central Lab CRF label here

(Attach label when sample is sent to central lab.)

Laboratory reports will stay at the site as part of the patient's source documentation.

Request βhCG test on Quest requisition for women of child-bearing potential. If the pregnancy test is positive, please withdraw the patient and complete the Serious Adverse Experiences form and forward it to SB within 24 hours.

Are there any **clinically significant** worsenings since the last assessment?

☐ No

☐ Yes ⟶ *If 'Yes', please record the findings and/or diagnosis in the Adverse Experiences section.*

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number		Investigator
207499/157		[redacted]		_ _

CRF TRACKING/REVIEW FORM (TRF) (BOOK 4)

Please submit COMPLETE modules only. Do not submit whole blank modules.

- *Mark the **Unused** box for all remaining modules that will **not** be completed and sent in-house*
- *Ensure the Missing Pages field is completed if pages are missing from modules*
- *Ensure the Patient Numbers entered match the information on the CRF*
- *Complete one TRF per batch of modules to be sent in-house*
- *Ensure all sections of the TRF are legible*

Module	Module Description	Page Range	Modules		Missing pages (if applicable)
			Sent to DM	Unused	
DIA10	Visit 10 Patient diary	1 - 6	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
MOD8	V11, AE, CM, Med Pro, COPD, RU	246 - 275	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
PFT10	Visit 11 PFT printout	n/a	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
DIA11	Visit 11 Patient diary	1 - 6	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
MOD9	V12, AE, CM, Med Pro, COPD, RU	276 - 302	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
ECG5	Visit 12 ECG Trace	n/a	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
PFT11	Visit 12 PFT printout	n/a	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
DIA12	Visit 12 Patient diary	1 - 6	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
SGRQ3	Visit 12 SGRQ	SG1-SG5	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
EQ5D3	Visit 12 EQ-5D	EQ1-EQ2	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
CONC4	Study Conclusion	303	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
SAE4	Serious Adverse Experiences	304 - 305	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
RPLAB7	Repeat Labs	306	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
RPLAB8	Repeat Labs	307	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
FORMD	Form D	n/a	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _

If multiple modules are submitted together, please ensure they are sorted according to the order above

Site Monitor's Name _ *(Print clearly)*

Site Monitor's Signature _ **Date Submitted** ☐☐ ☐☐ ☐☐ Day Month Yr

g_trf_01

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number		Investigator
207499/157		[redacted]		_____

CRF TRACKING/REVIEW FORM (TRF) (BOOK 4)

Site Monitor's comments (eg. protocol violations or deviations)

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

Site Monitor's Name _____ *(Print clearly)*

Site Monitor's Signature _____ **Date Submitted** | | | | Day Month Yr

g_trf_01

Protocol		Patient Number			Early Withdrawal
207499/157		[redacted]			

FAECAL OCCULT BLOOD TEST

The faecal occult blood test should be performed on three consecutive bowel movements or on bowel movements closely spaced in time between Early Withdrawal and the Follow-Up Visit. Patients were not to collect samples during or until 3 days after a menstrual period or while they had bleeding hemorrhoids or blood in the urine. They were not to take aspirin or other non-steroidal anti-inflammatory drugs for 7 days prior to and during the test period, and they were 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.

Did the patient follow these instructions?

☐ No ⟶ *If 'No', please specify:* _

☐ Yes

Test	Date of Collection Day Mth Yr	Result of faecal occult blood test
1	☐☐ ☐☐ ☐☐	[NEG] ☐ Negative [POS] ☐ Positive
2	☐☐ ☐☐ ☐☐	[NEG] ☐ Negative [POS] ☐ Positive
3	☐☐ ☐☐ ☐☐	[NEG] ☐ Negative [POS] ☐ Positive

Are these findings clinically significant ?

☐ No

☐ Yes ⟶ *If 'Yes' please record the findings and/or diagnosis in the Adverse Experiences section at the back of this module.*

SmithKline Beecham
Pharmaceuticals

Protocol		**Patient Number**			**Early Withdrawal**
207499/157		[redacted]			

INSTRUCTIONS TO THE INVESTIGATOR AT EARLY WITHDRAWAL

Is the patient willing to return for essential assessments?

☐ No

☐ Yes

If 'No', please schedule a Safety Follow-Up Visit in 7 (+/-3) days time and complete the Study Conclusion page at the back of this module.

If 'Yes', please schedule a Safety Follow-up visit in 7 (+/-3) days time, complete the Study Conclusion page at the back of this module and then ask the patient to return for the next scheduled visit.

*If the patient **will** return for essential assessments, please :*

		(tick if done)
•	***Remind the patient:***	☑
i	*to refrain from using salbutamol or anticholinergic agents during the **4 hours** immediately preceding the next visit.*	☐
ii	*to refrain from smoking for **2 hours** immediately preceding the visit.*	☐
iii	*to bring the study salbutamol inhaler and spacer, and the diary card.*	☐
iv	*to continue to take the anticholinergic medication, if prescribed, at a constant dose, and salbutamol when needed to control symptoms.*	☐
v	*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 occurrence.*	☐
vi	*Issue the patient with the faecal occult blood test kit. Instruct the patient to follow the Patient Instructions provided with the kit. In particular, patients are not to collect samples during or until 3 days after a menstrual period or while they have bleeding hemorrhoids or blood in the urine. In addition, patients are not to take aspirin or other non-steroidal anti-inflammatory drugs for 7 days prior to and during the test period, and they are 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. Samples should be collected as specified and returned by the Safety Follow-up visit.*	☐

Protocol	Centre Number	Patient Number
207499/157		[redacted]

CONFIDENTIAL

SmithKline Beecham
Pharmaceuticals

PROTOCOL 207499/157

EARLY WITHDRAWAL/ SAFETY FOLLOW-UP

A RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL GROUP STUDY TO EVALUATE THE EFFICACY, SAFETY AND TOLERABILITY OF ORAL CILOMILAST (15 MG BID) WHEN GIVEN AS MAINTENANCE TREATMENT FOR 12 MONTHS TO SUBJECTS 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 and centre number on all pages 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 | *= 1st January 2001*
Day Month Year

TIME

Unless specified otherwise, please use the 24 hour clock

e.g. | 1 5 | 3 0 | *= 3.30 p.m*
24hr:min

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*

SCHEDULE OF ASSESSMENTS

Visit	1	2	3	4	5	6	7	8	9	10	11	12		13
	Screen		Base-line									End of DB	Early With-drawal	Follow -up
Time relative to baseline (weeks)[1]	-4	-2	0	+2	+4	+8	+12	+20	+28	+36	+44	+52		+53
Signed written informed consent	x													
Medical & surgical history	x													
Pulmonary symptoms	x													
Postero-anterior chest X-ray[2]	x													
Medication history including influenza vaccination[3]	x													
Health Status Assessments: SGRQ and EQ-5D			x						x			x	x	
Patient global assessment			x						x			x	x	
Investigator global assessment			x						x			x	x	
Physical examination [4]	x		x									x	x	x[5]
Smoking status	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Exacerbation assessment	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Resource utilisation				x	x	x	x	x	x	x	x	x	x	x
Diary Card Review		x	x	x	x	x	x	x	x	x	x	x	x	
Baseline signs and symptoms [6]	x	x	x											
Adverse experiences [6]				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
Study medication compliance		x	x	x	x	x	x	x	x	x	x	x	x	
Resting 12-lead ECG	x		x				x		x			x	x	x[5]
Vital signs (BP, HR)[7]	x[7]	x	x[7]	x	x	x	x[7]	x	x[7]	x	x	x[7]	x[7]	x
PFTs pre and post salbutamol: Pre-dose [8]	x		x		x	x	x	x	x	x	x	x	x	x
PFTs: salbutamol reversibility [9]	x		x											
PFTs: ipratropium reversibility		x												
Residual Volume (body box) pre-/ post-salbutamol Selected sites only			x						x			x	x	
Laboratory tests	x		x[10]		x	x	x	x	x	x	x	x[10]	x[10]	x[5]
Faecal occult blood test [11]	x	x										x	x	
Dispense single-blind med	x[12]	x[13]												
Dispense double-blind med			x[14]	x[13]	x[15]	x[15]	x[15]	x[15]	x[15]	x[15]	x[15]			
Study conclusion record														x[16]

1 All visit dates must be scheduled at the visit interval listed here using the Baseline visit as Day 0.
2 Chest X-ray to be taken at entry to the run-in period or in the 3 months prior to entry to the run-in period
3 Details of 'flu vaccinations will be recorded at every visit
4 Includes respiratory examination.
5 Only if abnormalities are present at Visit 12/Early Withdrawal.
6 Does not include COPD exacerbations
7 Orthostatic vital signs to be measured at Visits 1, 3, 7, 9, and 12
8 Includes FEV_1, FVC, FEF_{25-75} and PEF measured by spirometry by the same study personnel at each visit before dose of study medication is taken.
9 Includes FEV_1, FVC, FEF_{25-75} and PEF measured by spirometry by the same study personnel at each visit 30 minutes after administration of 400 mcg of salbutamol via MDI with or without a spacer, and before dose of study medication is taken.
10 Includes Blood CD4+/CD8+ ratio and serum C Reactive Protein
11 In addition to the usual laboratory tests, three faecal occult blood tests will be performed between Visits 1 and 3, at the end of the treatment period and at Early Withdrawal
12 Register the patient with RAMOS.
13 The container of study medication issued at the previous visit will be re-issued at this visit
14 Call RAMOS to randomise the patient and to obtain study medication assignment and container number.
15 Call RAMOS to obtain study medication container number(s)
16 Or earlier if the subject withdraws from the study prior to Visit 12.

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			
207499/157		[redacted]			

2 0 7 4 9 9 1 5 7

MODEW

Please do not split modules

Module EW : **Early Withdrawal**

CRF Pages **308 - 319**

Unprocessed Forms : **Within this module the following occur which will generate attachments that need to be brought in-house.**

None

FOR OFFICE USE ONLY Module Comments:

Sent to Data Mngt	Review Complete Date: User:	First Entry Complete Date: User:
Second Entry Complete Date: User:	Validation Complete Date: User:	**Clintrial PID:**

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number		Visit Date (Day Month Year)	
207499/157		[redacted]			**Early Withdrawal**

PRESENTATION TO CLINIC

Note: ***Patients must wait for 4 hours after beta$_2$-agonist and / or anticholinergic administration before the pulmonary function tests are performed.***

Did the patient take a dose of beta$_2$ agonist in the past 24 hours?

☐ No

☐ Yes → Record date and time of the patient's last dose of beta$_2$ agonist: Day Month Yr 24hr:min

Did the patient take a dose of anticholinergic in the past 24 hours?

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: Day Month Yr 24hr:min

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes → Date and time of patient's last cigarette Day Month Yr 24hr:min

SMOKING STATUS

Does the patient currently smoke?

☐ No

☐ Yes → If 'Yes' please record the average number of cigarettes per day :

00000

SmithKline Beecham
Pharmaceuticals

Protocol		**Patient Number**			**Early Withdrawal**
207499/157		[redacted]			

ST. GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND EQ-5D

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

INFLUENZA VACCINATION

Has the patient had a vaccination for influenza since the last visit?

N.B. It is not necessary to record vaccinations on the Concomitant Medication or Medical Procedures page.

☐ No

☐ Yes ⟶ *If 'Yes', record date of vaccination :* ☐☐ ☐☐☐ ☐☐
Day Month Yr

Protocol		Patient Number			Early Withdrawal
207499/157		[redacted]			

INVESTIGATOR GLOBAL EVALUATION OF IMPROVEMENT

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

PATIENT GLOBAL EVALUATION OF IMPROVEMENT

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

00000

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number			Early Withdrawal
207499/157		[redacted]			

RESOLUTION OF COPD EXACERBATIONS

Have any COPD Exacerbations resolved since the last visit?

☐ No

☐ Yes ⟶ *If 'Yes', please record details in the COPD Exacerbation section at the back of this module.*

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes ⟶ *If 'Yes' please record details in the COPD Exacerbation section at the back of this module.*

Level 1 (Mild-self treated): Acute worsening of COPD that is self-managed by the patient at home by increasing the dose of relief salbutamol medication by > 2 occasions/24 hour period on two or more consecutive days compared with their baseline (baseline = mean of last 10 days of run-in period) or use of other additional bronchodilator medication

Level 2 (Moderate- physician, investigator treated): Acute worsening of symptoms (cough, sputum production, breathlessness) requiring treatment with oral corticosteroids prescribed by a physician or primary care doctor, or as a result of hospital out-patient visit (including Emergency Room).

Exacerbations requiring oral corticosteroids will be treated with a standardised course of prednisolone or prednisone tablets 30mg/day for 10 days, or methylprednisolone tablets 24mg/day for 10 days.

Level 3 (Severe - attendance at hospital): Acute worsening of COPD that requires the patient to be admitted to hospital for treatment.

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, including an increase in usual COPD medications, must be recorded in the COPD Medications or Procedures pages.

00000

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number			Early Withdrawal
207499/157		[redacted]			

RESOURCE UTILISATION

If the patient has received any COPD exacerbation-related medical care since the last visit, record details on the Resource Utilisation pages of the COPD Exacerbation section at the back of this module.

DIARY CARD REVIEW

Review the diary card in the presence of the patient. Question any increased symptoms for possible COPD exacerbations. Place diary in the plastic wallet at the back of this module.

ADVERSE EXPERIENCES

Please complete the Adverse Experiences 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 Experiences 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 Experiences section at the back of this module.*

Protocol		**Patient Number**			**Early Withdrawal**
207499/157		[redacted]			

FAECAL OCCULT BLOOD TEST

The faecal occult blood test should be performed on three consecutive bowel movements or on bowel movements closely spaced in time between Earl Withdrawal and the Follow-Up Visit. Patients were not to collect samples during or until 3 days after a menstrual period or while they had bleeding hemorrhoids or blood in the urine. They were not to take aspirin or other non-steroidal anti-inflammatory drugs for 7 days prior to and during the test period, and they were 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.

Did the patient follow these instructions?

☐ No ⟶ *If 'No', please specify:* _

☐ Yes

Test	**Date of Collection** Day Mth Yr	**Result of faecal occult blood test**
1	☐☐ ☐☐ ☐☐	[NEG] ☐ Negative [POS] ☐ Positive
2	☐☐ ☐☐ ☐☐	[NEG] ☐ Negative [POS] ☐ Positive
3	☐☐ ☐☐ ☐☐	[NEG] ☐ Negative [POS] ☐ Positive

Are these findings clinically significant ?

☐ No

☐ Yes ⟶ *If 'Yes' please record the findings and/or diagnosis in the Adverse Experiences section at the back of this module.*

Protocol		Patient Number			Early Withdrawal
207499/157		[redacted]			

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. bd)

Date and time of last dose of study medication prior to the study visit ____ ____ ____ (Day Month Yr) ____ ____ (24hr:min)

STUDY MEDICATION COMPLIANCE

Note : Tablets dispensed should be entered as the number of tablets returned from the previous visit.

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance ≥ 80% and ≤120%?

☐ No

☐ Yes

Protocol		Patient Number			Early Withdrawal
207499/157		[redacted]			

PULMONARY REHABILITATION PROGRAM

Has the patient entered a Pulmonary Rehabilitation Program since the last visit?

☐ No

☐ Yes

INVESTIGATOR INSTRUCTIONS

The following procedures (Vital Signs, ECG and Pulmonary Function Tests) must be performed greater than 4 hours after the patient's last salbutamol administration.

VITAL SIGNS

Time of assessment : ☐☐ 24hr:min

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
☐☐☐/☐☐☐	☐☐☐

Are there any **clinically significant worsenings** since the previous visit?

☐ No

☐ Yes ⟶ *If 'Yes' please record the findings and/or diagnosis in the Adverse Experiences section at the back of this module.*

VITAL SIGNS - ORTHOSTATIC CHANGE

Time of assessment : ☐☐ 24hr:min

1st Measurement: After 5 Minutes Supine		2nd Measurement: 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)
☐☐☐/☐☐☐	☐☐☐	☐☐☐/☐☐☐	☐☐☐

Have there been any clinically significant worsenings since the last assessment?

☐ No

☐ Yes⟶ *If 'Yes', please record the findings in the Adverse Experiences section at the back of this module.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number			Early Withdrawal
207499/157		[redacted]			

12 LEAD ELECTROCARDIOGRAM

Time of assessment : ☐☐ 24hr:min **The ECG should be performed after the patient has been semi-supine for 5 minutes**

Date ECG Performed (Day Month Year)	Atrial Rate (beats/min)	Ventricular Rate (beats/min)	PR (msec)	QRS (msec)	☐ Uncorrected QT ☐ Corrected QT (msec)	Axis
☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐ + ☐ - ☐☐☐

Interpretation

☐ **(F74301) Within normal limits**

☐ **Abnormal** ⟶ ***Mark appropriate boxes below***

Rhythm
- ☐ (F73360) Sinus arrhythmia
- ☐ (F73310) Sinus bradycardia
- ☐ (F73380) Sinus tachycardia
- ☐ (F73440) Wandering atrial pacemaker
- ☐ (F73450) Premature atrial contractions
- ☐ (F73510) Paroxysmal atrial tachycardia
- ☐ (F73530) Chronic ectopic atrial tachycardia
- ☐ (F73550) Multifocal atrial tachycardia
- ☐ (F73560) Atrial flutter
- ☐ (F73570) Atrial fibrillation
- ☐ (F73610) Junctional (AV nodal) premature contractions
- ☐ (F73650) Junctional (AV nodal) tachycardia
- ☐ (F73150) Supraventricular tachycardia
- ☐ (F73860) Accelerated idioventricular rhythm
- ☐ (F73710) Premature Ventricular Contractions (NOS)
- ☐ (F73720) Unifocal PVC's
- ☐ (F73730) Multifocal PVC's
- ☐ (F73711) Ventricular couplets
- ☐ (F73750) Bigeminy
- ☐ (F73870) Ventricular tachycardia
- ☐ (F73880) Ventricular fibrillation
- ☐ (F73340) Sick sinus syndrome
- ☐ (F73190) Pacemaker rhythm

P-Wave Morphology
- ☐ (F74214) Left atrial hypertrophy, P mitrale
- ☐ (F74213) Right atrial hypertrophy, P pulmonale

Conduction
- ☐ (F73930) First degree AV block
- ☐ (F73950) Second degree AV block, Type 1
- ☐ (F73960) Second degree AV block, Type 11
- ☐ (F73970) Third degree AV block
- ☐ (F74090) Wolff-Parkinson-White syndrome

Axis
- ☐ (F74120) Right Axis deviation
- ☐ (F74130) Left Axis deviation

QRS
- ☐ (F74010) Right bundle branch block
- ☐ (F74020) Left bundle branch block
- ☐ (F74030) Left anterior hemiblock
- ☐ (F74040) Left posterior hemiblock
- ☐ (F74002) Intraventricular conduction delay
- ☐ (F74212) Left ventricular hypertrophy
- ☐ (F74211) Right ventricular hypertrophy
- ☐ (F74308) Q-wave > 0.04 sec
- ☐ (F74222) R-wave amplitude increased
- ☐ (F74225) R-wave amplitude decreased
- ☐ (F74313) Prolonged QT-interval
- ☐ (F74318) Poor R-wave progression
- ☐ (M54750) Myocardial infarction, old
  - ☐ (M54751) Anterior ☐ (M54754) Inferior
  - ☐ (M54752) Lateral ☐ (M54755) Septal
  - ☐ (M54753) Posterior

ST-T
- ☐ (F74291) Nonspecific ST-T changes
- ☐ (F74294) ST segment depression > 1 mm
- ☐ (F74295) ST segment elevation > 1 mm
- ☐ (F74350) T-wave flat
- ☐ (F74351) T-wave inversion
- ☐ (F74352) T-wave peaked
- ☐ (F74340) U-wave
- ☐ (F74360) Digitalis effect
- ☐ (F74260) Myocardial ischemia
  - ☐ (F74261) Anterior ☐ (F74264) Inferior
  - ☐ (F74262) Lateral ☐ (F74265) Septal
  - ☐ (F74263) Posterior
- ☐ (M54720) Myocardial infarction, acute
  - ☐ (M54721) Anterior ☐ (M54724) Inferior
  - ☐ (M54722) Lateral ☐ (M54725) Septal
  - ☐ (M54723) Posterior

Other interpretations not listed _

Were there any clinically important changes observed since the last assessment?

[1] ☐ No

[2] ☐ Yes ⟶ *If 'Yes', enter details on the Adverse Experiences page at the back of this module.*

Place the ECG trace in the plastic wallet a the back of this module

Protocol		Patient Number			Early Withdrawal
207499/157		[redacted]			

PRE-SALBUTAMOL PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed at least 4 hours after the last dose of inhaled beta$_2$-agonist or anticholinergic agent.

Measure the patient's pulmonary function up to eight times to obtain three acceptable readings using the spirometer provided by SB. ***(Note: Please follow instructions in the Spirometry Manual).*** *For each set of three FEV_1 measurements, one FEV_1 must be within 10% of the highest. Please record the results of the effort with the highest FEV_1 below.*

Measurement	Time	FEV_1 (L)	FVC (L)	FEF_{25-75} (L/sec)	PEF (L/min)
1	24hr:min	.	.	.	

Place the spirometry reports in the plasic wallet at the back of this module.

POST-SALBUTAMOL PULMONARY FUNCTION TESTS

Provide the patient with a salbutamol MDI and spacer. Administer 400 mcg (4 puffs) of salbutamol via MDI with a spacer.

Record the time of salbutamol inhalation 24hr:min

Wait 30 minutes

Measure the patient's pulmonary function up to eight times to obtain three acceptable readings using the spirometer provided by SB. ***(Note: Please follow instructions in the Spirometry Manual).*** *For each set of three FEV_1 measurements, one FEV_1 must be within 10% of the highest. Please record the results of the effort with the highest FEV_1 below.*

Measurement	Time	FEV_1 (L)	FVC (L)	FEF_{25-75} (L/sec)	PEF (L/min)
1	24hr:min	.	.	.	

Place spirometry reports in the plastic wallets at the back of this module.

(AT SELECTED CENTRES ONLY) RESIDUAL VOLUME BY BODY PLETHYSMOGRAPHY (PRE- AND POST-SALBUTAMOL)

Time of pre-salbutamol RV assessment: 24hr:min

Time of post-salbutamol RV assessment: 24hr:min

Pre-Salbutamol

$RV_{Box} = TLC_{Box} - \max(|SVC|, |FVC|)$

$RV_{(Box)} =$. (L)

Post-Salbutamol

$RV_{Box} = TLC_{Box} - \max(|SVC|, |FVC|)$

$RV_{(Box)} =$. (L)

Please attach plethysmography source data to the back of this page.

SmithKline Beecham
Pharmaceuticals

Protocol **207499/157**		**Patient Number** [redacted]			**Early Withdrawal**

LABORATORY TESTS

Please take blood samples for haematology and blood chemistry (including serum beta-HCG for women of child-bearing potential,CD4/CD8 ratio, serum protein C) and a urine sample for urinalysis. Please refer to the instructions on the Quest shipping form and manual.

Blood Sample Date ☐☐ ☐☐ ☐☐
Day Month Yr

Attach a label from the 'Routine' laboratory requisition form used at this visit in the space below.

Attach label here

Are there any **clinically significant worsenings** since the last assessment?

☐ No

☐ Yes ⟶ *If 'Yes' please record the findings and/or diagnosis in the Adverse Experiences section at the back of this module.*

SmithKline Beecham
Pharmaceuticals

Protocol **207499/157**		**Patient Number** [redacted]			**Early Withdrawal**

INSTRUCTIONS TO THE INVESTIGATOR AT EARLY WITHDRAWAL

Is the patient willing to return for essential assessments?

☐ No

☐ Yes

If 'No', please schedule a Safety Follow-Up Visit in 7 (+/-3) days time and complete the Study Conclusion page at the back of this module.

If 'Yes', please ask the patient to return for the next scheduled visit for essential assessments only.

*If the patient **will** return for essential assessments, please :*

	(tick if done)
• ***Remind the patient:***	☑
i *to refrain from using salbutamol or anticholinergic agents during the **4 hours** immediately preceding the next visit.*	☐
ii *to refrain from smoking for **2 hours** immediately preceding the visit.*	☐
iii *to bring the study salbutamol inhaler and spacer, and the diary card.*	☐
iv *to continue to take the anticholinergic medication, if prescribed, at a constant dose, and salbutamol when needed to control symptoms.*	☐
v *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 occurrence.*	☐

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			
207499/157		[redacted]			

2 0 7 4 9 9 1 5 7

MODFU

Please do not split modules

Module FU : **Safety Follow-Up, Adverse Experiences, Concomitant Medications, Medical Procedures, COPD Exacerbations, Resource Utilisation**

CRF Pages **320 - 343**

Unprocessed Forms : **Within this module the following occur which will generate attachments that need to be brought in-house.**

None

FOR OFFICE USE ONLY Module Comments:

Sent to Data Mngt	Review Complete Date: User:	First Entry Complete Date: User:
Second Entry Complete Date: User:	Validation Complete Date: User:	**Clintrial PID:**

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number		Visit Date (Day Month Year)	Safety Follow-Up
207499/157		[redacted]			

PRESENTATION TO CLINIC

Note: ***Patients must wait for 4 hours after beta$_2$-agonist and / or anticholinergic administration before the pulmonary function tests are performed.***

Did the patient take a dose of beta$_2$ agonist in the past 24 hours?

☐ No

☐ Yes → Record date and time of the patient's last dose of beta$_2$ agonist: Day Month Yr 24hr:min

Did the patient take a dose of anticholinergic in the past 24 hours?

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: Day Month Yr 24hr:min

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes → Date and time of patient's last cigarette Day Month Yr 24hr:min

SMOKING STATUS

Does the patient currently smoke?

☐ No

☐ Yes → If 'Yes' please record the average number of cigarettes per day :

INFLUENZA VACCINATION

Has the patient had a vaccination for influenza since the last visit?

N.B. It is not necessary to record vaccinations on the Concomitant Medication or Medical Procedures page.

☐ No

☐ Yes → *If 'Yes', record date of vaccination :* Day Month Yr

00000

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number			Safety Follow-Up
207499/157		[redacted]			

RESOLUTION OF COPD EXACERBATIONS

Have any COPD Exacerbations resolved since the last visit?

☐ No

☐ Yes ⟶ *If 'Yes', please record details in the COPD Exacerbation section at the back of this module.*

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes ⟶ *If 'Yes' please record details in the COPD Exacerbation section at the back of this module.*

Level 1 (Mild-self treated): Acute worsening of COPD that is self-managed by the patient at home by increasing the dose of relief salbutamol medication by > 2 occasions/24 hour period on two or more consecutive days compared with their baseline (baseline = mean of last 10 days of run-in period) or use of other additional bronchodilator medication

Level 2 (Moderate- physician, investigator treated): Acute worsening of symptoms (cough, sputum production, breathlessness) requiring treatment with oral corticosteroids prescribed by a physician or primary care doctor, or as a result of hospital out-patient visit (including Emergency Room).

Exacerbations requiring oral corticosteroids will be treated with a standardised course of prednisolone or prednisone tablets 30mg/day for 10 days, or methylprednisolone tablets 24mg/day for 10 days.

Level 3 (Severe - attendance at hospital): Acute worsening of COPD that requires the patient to be admitted to hospital for treatment.

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, including an increase in usual COPD medications, must be recorded in the COPD Medications or Procedures pages.

00000

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number			Safety Follow-Up
207499/157		[redacted]			

RESOURCE UTILISATION

If the patient has received any COPD exacerbation-related medical care since the last visit, record details on the Resource Utilisation pages of the COPD Exacerbation section at the back of this module.

ADVERSE EXPERIENCES

Please complete the Adverse Experiences 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 Experiences 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)

Please complete this assessment only if abnormalities were detected at Visit 12/Early Withdrawal.

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 Experiences section at the back of this module.*

Protocol		Patient Number			Safety Follow-Up
207499/157		[redacted]			

FAECAL OCCULT BLOOD TEST

Please record the results of the faecal occult blood test in the Faecal Occult Blood Test section of the previous visit.

INVESTIGATOR INSTRUCTIONS

The following procedures (Vital Signs, ECG and Pulmonary Function Tests) must be performed greater than 4 hours after the patient's last salbutamol administration.

VITAL SIGNS

Time of assessment : ☐☐ 24hr:min

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
☐☐☐/☐☐☐	☐☐☐

Are there any **clinically significant worsenings** since the previous visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experiences section at the back of this module.*

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number			Safety Follow-Up
207499/157		[redacted]			

12 LEAD ELECTROCARDIOGRAM (only if abnormalities detected at Visit 12/Early Withdrawal.)

Time of assessment : ☐☐ 24hr:min **The ECG should be performed after the patient has been semi-supine for 5 minutes**

Date ECG Performed (Day Month Year)	Atrial Rate (beats/min)	Ventricular Rate (beats/min)	PR (msec)	QRS (msec)	☐ Uncorrected QT ☐ Corrected QT (msec)	Axis
☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐ + ☐ - ☐☐☐

Interpretation

☐ **(F74301) Within normal limits**

☐ **Abnormal** → ***Mark appropriate boxes below***

Rhythm
- ☐ (F73360) Sinus arrhythmia
- ☐ (F73310) Sinus bradycardia
- ☐ (F73380) Sinus tachycardia
- ☐ (F73440) Wandering atrial pacemaker
- ☐ (F73450) Premature atrial contractions
- ☐ (F73510) Paroxysmal atrial tachycardia
- ☐ (F73530) Chronic ectopic atrial tachycardia
- ☐ (F73550) Multifocal atrial tachycardia
- ☐ (F73560) Atrial flutter
- ☐ (F73570) Atrial fibrillation
- ☐ (F73610) Junctional (AV nodal) premature contractions
- ☐ (F73650) Junctional (AV nodal) tachycardia
- ☐ (F73150) Supraventricular tachycardia
- ☐ (F73860) Accelerated idioventricular rhythm
- ☐ (F73710) Premature Ventricular Contractions (NOS)
- ☐ (F73720) Unifocal PVC's
- ☐ (F73730) Multifocal PVC's
- ☐ (F73711) Ventricular couplets
- ☐ (F73750) Bigeminy
- ☐ (F73870) Ventricular tachycardia
- ☐ (F73880) Ventricular fibrillation
- ☐ (F73340) Sick sinus syndrome
- ☐ (F73190) Pacemaker rhythm

P-Wave Morphology
- ☐ (F74214) Left atrial hypertrophy, P mitrale
- ☐ (F74213) Right atrial hypertrophy, P pulmonale

Conduction
- ☐ (F73930) First degree AV block
- ☐ (F73950) Second degree AV block, Type 1
- ☐ (F73960) Second degree AV block, Type 11
- ☐ (F73970) Third degree AV block
- ☐ (F74090) Wolff-Parkinson-White syndrome

Axis
- ☐ (F74120) Right Axis deviation
- ☐ (F74130) Left Axis deviation

QRS
- ☐ (F74010) Right bundle branch block
- ☐ (F74020) Left bundle branch block
- ☐ (F74030) Left anterior hemiblock
- ☐ (F74040) Left posterior hemiblock
- ☐ (F74002) Intraventricular conduction delay
- ☐ (F74212) Left ventricular hypertrophy
- ☐ (F74211) Right ventricular hypertrophy
- ☐ (F74308) Q-wave > 0.04 sec
- ☐ (F74222) R-wave amplitude increased
- ☐ (F74225) R-wave amplitude decreased
- ☐ (F74313) Prolonged QT-interval
- ☐ (F74318) Poor R-wave progression
- ☐ (M54750) Myocardial infarction, old
  - ☐ (M54751) Anterior ☐ (M54754) Inferior
  - ☐ (M54752) Lateral ☐ (M54755) Septal
  - ☐ (M54753) Posterior

ST-T
- ☐ (F74291) Nonspecific ST-T changes
- ☐ (F74294) ST segment depression > 1 mm
- ☐ (F74295) ST segment elevation > 1 mm
- ☐ (F74350) T-wave flat
- ☐ (F74351) T-wave inversion
- ☐ (F74352) T-wave peaked
- ☐ (F74340) U-wave
- ☐ (F74360) Digitalis effect
- ☐ (F74260) Myocardial ischemia
  - ☐ (F74261) Anterior ☐ (F74264) Inferior
  - ☐ (F74262) Lateral ☐ (F74265) Septal
  - ☐ (F74263) Posterior
- ☐ (M54720) Myocardial infarction, acute
  - ☐ (M54721) Anterior ☐ (M54724) Inferior
  - ☐ (M54722) Lateral ☐ (M54725) Septal
  - ☐ (M54723) Posterior

Other interpretations not listed _

Were there any clinically important changes observed since the last assessment?

[1] ☐ No

[2] ☐ Yes → *If 'Yes', enter details on the Adverse Experiences page at the back of this module.*

Place the ECG trace in the plastic wallet a the back of this module

Protocol		Patient Number			Safety Follow-Up
207499/157		[redacted]			

PRE-SALBUTAMOL PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed at least 4 hours after the last dose of inhaled beta$_2$-agonist or anticholinergic agent.

Measure the patient's pulmonary function up to eight times to obtain three acceptable readings using the spirometer provided by SB. ***(Note: Please follow instructions in the Spirometry Manual).*** *For each set of three FEV_1 measurements, one FEV_1 must be within 10% of the highest. Please record the results of the effort with the highest FEV_1 below.*

Measurement	Time	FEV_1 (L)	FVC (L)	FEF_{25-75} (L/sec)	PEF (L/min)
1	24hr:min	.	.	.	

Place the spirometry reports in the plasic wallet at the back of this module.

POST-SALBUTAMOL PULMONARY FUNCTION TESTS

Administer 400 mcg (4 puffs) of salbutamol via MDI with a spacer.

Record the time of salbutamol inhalation 24hr:min

Wait 30 minutes

Measure the patient's pulmonary function up to eight times to obtain three acceptable readings using the spirometer provided by SB. ***(Note: Please follow instructions in the Spirometry Manual).*** *For each set of three FEV_1 measurements, one FEV_1 must be within 10% of the highest. Please record the results of the effort with the highest FEV_1 below.*

Measurement	Time	FEV_1 (L)	FVC (L)	FEF_{25-75} (L/sec)	PEF (L/min)
1	24hr:min	.	.	.	

Place spirometry reports in the plastic wallets at the back of this module.

00000

SmithKline Beecham
Pharmaceuticals

Protocol **207499/157**		**Patient Number** [redacted]			**Safety Follow-Up**

LABORATORY TESTS

Please complete this assessment only if abnormalities were detected at Visit 12/Early Withdrawal.

Please take blood samples for haematology and blood chemistry and a urine sample for urinalysis. Please refer to the instructions on the Quest shipping form and manual.

Blood Sample Date ☐☐ ☐☐ ☐☐
Day Month Yr

Attach a label from the 'Routine' laboratory requisition form used at this visit in the space below.

Attach label here

Are there any **clinically significant worsenings** since the last assessment?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experiences 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 at this visit.*

Is the patient pregnant ?

☐ No

☐ Yes → *If 'Yes', please record details in the Serious Adverse Experiences section at the back of this module and report the event to the Medical Monitor within 24 hours.*

INSTRUCTIONS TO THE INVESTIGATOR AT SAFETY FOLLOW-UP

Please complete the Study Conclusion page at the back of this book.

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 study procedures should be reported as a serious event

IF AN 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

g_ae_instr_01

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			Adverse Experiences
207499/157		[redacted]			

ADVERSE EXPERIENCES (Non-serious)

g_ae_01

*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 last visit?"*
*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).

☐ Please mark this box if no adverse experiences occurred since the last module

Adverse Experience *(please print clearly)*		
For SB		
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 SAE section and follow instructions given there***	[1] ☐ Resolved [2] ☐ Ongoing [3] ☐ Died	[1] ☐ Resolved [2] ☐ Ongoing [3] ☐ Died
Experience Course	[1] ☐ Intermittent → No. of episodes ☐ [2] ☐ Constant	[1] ☐ Intermittent → No. of episodes ☐ [2] ☐ Constant
Intensity (maximum)	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Action Taken with Respect to Investigational Drug	[1] ☐ None [2] ☐ Dose reduced [3] ☐ Dose increased [4] ☐ Drug interrupted/restarted [5] ☐ Drug stopped	[1] ☐ None [2] ☐ Dose reduced [3] ☐ Dose increased [4] ☐ Drug interrupted/restarted [5] ☐ Drug stopped
Relationship to Investigational Drug	[1] ☐ Not related [2] ☐ Unlikely [3] ☐ Suspected (reasonable possibility) [4] ☐ Probable	[1] ☐ Not related [2] ☐ Unlikely [3] ☐ Suspected (reasonable possibility) [4] ☐ Probable
Corrective Therapy *If 'Yes', record details in the Concomitant Medication section and/ or Medical Procedures section if appropriate*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No

SmithKline Beecham
Pharmaceuticals

Protocol	**Centre Number**	**Patient Number**			**Adverse Experiences**
207499/157		[redacted]			

ADVERSE EXPERIENCES (Non-serious) - Continued

g_ae_01

*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 last visit?"*
*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).

Adverse Experience *(please print clearly)*		
For SB		
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 SAE section and follow instructions given there***	[1] Resolved [2] Ongoing [3] Died	[1] Resolved [2] Ongoing [3] Died
Experience Course	[1] Intermittent → No. of episodes [2] Constant	[1] Intermittent → No. of episodes [2] Constant
Intensity (maximum)	[1] Mild [2] Moderate [3] Severe	[1] Mild [2] Moderate [3] Severe
Action Taken with Respect to Investigational Drug	[1] None [2] Dose reduced [3] Dose increased [4] Drug interrupted/restarted [5] Drug stopped	[1] None [2] Dose reduced [3] Dose increased [4] Drug interrupted/restarted [5] Drug stopped
Relationship to Investigational Drug	[1] Not related [2] Unlikely [3] Suspected (reasonable possibility) [4] Probable	[1] Not related [2] Unlikely [3] Suspected (reasonable possibility) [4] Probable
Corrective Therapy *If 'Yes', record details in the Concomitant Medication section and/ or Medical Procedures section if appropriate*	Yes No	Yes No
Was patient withdrawn due to this specific AE?	Yes No	Yes No

SmithKline Beecham Pharmaceuticals

Protocol	Centre Number	Patient Number			Adverse Experiences
207499/157		[redacted]			

ADVERSE EXPERIENCES (Non-serious) - Continued

g_ae_01

*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 last visit?"*
*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).

Adverse Experience *(please print clearly)*		
For SB		
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 SAE section and follow instructions given there***	[1] Resolved [2] Ongoing [3] Died	[1] Resolved [2] Ongoing [3] Died
Experience Course	[1] Intermittent → No. of episodes [2] Constant	[1] Intermittent → No. of episodes [2] Constant
Intensity (maximum)	[1] Mild [2] Moderate [3] Severe	[1] Mild [2] Moderate [3] Severe
Action Taken with Respect to Investigational Drug	[1] None [2] Dose reduced [3] Dose increased [4] Drug interrupted/restarted [5] Drug stopped	[1] None [2] Dose reduced [3] Dose increased [4] Drug interrupted/restarted [5] Drug stopped
Relationship to Investigational Drug	[1] Not related [2] Unlikely [3] Suspected (reasonable possibility) [4] Probable	[1] Not related [2] Unlikely [3] Suspected (reasonable possibility) [4] Probable
Corrective Therapy *If 'Yes', record details in the Concomitant Medication section and/ or Medical Procedures section if appropriate*	Yes No	Yes No
Was patient withdrawn due to this specific AE?	Yes No	Yes No

Protocol	Centre Number	Patient Number			Concomitant Medication
207499/157		[redacted]			

CONCOMITANT MEDICATION

Record any changes in concomitant medication taken since the last 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. At the patient's final study visit, record the end date for prn study rescue medication (salbutamol) use, using the date the study inhaler was returned.

☐ No concomitant medication changes since the last module

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded in the Adverse Experiences 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** (eg 500mg)	**Frequency** (eg bd, 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	
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							

** For Route, see general instructions for acceptable abbreviations.*

Protocol	Centre Number	Patient Number			Concomitant Medication
207499/157		[redacted]			

CONCOMITANT MEDICATION (Cont.)

Do not record any medication taken for COPD exacerbations in this section. Record all COPD exacerbation medication in the COPD Exacerbation section. At the patient's final study visit, record the end date for prn study rescue medication (salbutamol) use, using the date the study inhaler was returned.

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded in the Adverse Experiences 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** (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	
For SB							
For SB							
For SB							
For SB							
For SB							
For SB							
For SB							
For SB							
For SB							
For SB							

** For Route, see general instructions for acceptable abbreviations.*

g_conmed_01

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			Medical Procedures
207499/157		[redacted]			

MEDICAL PROCEDURES

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 last module?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below using standard medical terminology*

All indications for procedures should be recorded on the Adverse Experiences Form.

Procedure	Indication	Procedure Start Date Day Mth Yr	Procedure End Date Day Mth Yr
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			COPD Exacerbations (AE)
207499/157		[redacted]			

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 last 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***

Has the patient suffered any COPD Exacerbations since the last module ?

☐ No

☐ Yes → *If 'Yes', please complete page below*

Adverse Event	COPD EXACERBATION
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, STOP: delete details of this exacerbation and go to SAE COPD Exacerbation pages.***	[1] ☐ Resolved [2] ☐ Ongoing [3] ☐ Died
Event Course	[1] ☐ Intermittent → No. of episodes ☐ [2] ☐ Constant
Intensity (maximum) *See definitions page for Adverse Experiences form.*	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Action Taken with Respect to Investigational Drug	[1] ☐ None [2] ☐ Dose reduced [3] ☐ Dose increased [4] ☐ Drug interrupted/restarted [5] ☐ Drug stopped
Relationship to Investigational Drug	[1] ☐ Not related [2] ☐ Unlikely [3] ☐ Suspected (reasonable possibility) [4] ☐ Probable
Corrective Therapy *If 'Yes', record details on the COPD Medications or Procedures page*	☐ Yes ☐ No
Was patient withdrawn due to this specific event?	☐ Yes ☐ No

DEFINITIONS OF LEVELS OF EXACERBATION OF COPD

Level 1 (Mild-self treated): Acute worsening of COPD that is self-managed by the patient at home by increasing the dose of relief salbutamol medication by > 2 occasions/24 hour period on two or more consecutive days compared with their baseline (baseline = mean of last 10 days of run-in period) or use of other additional bronchodilator medication

Level 2 (Moderate- physician, investigator treated): Acute worsening of symptoms (cough, sputum production, breathlessness) requiring treatment with oral corticosteroids prescribed by a physician or primary care doctor, or as a result of hospital out-patient visit (including Emergency Room).

Exacerbations requiring oral corticosteroids will be treated with a standardised course of prednisolone or prednisone tablets 30mg/day for 10 days, or methylprednisolone tablets 24mg/day for 10 days.

Level 3 (Severe - attendance at hospital): Acute worsening of COPD that requires the patient to be admitted to hospital for treatment.

Protocol	Centre Number	Patient Number			COPD Exacerbations (AE)
207499/157		[redacted]			

FURTHER DETAILS OF COPD EXACERBATIONS

COPD exacerbation onset date : Day Month Yr

Level of exacerbation (see definitions on facing page):

[1] ☐ Level 1
[2] ☐ Level 2
[3] ☐ Level 3

Pumonary function test result (FEV_1) (if done):

☐.☐☐ L

Did the patient suffer from any of the following during the exacerbation:

[1] ☐ Chest pain
[2] ☐ Upper Respiratory Tract Infection
[3] ☐ Confusion
[4] ☐ Change in alertness
[5] ☐ Pneumonia
[6] ☐ Oedema
[7] ☐ Ankle swelling

ARTERIAL BLOOD GASES (only for COPD exacerbations)

Where feasible, an arterial blood gas sample is to be taken for analysis

COPD exacerbation onset date : Day Month Yr

PO_2 (mmHg)	**PCO_2** (mmHg)	**pH**	**Resting SaO_2** (%)
☐☐☐	☐☐	☐.☐☐	☐☐☐

RESOURCE UTILISATION

Please complete the Resource Utilisation pages for this exacerbation.

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			COPD Exacerbations (AE)
207499/157		[redacted]			

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 last 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 Event	COPD EXACERBATION
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, STOP: delete details of this exacerbation and go to SAE COPD Exacerbation pages.***	[1] ☐ Resolved [2] ☐ Ongoing [3] ☐ Died
Event Course	[1] ☐ Intermittent → No. of episodes ☐ [2] ☐ Constant
Intensity (maximum) *See definitions page for Adverse Experiences form.*	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Action Taken with Respect to Investigational Drug	[1] ☐ None [2] ☐ Dose reduced [3] ☐ Dose increased [4] ☐ Drug interrupted/restarted [5] ☐ Drug stopped
Relationship to Investigational Drug	[1] ☐ Not related [2] ☐ Unlikely [3] ☐ Suspected (reasonable possibility) [4] ☐ Probable
Corrective Therapy *If 'Yes', record details on the COPD Medications or Procedures page*	☐ Yes ☐ No
Was patient withdrawn due to this specific event?	☐ Yes ☐ No

DEFINITIONS OF LEVELS OF EXACERBATION OF COPD

Level 1 (Mild-self treated): Acute worsening of COPD that is self-managed by the patient at home by increasing the dose of relief salbutamol medication by > 2 occasions/24 hour period on two or more consecutive days compared with their baseline (baseline = mean of last 10 days of run-in period) or use of other additional bronchodilator medication

Level 2 (Moderate- physician, investigator treated): Acute worsening of symptoms (cough, sputum production, breathlessness) requiring treatment with oral corticosteroids prescribed by a physician or primary care doctor, or as a result of hospital out-patient visit (including Emergency Room).

Exacerbations requiring oral corticosteroids will be treated with a standardised course of prednisolone or prednisone tablets 30mg/day for 10 days, or methylprednisolone tablets 24mg/day for 10 days.

Level 3 (Severe - attendance at hospital): Acute worsening of COPD that requires the patient to be admitted to hospital for treatment.

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			COPD Exacerbations (AE)
207499/157					

FURTHER DETAILS OF COPD EXACERBATIONS

COPD exacerbation onset date : Day Month Yr

Level of exacerbation (see definitions on facing page):

[1] ☐ Level 1
[2] ☐ Level 2
[3] ☐ Level 3

Pumonary function test result (FEV_1) (if done):

☐.☐☐ L

Did the patient suffer from any of the following during the exacerbation:

[1] ☐ Chest pain
[2] ☐ Upper Respiratory Tract Infection
[3] ☐ Confusion
[4] ☐ Change in alertness
[5] ☐ Pneumonia
[6] ☐ Oedema
[7] ☐ Ankle swelling

ARTERIAL BLOOD GASES (only for COPD exacerbations)

Where feasible, an arterial blood gas sample is to be taken for analysis

COPD exacerbation onset date : Day Month Yr

PO_2 (mmHg)	**PCO_2** (mmHg)	**pH**	**Resting SaO_2** (%)
☐☐☐	☐☐	☐.☐☐	☐☐☐

RESOURCE UTILISATION

Please complete the Resource Utilisation pages for this exacerbation.

SmithKline Beecham Pharmaceuticals

Protocol	Centre Number	Patient Number		SB Receipt Date (Day Month Year)	COPD Exacerbations (SAE)
207499/157		[redacted]			

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation

Person Reporting SAE _____ *(Please print clearly)*

AEGIS Number _____ . _____

Serious Adverse Experience	**COPD Exacerbation**
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*	[1] ☐ Resolved [2] ☐ Ongoing [3] ☐ Died
Experience Course	[1] ☐ Intermittent → No. of episodes ☐ [2] ☐ Constant
Intensity *(maximum)*	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Action Taken with Respect to Investigational Drug	[1] ☐ None [2] ☐ Dose reduced [3] ☐ Dose increased [4] ☐ Drug interrupted/ restarted [5] ☐ Drug stopped
Relationship to Investigational Drug	[1] ☐ Not related [2] ☐ Unlikely [3] ☐ Suspected (reasonable possibility) [4] ☐ Probable
Corrective Therapy *If 'Yes', record details in the COPD Concomitant Medication section*	☐ Yes ☐ No
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No

→ *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

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 _____

00000

SmithKline Beecham
Pharmaceuticals

Protocol	**Centre Number**	**Patient Number**		**SB Receipt Date** Day Month Year	**COPD Exacerbations (SAE)**
207499/157		[redacted]			

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation

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 Number (please do NOT enter the container number): ☐☐☐☐☐

Investigator's Signature: _____ Date ☐☐ ☐☐ ☐☐☐☐
(confirming that the above data are accurate and complete) Day Month Year

Please PRINT Name _____

SB Medical Monitor's Signature: _____ Date ☐☐ ☐☐ ☐☐☐☐

Please PRINT Name _____ Day Month Year

DEFINITIONS OF LEVELS OF EXACERBATION OF COPD

Level 1 (Mild-self treated): Acute worsening of COPD that is self-managed by the patient at home by increasing the dose of relief salbutamol medication by > 2 occasions/24 hour period on two or more consecutive days compared with their baseline (baseline = mean of last 10 days of run-in period) or use of other additional bronchodilator medication

Level 2 (Moderate- physician, investigator treated): Acute worsening of symptoms (cough, sputum production, breathlessness) requiring treatment with oral corticosteroids prescribed by a physician or primary care doctor, or as a result of hospital out-patient visit (including Emergency Room).

Exacerbations requiring oral corticosteroids will be treated with a standardised course of prednisolone or prednisone tablets 30mg/day for 10 days, or methylprednisolone tablets 24mg/day for 10 days.

Level 3 (Severe - attendance at hospital): Acute worsening of COPD that requires the patient to be admitted to hospital for treatment.

00000

SmithKline Beecham
Pharmaceuticals

Protocol	**Centre Number**	**Patient Number**		**SB Receipt Date** Day Month Year	**COPD Exacerbations (SAE)**
207499/157		[redacted]			

FURTHER DETAILS OF SERIOUS COPD EXACERBATIONS

COPD exacerbation onset date : Day Month Yr

Level of exacerbation (see definitions on facing page):

[1] ☐ Level 1
[2] ☐ Level 2
[3] ☐ Level 3

Pumonary function test result (FEV_1) (if done):

☐.☐☐ L

Did the patient suffer from any of the following during the exacerbation:

[1] ☐ Chest pain
[2] ☐ Upper Respiratory Tract Infection
[3] ☐ Confusion
[4] ☐ Change in alertness
[5] ☐ Pneumonia
[6] ☐ Oedema
[7] ☐ Ankle swelling

ARTERIAL BLOOD GASES (only for serious COPD exacerbations)

Where feasible, an arterial blood gas sample is to be taken for analysis

COPD exacerbation onset date : Day Month Yr

PO_2 (mmHg)	**PCO_2** (mmHg)	**pH**	**Resting SaO_2** (%)
☐☐☐	☐☐	☐.☐☐	☐☐☐

RESOURCE UTILISATION

Please complete the Resource Utilisation pages for this exacerbation.

Protocol	**Centre Number**	**Patient Number**			**COPD Exacerbations (ConMed)**
207499/157		[redacted]			

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)	**Freq.** (eg bd, prn)	**Route***	**Medical Illness/ Diag.**	**Start Date** *(be as precise as possible)* Day Mth Yr	**End Date** *(or if Continuing mark box)* Day Mth Yr		COPD Exacerbation Onset Date
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								
				COPD			☐	
For SB								

** For Route, see General Instructions for acceptable abbreviations.*

SmithKline Beecham
Pharmaceuticals

Protocol	**Centre Number**	**Patient Number**			**COPD Exacerbations (ConMed)**
207499/157		[redacted]			

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** Day Mth Yr	**Procedure End Date** Day Mth Yr	COPD Exacerbation Onset Date
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				
	COPD			
For SB				

SmithKline Beecham
Pharmaceuticals

Protocol	**Centre Number**	**Patient Number**			**Resource Utilisation**
207499/157		[redacted]			

RESOURCE UTILISATION FOR COPD EXACERBATIONS

Has the patient had any medical care for COPD Exacerbations that have occurred since the previous module?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below*

Has the patient had any **Physician contact** (COPD care excluding scheduled protocol visits) since the previous module?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below*

Date of Contact Day Mth Yr	Telephone	Home Visit		Office/ Practice	Out-patients	Reason for contact	COPD Exacerbation Onset Date Day Mth Yr
		Day	Night				

Has the patient had any **Emergency Room (ER)/Urgent Care Visits/Procedures (i.e., lung surgery)** since the previous module?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below*

Date of Contact Day Mth Yr	**Reason for contact**	**Patient Admitted from ER?**		COPD Exacerbation Onset Date Day Mth Yr
		Yes	**No**	

Protocol	Centre Number	Patient Number			Resource Utilisation
207499/157		[redacted]			

RESOURCE UTILISATION FOR COPD EXACERBATIONS - (cont)

Has the patient had any **Hospitalisations** since the previous module?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below* ***(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**	**COPD Exacerbation Onset Date** **Day Mth Yr**

Has the patient had any **Intensive Care Unit (ICU) stays** ***(did the patient stay in the ICU during any of the above hospitalisations?)*** since the previous module?

☐ No

☐ Yes ⟶ *If 'Yes', please record details below*

Date Admitted to ICU Day Mth Yr	**Date Discharged from ICU** Day Mth Yr	**Reason for ICU Admission**	**COPD Exacerbation Onset Date** **Day Mth Yr**

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			
207499/157		[redacted]			

2 0 7 4 9 9 1 5 7

CONC5

Please do not split modules

Module: **Study Conclusion**

CRF Pages: **344**

Unprocessed Forms: **Within this module, the following tests / procedures occur which may generate attachments.**

None

FOR OFFICE USE ONLY Module Comments:

Sent to Data Mngt	Date: / User: Review Complete	Date: / User: First Entry Complete
Date: / User: Second Entry Complete	Date: / User: Validation Complete	**Clintrial PID:**

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			Study Conclusion
207499/157					

STUDY CONCLUSION

Did the patient complete the study according to the protocol? ***(For patients who have withdrawn from study medication but are continuing with essential assessment visits, please mark 'No' and the primary reason for withdrawal)***

☐ Yes

☐ No → If 'No', please mark the **primary** cause of withdrawal. *(Mark one box only).*

[1] ☐ Adverse experience *(please complete AE page)*

[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

g_stud_conc_01
Date of final dose ☐☐ ☐☐☐ ☐☐ Day Month Yr

INVESTIGATOR SIGNATURE

I certify that I have reviewed the data on this case report form, including laboratory data and that in the Baseline Signs and Symptoms, Adverse Experiences and Serious Adverse Experiences sections (if appropriate) and that all information is complete and accurate.

Investigator's Signature _ Date ☐☐ ☐☐☐ ☐☐ Day Month Yr

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			
207499/157		[redacted]			

2 0 7 4 9 9 1 5 7

SAEFU

Please do not split modules

Module : **Serious Adverse Experiences**

CRF Pages **345 - 346**

Unprocessed Forms : **Within this module the following occur which will generate attachments that need to be brought in-house.**

None

FOR OFFICE USE ONLY Module Comments:

Sent to Data Mngt	Review Complete Date: User:	First Entry Complete Date: User:
Second Entry Complete Date: User:	Validation Complete Date: User:	**Clintrial PID:**

REPORTING SERIOUS ADVERSE EXPERIENCES (SAE)

INSTRUCTIONS

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

g_sae_instr_01

SmithKline Beecham Pharmaceuticals

Protocol	Centre Number	Patient Number		SB Receipt Date (Day Month Year)	Serious Adverse Experiences
207499/157		[redacted]			

SERIOUS ADVERSE EXPERIENCE (SAE)

Person Reporting SAE *(Please print clearly)* _

AEGIS Number _ _ _ _ _ _ _ _ . _

Serious Adverse Experience *(Please print clearly)*

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*
[1] Resolved
[2] Ongoing
[3] Died

Experience Course
[1] Intermittent — No. of episodes
[2] Constant

Intensity *(maximum)*
[1] Mild
[2] Moderate
[3] Severe

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

Action Taken with Respect to Investigational Drug
[1] None
[2] Dose reduced
[3] Dose increased
[4] Drug interrupted restarted
[5] 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
[1] Not related
[2] Unlikely
[3] Suspected (reasonable possibility)
[4] 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

g_sae_01

00000

SmithKline Beecham Pharmaceuticals

Protocol	Centre Number	Patient Number		SB Receipt Date (Day Month Year)	Serious Adverse Experiences
207499/157		[redacted]			

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 Number (please do NOT enter the container number): ☐☐☐☐☐

Investigator's Signature: _____ Date ☐☐ ☐☐ ☐☐
(confirming that the above data are accurate and complete) Day Month Year

Please PRINT Name _____

SB Medical Monitor's Signature: _____ Date ☐☐ ☐☐ ☐☐

Please PRINT Name _____ Day Month Year

g_sae_01

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			
207499/157					

2 0 7 4 9 9 1 5 7

RPLAB9

Please do not split modules

Module: **Repeat / unscheduled laboratory assessments**

CRF Pages: **347**

Unprocessed Forms: **Within this module, the following tests / procedures occur which may generate attachments.**

None

FOR OFFICE USE ONLY Module Comments:

Sent to Data Mngt	Review Complete Date: User:	First Entry Complete Date: User:
Second Entry Complete Date: User:	Validation Complete Date: User:	**Clintrial PID:**

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			Repeat / Unscheduled Lab Tests
207499/157		[redacted]			

REPEAT / UNSCHEDULED LABORATORY TESTS

Visit Number (or last scheduled visit number): ☐☐ Sample Date ☐☐ ☐☐ ☐☐ Day Month Yr

Please take blood samples for hematology and/or blood chemistry (including serum beta-HCG for women of child-bearing potential) and/or a urine sample for urinalysis. Please refer to the instructions on the Quest shipping form and manual.

Please attach Central Lab CRF label here

(Attach label when sample is sent to central lab.)

Laboratory reports will stay at the site as part of the patient's source documentation.

Request βhCG test on Quest requisition for women of child-bearing potential. If the pregnancy test is positive, please withdraw the patient and complete the Serious Adverse Experiences form and forward it to SB within 24 hours.

Are there any **clinically significant** worsenings since the last assessment?

☐ No

☐ Yes ⟶ *If 'Yes', please record the findings and/or diagnosis in the Adverse Experiences section.*

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			
207499/157		[redacted]			

2 0 7 4 9 9 1 5 7

RLAB10

Please do not split modules

Module: **Repeat / unscheduled laboratory assessments**

CRF Pages: **348**

Unprocessed Forms: **Within this module, the following tests / procedures occur which may generate attachments.**

None

FOR OFFICE USE ONLY Module Comments:

Sent to Data Mngt	Date: / User: Review Complete	Date: / User: First Entry Complete
Date: / User: Second Entry Complete	Date: / User: Validation Complete	**Clintrial PID:**

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number			Repeat / Unscheduled Lab Tests
207499/157		[redacted]			

REPEAT / UNSCHEDULED LABORATORY TESTS

Visit Number (or last scheduled visit number): ☐☐ Sample Date ☐☐ ☐☐ ☐☐ Day Month Yr

Please take blood samples for hematology and/or blood chemistry (including serum beta-HCG for women of child-bearing potential) and/or a urine sample for urinalysis. Please refer to the instructions on the Quest shipping form and manual.

Please attach Central Lab CRF label here

(Attach label when sample is sent to central lab.)

Laboratory reports will stay at the site as part of the patient's source documentation.

Request βhCG test on Quest requisition for women of child-bearing potential. If the pregnancy test is positive, please withdraw the patient and complete the Serious Adverse Experiences form and forward it to SB within 24 hours.

Are there any **clinically significant** worsenings since the last assessment?

☐ No

☐ Yes ⟶ *If 'Yes', please record the findings and/or diagnosis in the Adverse Experiences section.*

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number		Investigator
207499/157		[redacted]		_ _

CRF TRACKING/REVIEW FORM (TRF) (EW/FU BOOK)

Please submit COMPLETE modules only. Do not submit whole blank modules.

☐ Screening Failure (archive only)

- *Mark the **Unused** box for all remaining modules that will **not** be completed and sent in-house*
- *Ensure the Missing Pages field is completed if pages are missing from modules*
- *Ensure the Patient Numbers entered match the information on the CRF*
- *Complete one TRF per batch of modules to be sent in-house*
- *Ensure all sections of the TRF are legible*

Module	Module Description	Page Range	Modules		Missing pages (if applicable)
			Sent to DM	Unused	
MODEW	Early Withdrawal Visit	308 - 319	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
SGRQEW	EW SGRQ	SG1-SG5	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
EQ5DEW	EW EQ-5D	EQ1-EQ2	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
ECGEW	EW ECG trace	n/a	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
PFTEW	EW PFT printout	n/a	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
MODFU	SFU, AE, CM, Med Pro, COPD, RU	320 - 343	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
PFTFU	SFU PFT printout	n/a	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
ECGFU	SFU ECG trace	n/a	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
CONC5	Study Conclusion	344	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
SAEFU	Serious Adverse Experiences	345 - 346	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
RPLAB9	Repeat Labs	347	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
RLAB10	Repeat Labs	348	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _
FORMD	Form D	n/a	☐	☐	_ _ _ _ _ _ _ _ _ _ _ _ _

If multiple modules are submitted together, please ensure they are sorted according to the order above

Site Monitor's Name _ *(Print clearly)*

Site Monitor's Signature _ **Date Submitted** ☐☐ ☐☐☐ ☐☐
Day Month Yr

g_trf_01

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number		Investigator
207499/157		[redacted]		_____

CRF TRACKING/REVIEW FORM (TRF) (EW/FU BOOK)

Site Monitor's comments (eg. protocol violations or deviations)

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

Site Monitor's Name _____ *(Print clearly)*

Site Monitor's Signature _____ **Date Submitted** Day Month Yr

g_trf_01

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number	Patient Initials		
207499/157		[redacted]			

2 0 7 4 9 9 1 5 7

GIAEF1

Please do not split modules

Module GIAEF1 : **Supplemental Report for Gastrointestinal Adverse Experience - Follow-Up**

CRF Pages **GF1 - GF4**

Unprocessed Forms : **Within this module the following occur which will generate attachments that need to be brought in-house.**

None

FOR OFFICE USE ONLY Module Comments:

Sent to Data Mngt	Date: / User: Review Complete	Date: / User: First Entry Complete
Date: / User: Second Entry Complete	Date: / User: Validation Complete	**Clintrial PID:**

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/157		[redacted]			

SUPPLEMENTAL REPORT FOR GASTROINTESTINAL ADVERSE EXPERIENCE - FOLLOW UP

Date of **this** Assessment: Day Month Yr

Date of **initial** supplemental report: Day Month Yr

Person performing assessment
(Please print clearly) _

Signature: _

If not Investigator, please submit results to Investigator by end of the day.

If new GI symptoms are reported at the follow-up assessment, a new Supplemental Report for Gastrointestinal AEs should be completed, with the exception of additional blood draw for laboratory analysis.

How do the GI symptom(s) at the time of this assessment compare with the previous assessment:

GI Symptom(s)	[1] Resolved	[2] Better	[3] Same	[4] Worse
☐ Black or bloody stool	☐	☐	☐	☐
☐ Abdominal pain or discomfort	☐	☐	☐	☐
☐ Diarrhea	☐	☐	☐	☐
☐ Vomiting	☐	☐	☐	☐
☐ Other GI symptoms, specify:				
	☐	☐	☐	☐
	☐	☐	☐	☐
	☐	☐	☐	☐

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/157		[redacted]			

SUPPLEMENTAL REPORT FOR GASTROINTESTINAL ADVERSE EXPERIENCE - FOLLOW UP

PHYSICAL EXAMINATION

Orthostatic Vital Signs - to be completed for all patients reporting GIAE of concern

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 ⟶ *If 'Yes' please record the findings and/or diagnosis in the Baseline Signs and Symptoms or the Adverse Experience page of the CRF.*

Fecal Occult Blood - to be completed for all patients reporting GIAE of concern

Test	Date of Collection Day Mth Yr	Result of fecal occult blood test
1	☐☐ ☐☐☐ ☐☐	[NEG] ☐ Negative [POS] ☐ Positive
2	☐☐ ☐☐☐ ☐☐	[NEG] ☐ Negative [POS] ☐ Positive
3	☐☐ ☐☐☐ ☐☐	[NEG] ☐ Negative [POS] ☐ Positive

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/157		[redacted]			

SUPPLEMENTAL REPORT FOR GASTROINTESTINAL ADVERSE EXPERIENCE - FOLLOW UP

LABORATORY SAMPLE

Please take blood samples for hematology and blood chemistry and a urine sample for urinalysis. Please refer to the instructions on the Quest shipping form and manual.

Sample Date ☐☐ ☐☐☐ ☐☐
Day Month Yr

Please attach Central Lab CRF label from the 'Unscheduled' laboratory requisition here

(Attach label when sample is sent to central lab.)

Laboratory reports will stay at the site as part of the patient's source documentation.

Please record any clinically significant findings and/or diagnosis in the Baseline Signs and Symptoms or the Adverse Experiences section.

ADDITIONAL TESTS

Additional tests may be ordered at the discretion of the investigator. Please mark (✓) the additional tests that have been ordered.

☐ X-ray
☐ CT of abdomen
☐ Rectal/pelvic examination
☐ Stool for ova and parasites
☐ Ultrasound of the abdomen
☐ Other, specify: _
☐ Colonoscopy

Was the patient referred to a gastroenterologist or other specialist?

☐ No
☐ Yes

Please record abnormal findings in the Baseline Signs and Symptoms or Adverse Experiences section of the CRF. Please forward results when available and record tests in the Medical Procedures page of the CRF.

Investigator's Remarks: _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/157		[redacted]			

SUPPLEMENTAL REPORT FOR GASTROINTESTINAL ADVERSE EXPERIENCE - FOLLOW UP

Investigator's Signature: _

Please PRINT name: _

Please review follow-up assessment and update Adverse Experience/Serious Adverse Experience page (e.g., end date), if applicable. If there is a worsening of the adverse experiences increases, please complete new AE/SAE page and fax to the SmithKline Beecham Medical Monitor.

If the patient took a new concomitant medication or changed the dose of a continuing medication, please record medication(s) on the concomitant medication page of the CRF.

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number	Patient Initials	Investigator
207499/157		[redacted]		_____

CRF TRACKING/REVIEW FORM

Please submit COMPLETE modules only. Do not submit whole blank modules.

- *Mark the **Unused** box for all remaining modules that will **not** be completed and sent in-house*
- *Ensure the **Missing Pages** field is completed if pages are missing from modules*
- *Ensure the **Patient Number** and **Patient Initials** entered match the information on the CRF*
- *Complete one TRF per batch of modules to be sent in-house*
- *Ensure all sections of the TRF are legible*

Module	Module Description	Page Range	Modules		Missing Pages (if Applicable)
			Sent to DM	Unused	
GIAEF1	FU GI AE Report	GF1 - GF4	☐	☐	_____

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

Protocol	Centre Number	Patient Number	Patient Initials		
207499/157		[redacted]			

2 0 7 4 9 9 1 5 7

GIAE1

Please do not split modules

Module GIAE1 : **Supplemental Report for Gastrointestinal Adverse Experience**

CRF Pages **G1 - G7**

Unprocessed Forms : **Within this module the following occur which will generate attachments that need to be brought in-house.**

None

FOR OFFICE USE ONLY Module Comments:

Sent to Data Mngt	Review Complete Date: User:	First Entry Complete Date: User:
Second Entry Complete Date: User:	Validation Complete Date: User:	**Clintrial PID:**

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number	Patient Initials		Supplemental Report For Gastrointestinal AE
207499/157		[redacted]			

SUPPLEMENTAL REPORT FOR GASTROINTESTINAL ADVERSE EXPERIENCE

This form is for GI symptoms which cause concern (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhea, vomiting) 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.

Date of Assessment:

Day Month Yr

Person performing assessment
(Please print clearly) _

Signature: _

*Please mark (✓) the gastrointestinal symptom(s) that prompted the report and mark **one** box that best describes how the symptoms at the time of this assessment compare with the onset:*

GI Symptom(s)	[1]Resolved	[2]Better	[3]Same	[4]Worse
☐ Black or bloody stool	☐	☐	☐	☐
☐ Abdominal pain or discomfort	☐	☐	☐	☐
☐ Diarrhea	☐	☐	☐	☐
☐ Vomiting	☐	☐	☐	☐
☐ Other GI symptoms, specify:				
	☐	☐	☐	☐
	☐	☐	☐	☐
	☐	☐	☐	☐

Was alcohol consumption associated with the GIAE symptom(s) of concern?

☐ No

☐ Yes ⟶ *If 'Yes' record number of units (a unit of alcohol = 8 oz [25cl, half a pint] of beer, 4 oz [125 mL, a medium-sized glass] of wine or 1 oz [24 mL, a measure] of spirits)* ☐☐

If the patient took a new concomitant medication or changed the dose of a continuing medication, please record this medication or change in the concomitant medication section of the CRF.

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number	Patient Initials		Supplemental Report For Gastrointestinal AE
207499/157		[redacted]			

SUPPLEMENTAL REPORT FOR GASTROINTESTINAL ADVERSE EXPERIENCE

Abdominal pain or discomfort

Did the patient report abdominal pain or discomfort?

☐ No

☐ Yes ⟶ *If 'Yes', please complete the following pain assessment.*

Location of pain or discomfort:

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.

☐ Right Hypochondriac ☐ Epigastric ☐ Left Hypochondriac

☐ Right Lateral ☐ Umbilical ☐ Left Lateral

☐ Right Inguinal ☐ Suprapubic ☐ Left Inguinal

Schematic of Abdomen

RIGHT LEFT

1	2	3
4	5	6
7	8	9

Onset of pain or discomfort:
(mark (✓) only one)

[1] ☐ Sudden

[2] ☐ Gradual

Quality of pain or discomfort (*mark (✓) all that apply*):

☐ Sharp ☐ Colicky ☐ Cramping

☐ Dull ☐ Burning ☐ Other, specify: _

☐ Achy ☐ Gnawing

☐ Pulsatile ☐ Boring/drilling

Does pain or discomfort radiate?

☐ No

☐ Yes ⟶ *If 'Yes' please mark location(s) to which pain or discomfort radiates.*

☐ Abdominal Area (see schematic above) specify: _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _

☐ Back

☐ Groin

☐ Shoulder tip

☐ Other, specify: _

00000

SmithKline Beecham Pharmaceuticals

Protocol	Centre Number	Patient Number	Patient Initials		Supplemental Report For Gastrointestinal AE
207499/157		[redacted]			

SUPPLEMENTAL REPORT FOR GASTROINTESTINAL ADVERSE EXPERIENCE

SYMPTOM ASSESSMENT *(Continued)*

Stool Assessment - Black or Bloody stool

Did the patient notice black or bloody stool?

☐ No

☐ Yes ⟶ *If 'Yes', please complete the following stool assessment*

Stool appearance *(mark (✓) all that apply):*

☐ Normal with red blood on outside
☐ Normal with red blood mixed throughout
☐ Black, tarry stool
☐ Normal stool with blood on toilet paper
☐ No formed stool, only blood
☐ Red toilet bowl water
☐ Other, specify: _ _ _ _ _ _ _ _ _ _

Does the patient have a history of black or bloody stool? ☐ No ☐ Yes

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

Does the patient presently have hemorrhoids? ☐ No ☐ Yes

Is the patient taking NSAIDS/aspirin products? ☐ No ☐ Yes

If female, is bloody stool possibly menstrual or uterine in origin? ☐ No ☐ Yes ☐ Not applicable

PHYSICAL EXAMINATION

	Present	Absent
Abdominal tenderness	[1] ☐	[2] ☐
Abdominal masses	[1] ☐	[2] ☐
Peritoneal signs	[1] ☐	[2] ☐

Other clinically significant GI physical examination findings, please specify: _ _ _ _ _ _ _ _ _ _ _ _ _ _

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number	Patient Initials		Supplemental Report For Gastrointestinal AE
207499/157		[redacted]			

SUPPLEMENTAL REPORT FOR GASTROINTESTINAL ADVERSE EXPERIENCE

PHYSICAL EXAMINATION (*continued*)

Weight
(light clothes, no shoes)

☐ kg
☐ lb

☐☐☐.☐

Orthostatic Vital Signs - to be completed for all patients reporting GIAE of concern

	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 ⟶ *If 'Yes' please record the findings and/or diagnosis in the Baseline Signs and Symptoms or the Adverse Experience page of the CRF.*

Fecal Occult Blood - to be completed for all patients reporting GIAE of concern

Test	Date of Collection Day Mth Yr	Result of fecal occult blood test
1	☐☐ ☐☐☐ ☐☐	[NEG] ☐ Negative [POS] ☐ Positive
2	☐☐ ☐☐☐ ☐☐	[NEG] ☐ Negative [POS] ☐ Positive
3	☐☐ ☐☐☐ ☐☐	[NEG] ☐ Negative [POS] ☐ Positive

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number	Patient Initials		Supplemental Report For Gastrointestinal AE
207499/157		[redacted]			

SUPPLEMENTAL REPORT FOR GASTROINTESTINAL ADVERSE EXPERIENCE

Laboratory Sample

Please take blood samples for hematology and blood chemistry and a urine sample for urinalysis. Please refer to the instructions on the Quest shipping form and manual.

Sample Date ___ ___ ___
Day Month Yr

Please attach Central Lab CRF label from the 'Unscheduled' laboratory requisition here

(Attach label when sample is sent to central lab.)

Laboratory reports will stay at the site as part of the patient's source documentation.

Please record any clinically significant findings and/or diagnosis in the Baseline Signs and Symptoms or the Adverse Experiences section.

ADDITIONAL TESTS

Additional tests may be ordered at the discretion of the investigator. Please mark (✓) the additional tests that have been ordered.

- ☐ X-ray
- ☐ CT of abdomen
- ☐ Rectal/pelvic examination
- ☐ Stool for ova and parasites
- ☐ Ultrasound of the abdomen
- ☐ Other, specify: _
- ☐ Colonoscopy

Was the patient referred to a gastroenterologist or other specialist?

- ☐ No
- ☐ Yes

Please record abnormal findings in the Baseline Signs and Symptoms or Adverse Experiences section of the CRF. Please forward results when available and record tests in the Medical Procedures page of the CRF.

Investigator's Remarks: _

- -

- -

- -

- -

- -

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number	Patient Initials		Supplemental Report For Gastrointestinal AE
207499/157		[redacted]			

SUPPLEMENTAL REPORT FOR GASTROINTESTINAL ADVERSE EXPERIENCE

PHARMACOKINETIC SAMPLE

Collect a blood sample (5mL) for pharmacokinetic evaluation.

Was a pharmacokinetic sample taken?

☐ No

☐ Yes → *If 'Yes', record date and time sample was taken* Day Month Yr 24hr:min

Check that the date you have recorded here is the same as that recorded on the PK sample requisition form.

Select the appropriate label pair from the PK sample requisition form; affix one copy to the plasma sample and the other copy here.

Attach pharmacokinetic sample label here (if sample was taken)

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

Have further doses of study medication been taken since the onset of this GI adverse experience?

☐ No

☐ Yes → *If 'Yes', record date and time of last dose of study medication prior to collection of the pharmacokinetic sample:* Day Month Yr 24hr:min

Was this dose taken with food?

☐ No

☐ Yes

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number	Patient Initials		Supplemental Report For Gastrointestinal AE
207499/157		[redacted]			

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.

[1] ☐ Adverse experience(s) (see Protocol Section 8.1.1)

[2] ☐ Serious adverse experience(s) (see Protocol Section 8.1.4)

If adverse experience, please record in the Baseline Signs and Symptoms (between Visits 1 and 3) or Non-Serious Adverse Experience (after first dose of randomized medication) 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 medical terminology and same onset date/time as in the CRF. Include only GIAEs in the space below).

Onset Date and Time

_ _ _ _

00000

SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number	Patient Initials	Investigator
207499/157	☐☐☐	[redacted]	☐☐☐☐	_____

CRF TRACKING/REVIEW FORM

Please submit COMPLETE modules only. Do not submit whole blank modules.

- *Mark the **Unused** box for all remaining modules that will **not** be completed and sent in-house*
- *Ensure the **Missing Pages** field is completed if pages are missing from modules*
- *Ensure the **Patient Number** and **Patient Initials** entered match the information on the CRF*
- *Complete one TRF per batch of modules to be sent in-house*
- *Ensure all sections of the TRF are legible*

Module	Module Description	Page Range	Modules		Missing Pages (if Applicable)
			Sent to DM	Unused	
GIAE1	Supp Report for Gastroint AE	G1 - G7	☐	☐	_____

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

00000

SmithKline Beecham
Pharmaceuticals

Protocol **207499/157**		**Patient Number** [redacted]			**Visit 10 Week 36**

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 10

Is the patient continuing in the study?

☐ No ⟶ *Go to '1' below.*

☐ Yes ⟶ *Go to '2' below.*

*1. If the patient is **not** continuing in the study, is the patient willing to return for essential assessments?*

If 'No', please complete the assessments for Visit 10, the additional assessments for patients withdrawing at Visit 10 and the Study Continuation/Withdrawal page at the back of this book. Please schedule a safety follow-up visit in 7 days (+/- 3 days).

If 'Yes', please complete the assessments for Visit 10, the additional assessments for patients withdrawing at Visit 10 and the Study Continuation/Withdrawal page at the back of this book. Ask the patient to return for a safety follow-up visit in 7 days (+/- 3 days) and then for their next scheduled visit 49 (+/- 6 days) later for essential assessments only.

*2. If the patient **is** continuing in the study, please:* (tick if done) ☑

- *Issue the patient a new diary card and remind the patient to complete the diary each morning until the next visit.* ☐
- *Ask the patient to return for the next visit in 56 +/- 6 days at the same time of day.* ☐
- *For patients who have consented to an additional faecal occult test, issue a faecal occult blood test kit and ask the patient to follow the instructions provided on the kit. Ask the patient to undertake the test in the two weeks prior to visit 11 and to return the sample at visit 11.* ☐
- ***Remind the patient:***
  - i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after their breakfast.* ☐
  - ii ***not** to take their dose of study medication for at least 8 hours prior to their next study visit appointment.* ☐
  - iii *to refrain from using salbutamol or anticholinergic agents during the **4 hours** immediately preceding 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, the study salbutamol inhaler and spacer, and the diary card.* ☐
  - vi *to continue to take the anticholinergic medication, if prescribed, at a constant dose, and salbutamol when needed to control symptoms.* ☐
  - vii *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 occurrence.* ☐

SmithKline Beecham
Pharmaceuticals

Protocol 207499/157		Patient Number			Visit 11 Week 44

INVESTIGATOR INSTRUCTIONS

The following procedures (Vital Signs and Pulmonary Function Tests) must be performed greater than 4 hours after the patient's last salbutamol administration.

VITAL SIGNS

Time of assessment : ☐☐ 24hr:min

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
☐☐☐/☐☐☐	☐☐☐

Are there any **clinically significant worsenings** since the previous visit?

☐ No

☐ Yes ⟶ *If 'Yes' please record the findings and/or diagnosis in the Adverse Experiences section at the back of this module.*

OPTIONAL FAECAL OCCULT BLOOD TEST (Specific consent required)

Has the patient consented to the additional Visit 11 FOB test ? ☐ No ☐ Yes ⟶ *If 'Yes', complete below.*

The faecal occult blood test should be performed on three consecutive bowel movements within 14 days of Visit 11. Patients are not to take samples during or up-to 3-days after a menstrual period or while having bleeding haemorrhoids or blood in the urine. Patients are not to take aspirin or other non-steroidal anti-inflammatory drugs for 7 days prior to and during the test period and they are to avoid Vitamin C in excess of 250mg 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.

Did the patient follow these instructions?

☐ No ⟶ *If 'No', please specify:* _

☐ Yes

Test	Date of Collection Day Mth Yr	Result of faecal occult blood test
1	☐☐ ☐☐☐ ☐☐	[NEG] ☐ Negative [POS] ☐ Positive
2	☐☐ ☐☐☐ ☐☐	[NEG] ☐ Negative [POS] ☐ Positive
3	☐☐ ☐☐☐ ☐☐	[NEG] ☐ Negative [POS] ☐ Positive

Are these findings clinically significant ?

☐ No

☐ Yes ⟶ *If 'Yes' please record the findings and/or diagnosis in the Adverse Experiences section at the back of this module.*

SmithKline Beecham
Pharmaceuticals

Protocol 207499/157		**Patient Number**			**Visit 11 Week 44**

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 11

Is the patient continuing in the study?

☐ No ⟶ *Go to '1' below.*

☐ Yes ⟶ *Go to '2' below.*

*1. If the patient is **not** continuing in the study, is the patient willing to return for essential assessments?*

If 'No', please complete the assessments for Visit 11, the additional assessments for patients withdrawing at Visit 11 and the Study Conclusion page at the back of this book. Please schedule a safety follow-up visit in 7 days (+/- 3 days).

If 'Yes', please complete the assessments for Visit 11, the additional assessments for patients withdrawing at Visit 11 and the Study Conclusion page at the back of this book. Ask the patient to return for a safety follow-up visit in 7 days (+/- 3 days) and then for their next scheduled visit 49 (+/- 6 days) later for essential assessments only.

*2. If the patient **is** continuing in the study, please:* (tick if done)

- *Issue the patient a new diary card and remind the patient to complete the diary each morning until the next visit.* ☐
- *Ask the patient to return for the next visit in 56 +/- 6 days at the same time of day.* ☐
- ***Remind the patient:***
  - i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after their breakfast.* ☐
  - ii ***not** to take their dose of study medication for at least 8 hours prior to their next study visit appointment.* ☐
  - iii *to refrain from using salbutamol or anticholinergic agents during the **4 hours** immediately preceding 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, the study salbutamol inhaler and spacer, and the diary card.* ☐
  - vi *to continue to take the anticholinergic medication, if prescribed, at a constant dose, and salbutamol when needed to control symptoms.* ☐
  - vii *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 occurrence.* ☐
  - viii *if the additional faecal occult blood test has not been provided at visit 11 and the patient has consented to undertake this test, ask the patient to complete the faecal occult blood test and return it within 14 days.* ☐

Protocol	Centre Number	Patient Number
207499/157		[redacted]

CONFIDENTIAL

SmithKline Beecham
Pharmaceuticals

PROTOCOL 207499/157
PATIENT DIARY CARD

Date and time of next clinic visit : Day Month Yr 24hr:min

Doctor's name: _

Hospital/Clinic Address: _

_ _

Hospital/Clinic telephone number: _

Start date of daily record card : Day Month Yr

IMPORTANT: If this Daily Record Card is found, please return immediately to the above address.

Please indicate below the visit at which this diary card was dispensed

Visit	1	2	3	4	5	6	7	8	9	10	11
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

I confirm that all of the pages of this Daily Record Card have been reviewed and that any Adverse Events or Changes in Medication details have been added to the Case Report Form.

Monitor's signature: _

Monitor's name - PRINT: _

Date of signature: Day Month Yr 24hr:min

English

COMPLETE YOUR DIARY CARD IN PEN (*DO NOT USE PENCIL*)

1. **How to fill in the diary:**
   - *Fill in one column each morning when you get up:*
   - *As far as possible, keep to the same times each day (e.g. 7-8 am)*

2. **Peak Flow**
   - *Your doctor will explain to you how to measure your peak flow*
   - *Always sit down to do your peak flow*
   - *Always take your peak flow **before** taking any medicine, particularly your inhalers*
   - *Record the highest of 3 measurements*
   - *If you have not made a measurement, put a * in the appropriate box*

3. **Symptoms**
   - *Circle the appropriate score number for each of your chest symptoms using the scoring system provided.*

KEY TO SYMPTOM SCORES

Breathlessness

How breathless have you been in the last 24 hours?

0 = Not breathless at rest or on exertion
1 = Not breathless at rest but breathless on moderate exertion (e.g. walking quickly, climbing stairs)
2 = Not breathless at rest but breathless on mild exertion (e.g. walking on the level)
3 = Not breathless at rest but breathless on minimal exertion (e.g. getting washed or dressed)
4 = Breathless at rest (e.g. sitting down reading or watching TV)

Cough

How much have you coughed in the last 24 hours?

0 = No cough
1 = Mild cough (e.g. some coughing mostly in the morning)
2 = Moderate cough (e.g. coughing in the morning and sometimes during the day)
3 = Severe cough (e.g. coughing in the morning and throughout the day)

Sputum Production

How much sputum have you produced in the last 24 hours?

0 = None
1 = Mild sputum production (e.g. only in the morning)
2 = Moderate sputum production (e.g. in the morning and sometimes during the day)
3 = Severe sputum production (e.g. throughout the whole day)

Sputum Colour

What colour has your sputum been in the last 24 hours?

0 = No sputum produced today
1 = Colourless
2 = White/grey
3 = Light yellow/green
4 = Dark yellow/green

SmithKline Beecham
Pharmaceuticals

Protocol	207499/157	Patient Number	[redacted]	Page	1

Please complete when you get up each morning before taking any inhalers or study medication. Fill in the appropriate score for each of your symptoms using the key to symptom scores on the facing page.

	eg	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Date ***dd mm***	15/10	/	/	/	/	/	/	/
1. Measure your Peak Flow three times (before taking any medications, particularly your inhalers) and enter the highest value.	210							
2. How many **times *(not puffs)*** did you use your salbutamol inhaler in the last 24 hours? *(enter number of times)*	2							
3. How many times did you awake during last night because of your chest problems? *(enter number of times)*	1							
4. How breathless have you been in the last 24 hours? Score (0-4) *(circle appropriate score)*	(0)	0	0	0	0	0	0	0
	1	1	1	1	1	1	1	1
	2	2	2	2	2	2	2	2
	3	3	3	3	3	3	3	3
	4	4	4	4	4	4	4	4
5. How much have you coughed in the last 24 hours? Score (0-3) *(circle appropriate score)*	(0)	0	0	0	0	0	0	0
	1	1	1	1	1	1	1	1
	2	2	2	2	2	2	2	2
	3	3	3	3	3	3	3	3
6. How much sputum have you produced in the last 24 hours? Score (0-3) *(circle appropriate score)*	(0)	0	0	0	0	0	0	0
	1	1	1	1	1	1	1	1
	2	2	2	2	2	2	2	2
	3	3	3	3	3	3	3	3
7. What colour has your sputum been in the last 24 hours? Score (0-4) *(circle appropriate score)*	(0)	0	0	0	0	0	0	0
	1	1	1	1	1	1	1	1
	2	2	2	2	2	2	2	2
	3	3	3	3	3	3	3	3
	4	4	4	4	4	4	4	4
8. Have you missed any time from work or usual activities in the last 24 hours because of your chest problems? *(circle appropriate answer)*	(None)	None	None	None	None	None	None	None
	Half day	Half day	Half day	Half day	Half day	Half day	Half day	Half day
	Full day	Full day	Full day	Full day	Full day	Full day	Full day	Full day
9. Have you needed any assistance from a caregiver (paid or unpaid) in the last 24 hours because of your chest problems? *(circle appropriate answer)*	(None)	None	None	None	None	None	None	None
	Half day	Half day	Half day	Half day	Half day	Half day	Half day	Half day
	Full day	Full day	Full day	Full day	Full day	Full day	Full day	Full day
10. Have you changed any of your medications in the last 24 hours, or had to contact the doctor because of your chest? *(circle YES/NO)* ***If YES, write details on the last page of this Daily Record card.***	(Yes)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	No	No	No	No	No	No	No	No

COMPLETE YOUR DIARY CARD IN PEN (*DO NOT USE PENCIL*)

1. **How to fill in the diary:**
   - *Fill in one column each morning when you get up:*
   - *As far as possible, keep to the same times each day (e.g. 7-8 am)*

2. **Peak Flow**
   - *Your doctor will explain to you how to measure your peak flow*
   - *Always sit down to do your peak flow*
   - *Always take your peak flow **before** taking any medicine, particularly your inhalers*
   - *Record the highest of 3 measurements*
   - *If you have not made a measurement, put a * in the appropriate box*

3. **Symptoms**
   - *Circle the appropriate score number for each of your chest symptoms using the scoring system provided.*

KEY TO SYMPTOM SCORES

Breathlessness

How breathless have you been in the last 24 hours?

0 = Not breathless at rest or on exertion
1 = Not breathless at rest but breathless on moderate exertion (e.g. walking quickly, climbing stairs)
2 = Not breathless at rest but breathless on mild exertion (e.g. walking on the level)
3 = Not breathless at rest but breathless on minimal exertion (e.g. getting washed or dressed)
4 = Breathless at rest (e.g. sitting down reading or watching TV)

Cough

How much have you coughed in the last 24 hours?

0 = No cough
1 = Mild cough (e.g. some coughing mostly in the morning)
2 = Moderate cough (e.g. coughing in the morning and sometimes during the day)
3 = Severe cough (e.g. coughing in the morning and throughout the day)

Sputum Production

How much sputum have you produced in the last 24 hours?

0 = None
1 = Mild sputum production (e.g. only in the morning)
2 = Moderate sputum production (e.g. in the morning and sometimes during the day)
3 = Severe sputum production (e.g. throughout the whole day)

Sputum Colour

What colour has your sputum been in the last 24 hours?

0 = No sputum produced today
1 = Colourless
2 = White/grey
3 = Light yellow/green
4 = Dark yellow/green

SmithKline Beecham
Pharmaceuticals

Protocol	207499/157	Patient Number	[redacted]	Page	2

Please complete when you get up each morning before taking any inhalers or study medication. Fill in the appropriate score for each of your symptoms using the key to symptom scores on the facing page.

	eg	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
Date ***dd mm***	15/10	/	/	/	/	/	/	/
1. Measure your Peak Flow three times (before taking any medications, particularly your inhalers) and enter the highest value.	210							
2. How many **times *(not puffs)*** did you use your salbutamol inhaler in the last 24 hours? *(enter number of times)*	2							
3. How many times did you awake during last night because of your chest problems? *(enter number of times)*	1							
4. How breathless have you been in the last 24 hours? Score (0-4) *(circle appropriate score)*	(0)	0	0	0	0	0	0	0
	1	1	1	1	1	1	1	1
	2	2	2	2	2	2	2	2
	3	3	3	3	3	3	3	3
	4	4	4	4	4	4	4	4
5. How much have you coughed in the last 24 hours? Score (0-3) *(circle appropriate score)*	(0)	0	0	0	0	0	0	0
	1	1	1	1	1	1	1	1
	2	2	2	2	2	2	2	2
	3	3	3	3	3	3	3	3
6. How much sputum have you produced in the last 24 hours? Score (0-3) *(circle appropriate score)*	(0)	0	0	0	0	0	0	0
	1	1	1	1	1	1	1	1
	2	2	2	2	2	2	2	2
	3	3	3	3	3	3	3	3
7. What colour has your sputum been in the last 24 hours? Score (0-4) *(circle appropriate score)*	(0)	0	0	0	0	0	0	0
	1	1	1	1	1	1	1	1
	2	2	2	2	2	2	2	2
	3	3	3	3	3	3	3	3
	4	4	4	4	4	4	4	4
8. Have you missed any time from work or usual activities in the last 24 hours because of your chest problems? *(circle appropriate answer)*	(None)	None	None	None	None	None	None	None
	Half day	Half day	Half day	Half day	Half day	Half day	Half day	Half day
	Full day	Full day	Full day	Full day	Full day	Full day	Full day	Full day
9. Have you needed any assistance from a caregiver (paid or unpaid) in the last 24 hours because of your chest problems? *(circle appropriate answer)*	(None)	None	None	None	None	None	None	None
	Half day	Half day	Half day	Half day	Half day	Half day	Half day	Half day
	Full day	Full day	Full day	Full day	Full day	Full day	Full day	Full day
10. Have you changed any of your medications in the last 24 hours, or had to contact the doctor because of your chest? *(circle YES/NO)* ***If YES, write details on the last page of this Daily Record card.***	(Yes)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	No	No	No	No	No	No	No	No

COMPLETE YOUR DIARY CARD IN PEN (*DO NOT USE PENCIL*)

1. **How to fill in the diary:**
   - *Fill in one column each morning when you get up:*
   - *As far as possible, keep to the same times each day (e.g. 7-8 am)*

2. **Peak Flow**
   - *Your doctor will explain to you how to measure your peak flow*
   - *Always sit down to do your peak flow*
   - *Always take your peak flow **before** taking any medicine, particularly your inhalers*
   - *Record the highest of 3 measurements*
   - *If you have not made a measurement, put a * in the appropriate box*

3. **Symptoms**
   - *Circle the appropriate score number for each of your chest symptoms using the scoring system provided.*

KEY TO SYMPTOM SCORES

Breathlessness

How breathless have you been in the last 24 hours?

0 = Not breathless at rest or on exertion
1 = Not breathless at rest but breathless on moderate exertion (e.g. walking quickly, climbing stairs)
2 = Not breathless at rest but breathless on mild exertion (e.g. walking on the level)
3 = Not breathless at rest but breathless on minimal exertion (e.g. getting washed or dressed)
4 = Breathless at rest (e.g. sitting down reading or watching TV)

Cough

How much have you coughed in the last 24 hours?

0 = No cough
1 = Mild cough (e.g. some coughing mostly in the morning)
2 = Moderate cough (e.g. coughing in the morning and sometimes during the day)
3 = Severe cough (e.g. coughing in the morning and throughout the day)

Sputum Production

How much sputum have you produced in the last 24 hours?

0 = None
1 = Mild sputum production (e.g. only in the morning)
2 = Moderate sputum production (e.g. in the morning and sometimes during the day)
3 = Severe sputum production (e.g. throughout the whole day)

Sputum Colour

What colour has your sputum been in the last 24 hours?

0 = No sputum produced today
1 = Colourless
2 = White/grey
3 = Light yellow/green
4 = Dark yellow/green

SmithKline Beecham
Pharmaceuticals

Protocol	207499/157	Patient Number	[redacted]	Page	3

Please complete when you get up each morning before taking any inhalers or study medication. Fill in the appropriate score for each of your symptoms using the key to symptom scores on the facing page.

	eg	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21
Date ***dd mm***	15/10	/	/	/	/	/	/	/
1. Measure your Peak Flow three times (before taking any medications, particularly your inhalers) and enter the highest value.	210							
2. How many **times *(not puffs)*** did you use your salbutamol inhaler in the last 24 hours? *(enter number of times)*	2							
3. How many times did you awake during last night because of your chest problems? *(enter number of times)*	1							
4. How breathless have you been in the last 24 hours? Score (0-4) *(circle appropriate score)*	(0)	0	0	0	0	0	0	0
	1	1	1	1	1	1	1	1
	2	2	2	2	2	2	2	2
	3	3	3	3	3	3	3	3
	4	4	4	4	4	4	4	4
5. How much have you coughed in the last 24 hours? Score (0-3) *(circle appropriate score)*	(0)	0	0	0	0	0	0	0
	1	1	1	1	1	1	1	1
	2	2	2	2	2	2	2	2
	3	3	3	3	3	3	3	3
6. How much sputum have you produced in the last 24 hours? Score (0-3) *(circle appropriate score)*	(0)	0	0	0	0	0	0	0
	1	1	1	1	1	1	1	1
	2	2	2	2	2	2	2	2
	3	3	3	3	3	3	3	3
7. What colour has your sputum been in the last 24 hours? Score (0-4) *(circle appropriate score)*	(0)	0	0	0	0	0	0	0
	1	1	1	1	1	1	1	1
	2	2	2	2	2	2	2	2
	3	3	3	3	3	3	3	3
	4	4	4	4	4	4	4	4
8. Have you missed any time from work or usual activities in the last 24 hours because of your chest problems? *(circle appropriate answer)*	(None)	None	None	None	None	None	None	None
	Half day	Half day	Half day	Half day	Half day	Half day	Half day	Half day
	Full day	Full day	Full day	Full day	Full day	Full day	Full day	Full day
9. Have you needed any assistance from a caregiver (paid or unpaid) in the last 24 hours because of your chest problems? *(circle appropriate answer)*	(None)	None	None	None	None	None	None	None
	Half day	Half day	Half day	Half day	Half day	Half day	Half day	Half day
	Full day	Full day	Full day	Full day	Full day	Full day	Full day	Full day
10. Have you changed any of your medications in the last 24 hours, or had to contact the doctor because of your chest? *(circle YES/NO)* ***If YES, write details on the last page of this Daily Record card.***	(Yes)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	No	No	No	No	No	No	No	No

COMPLETE YOUR DIARY CARD IN PEN (*DO NOT USE PENCIL*)

1. **How to fill in the diary:**
   - *Fill in one column each morning when you get up:*
   - *As far as possible, keep to the same times each day (e.g. 7-8 am)*

2. **Peak Flow**
   - *Your doctor will explain to you how to measure your peak flow*
   - *Always sit down to do your peak flow*
   - *Always take your peak flow **before** taking any medicine, particularly your inhalers*
   - *Record the highest of 3 measurements*
   - *If you have not made a measurement, put a * in the appropriate box*

3. **Symptoms**
   - *Circle the appropriate score number for each of your chest symptoms using the scoring system provided.*

KEY TO SYMPTOM SCORES

Breathlessness

How breathless have you been in the last 24 hours?

0 = Not breathless at rest or on exertion
1 = Not breathless at rest but breathless on moderate exertion (e.g. walking quickly, climbing stairs)
2 = Not breathless at rest but breathless on mild exertion (e.g. walking on the level)
3 = Not breathless at rest but breathless on minimal exertion (e.g. getting washed or dressed)
4 = Breathless at rest (e.g. sitting down reading or watching TV)

Cough

How much have you coughed in the last 24 hours?

0 = No cough
1 = Mild cough (e.g. some coughing mostly in the morning)
2 = Moderate cough (e.g. coughing in the morning and sometimes during the day)
3 = Severe cough (e.g. coughing in the morning and throughout the day)

Sputum Production

How much sputum have you produced in the last 24 hours?

0 = None
1 = Mild sputum production (e.g. only in the morning)
2 = Moderate sputum production (e.g. in the morning and sometimes during the day)
3 = Severe sputum production (e.g. throughout the whole day)

Sputum Colour

What colour has your sputum been in the last 24 hours?

0 = No sputum produced today
1 = Colourless
2 = White/grey
3 = Light yellow/green
4 = Dark yellow/green

SmithKline Beecham
Pharmaceuticals

Protocol	207499/157	Patient Number	[redacted]	Page	4

Please complete when you get up each morning before taking any inhalers or study medication. Fill in the appropriate score for each of your symptoms using the key to symptom scores on the facing page.

	eg	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28
Date ***dd mm***	15/10	/	/	/	/	/	/	/
1. Measure your Peak Flow three times (before taking any medications, particularly your inhalers) and enter the highest value.	210							
2. How many **times *(not puffs)*** did you use your salbutamol inhaler in the last 24 hours? *(enter number of times)*	2							
3. How many times did you awake during last night because of your chest problems? *(enter number of times)*	1							
4. How breathless have you been in the last 24 hours? Score (0-4) *(circle appropriate score)*	(0)	0	0	0	0	0	0	0
	1	1	1	1	1	1	1	1
	2	2	2	2	2	2	2	2
	3	3	3	3	3	3	3	3
	4	4	4	4	4	4	4	4
5. How much have you coughed in the last 24 hours? Score (0-3) *(circle appropriate score)*	(0)	0	0	0	0	0	0	0
	1	1	1	1	1	1	1	1
	2	2	2	2	2	2	2	2
	3	3	3	3	3	3	3	3
6. How much sputum have you produced in the last 24 hours? Score (0-3) *(circle appropriate score)*	(0)	0	0	0	0	0	0	0
	1	1	1	1	1	1	1	1
	2	2	2	2	2	2	2	2
	3	3	3	3	3	3	3	3
7. What colour has your sputum been in the last 24 hours? Score (0-4) *(circle appropriate score)*	(0)	0	0	0	0	0	0	0
	1	1	1	1	1	1	1	1
	2	2	2	2	2	2	2	2
	3	3	3	3	3	3	3	3
	4	4	4	4	4	4	4	4
8. Have you missed any time from work or usual activities in the last 24 hours because of your chest problems? *(circle appropriate answer)*	(None)	None	None	None	None	None	None	None
	Half day	Half day	Half day	Half day	Half day	Half day	Half day	Half day
	Full day	Full day	Full day	Full day	Full day	Full day	Full day	Full day
9. Have you needed any assistance from a caregiver (paid or unpaid) in the last 24 hours because of your chest problems? *(circle appropriate answer)*	(None)	None	None	None	None	None	None	None
	Half day	Half day	Half day	Half day	Half day	Half day	Half day	Half day
	Full day	Full day	Full day	Full day	Full day	Full day	Full day	Full day
10. Have you changed any of your medications in the last 24 hours, or had to contact the doctor because of your chest? *(circle YES/NO)* ***If YES, write details on the last page of this Daily Record card.***	(Yes)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	No	No	No	No	No	No	No	No

COMPLETE YOUR DIARY CARD IN PEN (*DO NOT USE PENCIL*)

1. **How to fill in the diary:**
   - *Fill in one column each morning when you get up:*
   - *As far as possible, keep to the same times each day (e.g. 7-8 am)*

2. **Peak Flow**
   - *Your doctor will explain to you how to measure your peak flow*
   - *Always sit down to do your peak flow*
   - *Always take your peak flow **before** taking any medicine, particularly your inhalers*
   - *Record the highest of 3 measurements*
   - *If you have not made a measurement, put a * in the appropriate box*

3. **Symptoms**
   - *Circle the appropriate score number for each of your chest symptoms using the scoring system provided.*

KEY TO SYMPTOM SCORES

Breathlessness

How breathless have you been in the last 24 hours?

0 = Not breathless at rest or on exertion
1 = Not breathless at rest but breathless on moderate exertion (e.g. walking quickly, climbing stairs)
2 = Not breathless at rest but breathless on mild exertion (e.g. walking on the level)
3 = Not breathless at rest but breathless on minimal exertion (e.g. getting washed or dressed)
4 = Breathless at rest (e.g. sitting down reading or watching TV)

Cough

How much have you coughed in the last 24 hours?

0 = No cough
1 = Mild cough (e.g. some coughing mostly in the morning)
2 = Moderate cough (e.g. coughing in the morning and sometimes during the day)
3 = Severe cough (e.g. coughing in the morning and throughout the day)

Sputum Production

How much sputum have you produced in the last 24 hours?

0 = None
1 = Mild sputum production (e.g. only in the morning)
2 = Moderate sputum production (e.g. in the morning and sometimes during the day)
3 = Severe sputum production (e.g. throughout the whole day)

Sputum Colour

What colour has your sputum been in the last 24 hours?

0 = No sputum produced today
1 = Colourless
2 = White/grey
3 = Light yellow/green
4 = Dark yellow/green

SmithKline Beecham
Pharmaceuticals

Protocol	207499/157	Patient Number	[redacted]	Page	5

Please complete when you get up each morning before taking any inhalers or study medication. Fill in the appropriate score for each of your symptoms using the key to symptom scores on the facing page.

	eg	Day 29	Day 30	Day 31	Day 32	Day 33	Day 34	Day 35
Date ***dd mm***	15/10	/	/	/	/	/	/	/
1. Measure your Peak Flow three times (before taking any medications, particularly your inhalers) and enter the highest value.	210							
2. How many **times *(not puffs)*** did you use your salbutamol inhaler in the last 24 hours? *(enter number of times)*	2							
3. How many times did you awake during last night because of your chest problems? *(enter number of times)*	1							
4. How breathless have you been in the last 24 hours? Score (0-4) *(circle appropriate score)*	(0)	0	0	0	0	0	0	0
	1	1	1	1	1	1	1	1
	2	2	2	2	2	2	2	2
	3	3	3	3	3	3	3	3
	4	4	4	4	4	4	4	4
5. How much have you coughed in the last 24 hours? Score (0-3) *(circle appropriate score)*	(0)	0	0	0	0	0	0	0
	1	1	1	1	1	1	1	1
	2	2	2	2	2	2	2	2
	3	3	3	3	3	3	3	3
6. How much sputum have you produced in the last 24 hours? Score (0-3) *(circle appropriate score)*	(0)	0	0	0	0	0	0	0
	1	1	1	1	1	1	1	1
	2	2	2	2	2	2	2	2
	3	3	3	3	3	3	3	3
7. What colour has your sputum been in the last 24 hours? Score (0-4) *(circle appropriate score)*	(0)	0	0	0	0	0	0	0
	1	1	1	1	1	1	1	1
	2	2	2	2	2	2	2	2
	3	3	3	3	3	3	3	3
	4	4	4	4	4	4	4	4
8. Have you missed any time from work or usual activities in the last 24 hours because of your chest problems? *(circle appropriate answer)*	(None)	None	None	None	None	None	None	None
	Half day	Half day	Half day	Half day	Half day	Half day	Half day	Half day
	Full day	Full day	Full day	Full day	Full day	Full day	Full day	Full day
9. Have you needed any assistance from a caregiver (paid or unpaid) in the last 24 hours because of your chest problems? *(circle appropriate answer)*	(None)	None	None	None	None	None	None	None
	Half day	Half day	Half day	Half day	Half day	Half day	Half day	Half day
	Full day	Full day	Full day	Full day	Full day	Full day	Full day	Full day
10. Have you changed any of your medications in the last 24 hours, or had to contact the doctor because of your chest? *(circle YES/NO)* ***If YES, write details on the last page of this Daily Record card.***	(Yes)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	No	No	No	No	No	No	No	No

SmithKline Beecham
Pharmaceuticals

Protocol	207499/157	Patient Number	[redacted]	Page	6

If you have any medical problems or need to take any new medications, please make a note of them below:

Date day month year	Medical problem	Doctor or nurse contacted ✔ YES	 NO	Treatment
e.g. 12 04 98	***Chest infection***	✔		***Antibiotics***

207499/157

ST. GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE (SGRQ)

Please indicate the current visit by ticking the appropriate box below.

Visit	3	9	12	EW
	☐	☐	☐	☐

English

00000

SmithKline Beecham
Pharmaceuticals

Page	**SG1**

Protocol	**Centre Number**	**Patient Number**			**Enter Visit Number :**
207499/157					

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.

St. George's Hospital Respiratory Questionnaire. Reproduced and used with permission from PW Jones.

207499/157

EUROQOL (EQ-5D)

Please indicate the current visit by ticking the appropriate box below.

Visit	3	9	12	EW
	☐	☐	☐	☐

English

00000

SmithKline Beecham
Pharmaceuticals

Page	**EQ1**

Protocol	**Centre Number**	**Patient Number**			**Enter Visit Number :**
207499/157		[redacted]			

EUROQOL (PAGE 1 OF 2)

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

LIST OF INVESTIGATORS FOR SB-207499/157 (GM2004/00073/00)

Investigator	Center #	Institution
Australia		
Dr [redacted]	[redacted]	[redacted] Australia
Dr. [redacted]	[redacted]	[redacted] Australia
Dr. [redacted]	[redacted]	[redacted] Australia [redacted]
Dr. [redacted]	[redacted]	[redacted] Australia
A/Professor [redacted]	[redacted]	[redacted] Australia
Professor [redacted]	[redacted]	[redacted] Australia
Dr. [redacted]	[redacted]	[redacted] Australia
Dr [redacted]	[redacted]	[redacted] Australia
Professor [redacted]	[redacted]	[redacted] Australia

* Site which did not recruit

Investigator	Center #	Institution
Dr. [redacted]	[redacted]	[redacted] Australia [redacted]
Belgium		
Dr. [redacted]	[redacted]	[redacted] Belgium [redacted]
Professor [redacted]	[redacted]	[redacted] Belgium
Professor [redacted]	[redacted]	[redacted] Belgium
Dr. [redacted]	[redacted]	[redacted] Belgium
Dr [redacted]	[redacted]	[redacted] Belgium
Dr. [redacted]	[redacted]	[redacted] Belgium
Czech Republic		
Dr. [redacted]	[redacted]	[redacted] Czech Republic
Dr. [redacted]	[redacted]	[redacted] Czech Republic [redacted]
Dr. [redacted]	[redacted]	[redacted] Czech Republic [redacted]
Dr. [redacted]	[redacted]	[redacted] Czech Republic [redacted]
Dr. [redacted]	[redacted]	[redacted] Czech Republic [redacted]
Dr. [redacted]	[redacted]	[redacted] Czech Republic [redacted]

Investigator	Center #	Institution
Denmark		
Dr. [redacted]	[redacted]	[redacted] Denmark
Dr. [redacted]	[redacted]	[redacted] Denmark
Dr. [redacted]	[redacted]	[redacted] Denmark
Dr. [redacted]	[redacted]	[redacted] Denmark
Dr [redacted]	[redacted]	[redacted] Denmark
Finland		
Dr. [redacted]	[redacted]	[redacted] Finland
Dr [redacted]	[redacted]	[redacted] Finland
Dr. [redacted]	[redacted]	[redacted] Finland
Dr. [redacted]	[redacted]	[redacted] Finland
France		
Dr. [redacted]	[redacted]	[redacted] France
Professor [redacted]	[redacted]	[redacted] France [redacted]

Investigator	Center #	Institution
Dr. [redacted]	[redacted]	[redacted] France
Professor. [redacted]	[redacted]	[redacted] France
Dr. [redacted]	[redacted]	[redacted] France
Dr. [redacted]	[redacted]	[redacted] France
Dr. [redacted]	[redacted]	[redacted] France
Dr. [redacted]	[redacted]	[redacted] France
Prof. [redacted]	[redacted]	[redacted] France
Dr. [redacted]	[redacted]	[redacted] France
Dr. [redacted]	[redacted]	[redacted] France
Dr. [redacted]	[redacted]	[redacted] France
Professor [redacted]	[redacted]	[redacted] France

Investigator	Center #	Institution
Germany		
Dr. [redacted]	[redacted]	[redacted] Germany
Dr [redacted]	[redacted]	[redacted] Germany
Dr [redacted]	[redacted]	[redacted] Germany
Dr. [redacted]	[redacted]	[redacted] Germany [redacted]
Dr. [redacted]	[redacted]	[redacted] Germany [redacted]
Dr. [redacted]	[redacted]	[redacted] Germany [redacted]
Dr. [redacted]	[redacted]	[redacted] Germany [redacted]
Dr. [redacted]	[redacted]	[redacted] Germany [redacted]
Dr. [redacted]	[redacted]	[redacted] Germany [redacted]
Dr. [redacted]	[redacted]	[redacted] Germany [redacted]
Dr. [redacted]	[redacted]	[redacted] Germany [redacted]
Dr. [redacted]	[redacted]	[redacted] Germany [redacted]
Dr. [redacted]	[redacted]	[redacted] Germany [redacted]
Dr [redacted]	[redacted]	[redacted] Germany
Dr. [redacted]	[redacted]	[redacted] Germany [redacted]
Dr [redacted]	[redacted]	[redacted] Germany
Dr [redacted]	[redacted]	[redacted] Germany
Dr [redacted]	[redacted]	[redacted] Germany
Dr. [redacted]	[redacted]	[redacted] Germany [redacted]
Dr [redacted]	[redacted]	[redacted] Germany

Investigator	Center #	Institution
Dr. [redacted]	[redacted]	[redacted] Germany
Dr. [redacted]	[redacted]	[redacted] Germany
Dr [redacted]	[redacted]	[redacted] Germany
Dr. [redacted]	[redacted]	[redacted] Germany
Dr. [redacted]	[redacted]	[redacted] Germany
Dr [redacted]	[redacted]	[redacted] Germany
Dr [redacted]	[redacted]	[redacted] Germany
Dr [redacted]	[redacted]	[redacted] Germany
Dr [redacted]	[redacted]	[redacted] Germany
Italy		
Professor [redacted]	[redacted]	[redacted] Italy
Professor [redacted]	[redacted]	[redacted] Italy
Professor [redacted]	[redacted]	[redacted] Italy
Dr. [redacted]	[redacted]	[redacted] Italy
Dr [redacted]	[redacted]	[redacted] Italy
Dr. [redacted]	[redacted]	[redacted] Italy

Investigator	Center #	Institution
Dr. [redacted]	[redacted]	[redacted] Italy
Professor [redacted]	[redacted]	[redacted] Italy
Dr. [redacted]	[redacted]	[redacted] Italy
Dr. [redacted]	[redacted]	[redacted] Italy
Dr. [redacted]	[redacted]	[redacted] Italy
Professor [redacted]	[redacted]	[redacted] - [redacted] Italy
Netherlands		
Dr. [redacted]	[redacted]	[redacted] Netherlands
Dr. [redacted]	[redacted]	[redacted] Netherlands
Dr. [redacted]	[redacted]	[redacted] Netherlands
Dr. [redacted]	[redacted]	[redacted] Netherlands
Dr. [redacted]	[redacted]	[redacted] Netherlands
Dr. [redacted]	[redacted]	[redacted] Netherlands

Investigator	Center #	Institution
Dr. [redacted]	[redacted]	[redacted] Netherlands [redacted]
Dr. [redacted]	[redacted]	[redacted] Netherlands [redacted]
Dr. [redacted]	[redacted]	[redacted] Netherlands [redacted]
Dr. [redacted]	[redacted]	[redacted] Netherlands [redacted]
Dr. [redacted]	[redacted]	[redacted] Netherlands [redacted]
Dr [redacted]	[redacted]	[redacted] Netherlands
New Zealand		
Dr. [redacted]	[redacted]	[redacted] New Zealand
Dr. [redacted]	[redacted]	[redacted] New Zealand
Dr. [redacted]	[redacted]	[redacted] New Zealand
Dr [redacted]	[redacted]	[redacted] New Zealand
Dr. [redacted]	[redacted]	[redacted] New Zealand
Dr. [redacted]	[redacted]	[redacted] New Zealand

Investigator	Center #	Institution
Poland		
Professor		Poland
Professor		Poland
Dr.		Poland
Professor		Poland
Professor		Poland
Professor		Poland
Dr.		Poland
Professor		Poland
Russia		
Professor		Russia
Dr.		Russia
Professor		Russia

Investigator	Center #	Institution
Slovak Republic		
Dr. [redacted]	[redacted]	[redacted] Slovak Rep [redacted]
Dr. [redacted]	[redacted]	[redacted] Slovak Rep [redacted]
Dr. [redacted]	[redacted]	[redacted] Slovak Rep [redacted]
Dr. [redacted]	[redacted]	[redacted] Slovak Rep [redacted]
South Africa		
Dr. [redacted]	[redacted]	[redacted] South Africa [redacted]
Prof. [redacted]	[redacted]	[redacted] South Africa [redacted]
Professor [redacted]	[redacted]	[redacted] South Africa [redacted]
Dr. [redacted]	[redacted]	[redacted] South Africa [redacted]
Dr. [redacted]	[redacted]	[redacted] South Africa [redacted]

Investigator	Center #	Institution
Spain		
Dr. [redacted]	[redacted]	[redacted] Spain
Dr. [redacted]	[redacted]	[redacted] Spain
Dr. [redacted]	[redacted]	[redacted] Spain
Dr [redacted]	[redacted]	[redacted] Spain
Dr. [redacted]	[redacted]	[redacted] Spain
Dr. [redacted]	[redacted]	[redacted] Spain
Dr. [redacted]	[redacted]	[redacted] Spain
Dr. [redacted]	[redacted]	[redacted] Spain
Dr [redacted]	[redacted]	[redacted] Spain
Dr. [redacted]	[redacted]	[redacted] Spain
Dr. [redacted]	[redacted]	[redacted] Spain
Dr. [redacted]	[redacted]	[redacted] Spain
Dr. [redacted]	[redacted]	[redacted] Spain
Dr [redacted]	[redacted]	[redacted] Spain

Investigator	Center #	Institution
Dr. [redacted]	[redacted]	[redacted] Spain
Dr [redacted]	[redacted]	[redacted] SPAIN
Dr. [redacted]	[redacted]	[redacted] Spain
Dr. [redacted]	[redacted]	[redacted] Spain
Sweden		
Dr [redacted]	[redacted]	[redacted]
Dr. [redacted]	[redacted]	[redacted] Sweden
Dr. [redacted]	[redacted]	[redacted] Sweden
Professor [redacted]	[redacted]	[redacted] Sweden
Dr. [redacted]	[redacted]	[redacted] Sweden
Taiwan		
Dr. [redacted]	[redacted]	[redacted] Taiwan
Dr. [redacted]	[redacted]	[redacted] Taiwan
Dr. [redacted]	[redacted]	[redacted] Taiwan

Investigator	Center #	Institution
Dr. [redacted]	[redacted]	[redacted] Taiwan
United Kingdom		
Professor [redacted]	[redacted]	[redacted] United Kingdom [redacted]
Dr. [redacted]	[redacted]	[redacted] United Kingdom
Dr. [redacted]	[redacted]	[redacted] United Kingdom [redacted]
Dr [redacted]	[redacted]	[redacted] UK
Dr. [redacted]	[redacted]	[redacted] United Kingdom [redacted]
Dr. [redacted]	[redacted]	[redacted] United Kingdom [redacted]
Dr [redacted]	[redacted]	[redacted] UK
Dr. [redacted]	[redacted]	[redacted] United Kingdom [redacted]
Dr. [redacted]	[redacted]	[redacted] United Kingdom [redacted]
Professor [redacted]	[redacted]	[redacted] United Kingdom [redacted]

Investigator	Center #	Institution
Dr. [redacted]	[redacted]	[redacted] United Kingdom [redacted]

This section contained Principal Investigator's Curriculum Vitae and has been excluded to protect Principal Investigator privacy.

Ariflo/157

Randomization Code Listing

Randomization Number	Period 1
[redacted]	B
	A
	A
	B
	A
	B
	B
	A
	A
	B
	A
	B
	A
	A
	B
	B
	A
	B
	B
	A
	B
	A
	A
	B
	A
	A
	B
	B
	B
	A
	B
	A
	A
	A
	B
	B

Ariflo/157

Randomization Code Listing

Randomization Number	Period 1
[redacted]	A
	B
	B
	A
	B
	A
	A
	B
	A
	B
	A
	B
	B
	B
	A
	A
	B
	A
	A
	B
	A
	A
	B
	B
	A
	B
	A
	B
	A
	A
	B
	B
	A
	B
	B
	A

Ariflo/157

Randomization Code Listing

Randomization Number	Period 1
[redacted]	A
	B
	B
	A
	A
	B
	A
	B
	A
	B
	B
	A
	A
	B
	B
	A
	A
	B
	A
	B
	B
	B
	A
	A
	A
	A
	B
	B
	B
	B
	A
	A
	B
	A
	A
	B

Ariflo/157

Randomization Code Listing

Randomization Number	Period 1
[redacted]	A
	A
	B
	B
	B
	B
	A
	A
	A
	B
	A
	B
	A
	B
	A
	B
	A
	B
	B
	A
	A
	A
	B
	B
	A
	B
	B
	A
	B
	B
	A
	A
	A
	B
	A
	B

Ariflo/157

Randomization Code Listing

Randomization Number	Period 1
[redacted]	A
	B
	A
	B
	B
	B
	A
	A
	A
	B
	B
	A
	A
	B
	B
	A
	A
	A
	B
	B
	B
	B
	A
	A
	A
	B
	A
	B
	B
	B
	A
	A
	A
	A
	B
	B

Ariflo/157

Randomization Code Listing

Randomization Number	Period 1
[redacted]	A
	B
	A
	B
	B
	A
	B
	A
	B
	A
	A
	B
	B
	B
	A
	A
	B
	A
	B
	A
	A
	B
	A
	B
	A
	A
	B
	B
	A
	B
	A
	B
	A
	B
	B
	A

Randomization Number	Period 1
[redacted]	A
	B
	A
	B
	B
	A
	A
	B
	B
	B
	A
	A
	B
	A
	A
	B
	B
	B
	A
	A
	B
	A
	B
	A
	A
	A
	B
	B
	A
	B
	B
	A
	A
	A
	B
	B

Randomization Number	Period 1
[redacted]	B
	B
	A
	A
	A
	B
	B
	A
	B
	B
	A
	A
	A
	A
	B
	B
	A
	A
	B
	B
	A
	A
	B
	B
	A
	B
	B
	A
	B
	B
	A
	A
	A
	B
	B
	A

Ariflo/157

Randomization Code Listing

Randomization Number	Period 1
[redacted]	A
	B
	B
	A
	B
	A
	B
	A
	A
	B
	B
	A
	A
	B
	A
	B
	A
	B
	A
	B
	A
	A
	B
	B
	B
	A
	A
	B
	A
	B
	A
	B
	B
	A
	B
	A

Ariflo/157

Randomization Code Listing

Randomization Number	Period 1
[redacted]	B
	A
	B
	A
	A
	A
	B
	B
	B
	B
	A
	A
	B
	A
	A
	B
	B
	A
	A
	B
	B
	B
	A
	A
	A
	A
	B
	B
	B
	A
	A
	B
	A
	B
	A
	B

Ariflo/157

Randomization Code Listing

Randomization Number	Period 1
[redacted]	A
	A
	B
	B
	B
	A
	A
	B
	B
	A
	B
	A
	A
	A
	B
	B
	B
	B
	A
	A
	B
	A
	B
	A
	A
	A
	B
	B
	A
	B
	B
	A
	B
	A
	A
	B

Ariflo/157

Randomization Code Listing

Randomization Number	Period 1
[redacted]	B
	B
	A
	A
	B
	B
	A
	A
	B
	B
	A
	A
	B
	A
	B
	A
	A
	B
	A
	B
	A
	A
	B
	B
	A
	A
	B
	B
	B
	A
	B
	A
	A
	B
	A
	B

Ariflo/157

Randomization Code Listing

Randomization Number	Period 1
[redacted]	B
	B
	A
	A
	A
	B
	A
	B
	A
	B
	A
	B
	A
	B
	A
	B
	A
	B
	B
	A
	A
	B
	B
	A
	A
	B
	B
	A
	A
	B
	B

Ariflo/157

Randomization Code Listing

Randomization Number	Period 1
[redacted]	A
	B
	A
	B
	B
	A
	A
	B
	B
	B
	A
	A
	A
	B
	A
	B
	A
	B
	A
	B
	B
	A
	B
	A
	B
	A
	B
	A
	B
	A
	B
	B
	A
	A
	B
	B
	A

Randomization Number	Period 1
[redacted]	B
	B
	A
	A
	A
	A
	B
	B
	B
	A
	A
	B
	A
	B
	A
	B
	B
	B
	A
	A
	A
	A
	B
	B
	A
	B
	B
	A
	A
	B
	B
	A
	A
	A
	B
	B

Ariflo/157

Randomization Code Listing

Randomization Number	Period 1
[redacted]	B
	B
	A
	A
	B
	A
	B
	A
	A
	A
	B
	B
	B
	B
	A
	A
	A
	A
	B
	B
	B
	A
	A
	B
	B
	A
	A
	B
	B
	B
	A
	A
	A
	A
	B
	B

Ariflo/157

Randomization Code Listing

Randomization Number	Period 1
[redacted]	A
	B
	B
	A
	B
	B
	A
	A
	A
	B
	B
	A
	B
	A
	A
	B
	A
	B
	B
	A
	B
	A
	B
	A
	B
	B
	A
	A
	A
	A
	B
	B
	A
	A
	B
	B

Ariflo/157

Randomization Code Listing

Randomization Number	Period 1
[redacted]	A
	B
	A
	B
	A
	B
	A
	B
	B
	B
	A
	A
	A
	B
	B
	A
	A
	B
	A
	B
	B
	A
	A
	B
	B
	B
	A
	A
	B
	A
	A
	B
	A
	B
	A
	B

Ariflo/157

Randomization Code Listing

Randomization Number	Period 1
[redacted]	A
	A
	B
	B
	A
	B
	A
	B
	B
	A
	B
	A
	A
	B
	B
	A
	A
	B
	A
	B
	B
	A
	B
	A
	A
	B
	A
	B
	B
	A
	B
	A
	B
	B
	A
	A

Ariflo/157

Randomization Code Listing

Randomization Number	Period 1
[redacted]	A
	B
	B
	A
	B
	B
	A
	A
	A
	B
	B
	A
	A
	B
	A
	B
	B
	A
	B
	A
	A
	B
	B
	A
	A
	B
	A
	B
	B
	B
	A
	A
	A
	B
	A
	B

Randomization Number	Period 1
[redacted]	A
	B
	B
	A
	B
	A
	B
	A
	A
	B
	B
	A
	A
	A
	B
	B
	B
	A
	B
	A
	A
	A
	B
	B
	B
	B
	A
	A
	B
	A
	A
	B
	B
	A
	A
	B

Ariflo/157

Randomization Code Listing

Randomization Number	Period 1
[redacted]	A
	B
	A
	B
	A
	B
	B
	A
	B
	A
	A
	B
	B
	A
	A
	B
	B
	A
	B
	A
	B
	B
	A
	A
	B
	A
	A
	B
	B
	A
	A
	B
	B
	A
	B
	A

Randomization Number	Period 1
[redacted]	B
	B
	A
	A
	B
	A
	A
	B
	A
	A
	B
	B
	A
	A
	B
	B
	B
	B
	A
	A
	A
	B
	A
	B
	A
	A
	B
	B
	A
	B
	B
	A
	B
	A
	B
	A

Ariflo/157

Randomization Code Listing

Randomization Number	Period 1
[redacted]	A
	B
	A
	B
	B
	A
	B
	A
	B
	A
	A
	B
	B
	A
	B
	A
	B
	B
	A
	A
	A
	B
	B
	A
	B
	B
	A
	A
	A
	B
	A
	B
	A
	B
	A
	B

Ariflo/157

Randomization Code Listing

Randomization Number	Period 1
[redacted]	A
	B
	A
	B
	A
	B
	A
	B
	B
	A
	A
	B
	B
	A
	B
	A
	A
	A
	B
	B
	A
	A
	B
	B
	B
	A
	A
	B
	B
	B
	A
	A
	B
	A
	A
	B

Randomization Number	Period 1
[redacted]	B
	B
	A
	A
	B
	A
	A
	B
	B
	B
	A
	A
	B
	A
	A
	B
	B
	A
	A
	B
	B
	A
	B
	A
	B
	B
	A
	A
	A
	B
	A
	B
	B
	A
	A
	B

Ariflo/157

Randomization Code Listing

Randomization Number	Period 1
[redacted]	A
	B
	B
	A
	A
	B
	A
	B
	A
	B
	A
	B
	A
	A
	B
	B
	B
	B
	A
	A
	B
	B
	A
	A
	A
	A
	B
	B
	B
	A
	A
	B
	A
	B
	B
	A

Ariflo/157

Randomization Code Listing

Randomization Number	Period 1
[redacted]	A
	A
	B
	B
	A
	B
	B
	A
	A
	A
	B
	B
	B
	B
	A
	A
	A
	A
	B
	B
	A
	B
	B
	A
	B
	A
	A
	B
	A
	B
	A
	B
	A
	B
	B
	A

Ariflo/157

Randomization Code Listing

Randomization Number	Period 1
[redacted]	A
	A
	B
	B
	B
	B
	A
	A
	B
	A
	A
	B
	B
	A
	A
	B
	A
	B
	B
	A
	B
	B
	A
	A
	A
	B
	B
	A
	B
	B
	A
	A
	A
	B
	A
	B

Ariflo/157

Randomization Code Listing

Randomization Number	Period 1
[redacted]	A
	B
	A
	B
	A
	B
	B
	A
	A
	A
	B
	B
	A
	B
	A
	B
	A
	B
	B
	A
	B
	A
	B
	A
	A
	B
	A
	B
	B
	B
	A
	A
	A
	B
	A
	B

Randomization Number	Period 1
[redacted]	A
	B
	A
	B
	B
	A
	B
	A
	A
	B
	B
	A
	A
	B
	A
	B
	A
	B
	B
	A
	A
	B
	A
	B
	A
	A
	B
	B
	B
	A
	A
	B
	A
	A
	B
	B

Randomization Number	Period 1
[redacted]	A
	A
	B
	B
	A
	A
	B
	B
	B
	A
	A
	B
	B
	B
	A
	A
	B
	B
	A
	A
	B
	A
	A
	B
	A
	B
	A
	B
	A
	B
	B
	A
	B
	A
	B
	A

Ariflo/157

Randomization Code Listing

Randomization Number	Period 1
[redacted]	B
	B
	A
	A
	B
	A
	B
	A
	A
	A
	B
	B
	B
	A
	A
	B
	B
	B
	A
	A
	B
	A
	A
	B
	B
	A
	A
	B
	B
	A
	B
	A
	A
	B
	A
	B

Ariflo/157

Randomization Code Listing

Randomization Number	Period 1
[redacted]	A
	A
	B
	B
	A
	B
	B
	A
	B
	A
	A
	B
	B
	A
	A
	B
	B
	B
	A
	A
	A
	A
	B
	B
	A
	B
	A
	B
	B
	A
	A
	B
	B
	A
	A
	B

Randomization Number	Period 1
[redacted]	B
	A
	A
	B
	A
	A
	B
	B
	B
	B
	A
	A
	B
	A
	A
	B
	A
	A
	B
	B
	B
	A
	A
	B
	B
	A
	A
	B
	A
	B
	B
	A
	B
	A
	B
	A

Randomization Number	Period 1
[redacted]	A
	B
	B
	A
	A
	A
	B
	B
	B
	A
	B
	A
	A
	A
	B
	B
	B
	B
	A
	A
	A
	B
	A
	B
	B
	A
	B
	A
	A
	A
	B
	B
	A
	B
	B
	A

Randomization Number	Period 1
[redacted]	A
	B
	B
	A
	B
	B
	A
	A
	A
	B
	A
	B
	B
	A
	B
	A
	B
	B
	A
	A
	B
	B
	A
	A
	A
	B
	B
	B
	B
	A
	A
	B
	A
	B
	A

Randomization Number	Period 1
[redacted]	A
	B
	B
	A
	B
	A
	A
	B
	A
	A
	B
	B
	B
	A
	B
	A
	B
	A
	B
	A
	A
	B
	A
	B
	B
	B
	A
	A
	A
	A
	B
	B
	B
	B
	A
	A

Randomization Number	Period 1
[redacted]	B
	B
	A
	A
	A
	B
	A
	B
	A
	B
	A
	B
	B
	A
	B
	A
	A
	B
	B
	A
	B
	B
	A
	A
	A
	B
	A
	B
	A
	A
	B
	B
	A
	B
	B
	A

Randomization Number	Period 1
[redacted]	B
	A
	B
	A
	B
	A
	A
	B
	A
	A
	B
	B
	B
	A
	B
	A
	B
	A
	A
	B
	B
	A
	B
	A
	A
	A
	B
	B
	A
	B
	A
	B
	B
	A
	B
	A

Randomization Number	Period 1
[redacted]	B
	B
	A
	A
	A
	B
	B
	A
	A
	B
	A
	B
	A
	B
	A
	B
	A
	A
	B
	B
	B
	A
	B
	A
	B
	A
	A
	B
	A
	B
	B
	A
	A
	A
	B
	B

Ariflo/157

Randomization Code Listing

Randomization Number	Period 1
[redacted]	A
	A
	B
	B
	B
	B
	A
	A
	B
	A
	A
	B
	A
	A
	B
	B
	B
	A
	B
	A
	A
	B
	A
	B
	A
	B
	B
	A
	A
	B
	A
	B
	B
	A
	A
	B

Ariflo/157

Randomization Code Listing

Randomization Number	Period 1
[redacted]	A
	B
	B
	A
	A
	B
	B
	A
	A
	B
	B
	A
	A
	A
	B
	B
	B
	A
	B
	A
	B
	A
	A
	B
	B
	B
	A
	A
	A
	A
	B
	B
	B
	B
	A
	A

Randomization Number	Period 1
[redacted]	A
	A
	B
	B
	A
	B
	A
	B
	A
	B
	B
	A
	B
	B
	A
	A
	A
	B
	B
	A
	A
	A
	B
	B
	B
	B
	A
	A
	B
	B
	A
	A
	B
	B
	A
	A

Randomization Number	Period 1
[redacted]	B
	B
	A
	A
	B
	A
	A
	B
	B
	A
	A
	B
	A
	B
	A
	B
	B
	B
	A
	A
	B
	A
	A
	B
	B
	A
	B
	A
	B
	B
	A
	A
	A
	A
	B
	B

Randomization Number	Period 1
[redacted]	B
	A
	A
	B
	A
	A
	B
	B
	B
	B
	A
	A
	B
	A
	B
	A
	A
	B
	A
	B
	B
	A
	A
	B
	A
	B
	B
	A
	A
	A
	B
	B
	A
	B
	A
	B

Randomization Number	Period 1
[redacted]	B
	A
	B
	A
	B
	A
	B
	A
	B
	A
	A
	B
	B
	A
	A
	B
	A
	B
	A
	B
	B
	A
	A
	B
	A
	A
	B
	B
	B
	B
	A
	A
	B
	B
	A
	A

Randomization Number	Period 1
[redacted]	B
	B
	A
	A
	B
	A
	B
	A
	A
	B
	B
	A
	A
	A
	B
	B
	B
	A
	A
	B
	A
	B
	B
	A
	B
	B
	A
	A
	A
	B
	B
	A
	A
	B
	A
	B

Randomization Number	Period 1
[redacted]	A
	B
	A
	B
	B
	B
	A
	A
	B
	B
	A
	A
	B
	A
	B
	A
	A
	B
	A
	B
	B
	B
	A
	A
	A
	B
	B
	A
	B
	A
	A
	B
	B
	A
	A
	B

Randomization Number	Period 1
[redacted]	B
	A
	B
	A
	B
	A
	A
	B
	A
	A
	B
	B
	A
	B
	B
	A
	B
	B
	A
	A
	B
	A
	A
	B
	B
	B
	A
	A
	B
	A
	B
	A
	B
	A
	A
	B

Randomization Number	Period 1
[redacted]	A
	B
	B
	A
	A
	A
	B
	B
	A
	B
	B
	A
	A
	B
	B
	A
	B
	A
	B
	A
	A
	B
	B
	A
	B
	B
	A
	A
	A
	B
	B
	A
	A
	B
	B
	A

Randomization Number	Period 1
[redacted]	B
	B
	A
	A
	A
	B
	B
	A
	B
	B
	A
	A
	B
	B
	A
	A
	B
	A
	A
	B
	A
	A
	B
	B
	B
	B
	A
	A
	B
	A
	B
	A
	A
	A
	B
	B

Randomization Number	Period 1
[redacted]	B
	A
	A
	B
	A
	B
	B
	A
	B
	B
	A
	A
	A
	A
	B
	B
	A
	B
	A
	B
	B
	A
	B
	A
	B
	B
	A
	A
	A
	B
	A
	B
	B
	A
	B
	A

Ariflo/157

Randomization Code Listing

Randomization Number	Period 1
[redacted]	A
	A
	B
	B
	B
	B
	A
	A
	A
	A
	B
	B
	B
	A
	A
	B
	B
	A
	A
	B
	B
	A
	A
	B
	B
	B
	A
	A
	A
	B
	A
	B
	B
	A
	A
	B

Randomization Number	Period 1
[redacted]	A
	A
	B
	B
	A
	B
	A
	B
	A
	B
	A
	B
	B
	B
	A
	A
	A
	B
	A
	B
	B
	A
	A
	B
	A
	B
	B
	A
	A
	A
	B
	B
	B
	A
	A
	B

Randomization Number	Period 1
[redacted]	B
	A
	B
	A
	A
	B
	A
	B
	A
	B
	B
	A
	B
	A
	B
	A
	B
	A
	A
	B
	A
	B
	A
	B
	A
	B
	B
	A
	B
	A
	B
	A
	B
	A
	B
	B
	A
	A

Randomization Number	Period 1
[redacted]	A
	A
	B
	B
	B
	A
	A
	B
	B
	B
	A
	A
	B
	A
	B
	A
	B
	A
	B
	A
	A
	B
	A
	B
	A
	A
	B
	B
	B
	B
	A
	B
	A
	B
	A
	A
	B

Randomization Number	Period 1
[redacted]	A
	A
	B
	B
	A
	B
	B
	A
	B
	A
	B
	A
	B
	B
	A
	A
	B
	A
	B
	A
	A
	A
	B
	B
	A
	A
	B
	B
	B
	A
	A
	B
	B
	B
	A
	A

Ariflo/157

Randomization Code Listing

Randomization Number	Period 1
[redacted]	A
	B
	A
	B
	A
	B
	A
	B
	B
	B
	A
	A
	A
	B
	B
	A
	A
	B
	A
	B
	B
	A
	A
	B
	A
	B
	A
	B
	A
	B
	B
	A
	A
	B
	A
	B

Randomization Number	Period 1
[redacted]	B
	A
	B
	A
	A
	B
	B
	A
	B
	A
	A
	B
	B
	B
	A
	A
	A
	B
	A
	B
	A
	B
	A
	B
	B
	A
	B
	A
	B
	B
	A
	A
	A
	A
	B
	B

Randomization Number	Period 1
[redacted]	B
	B
	A
	A
	B
	A
	A
	B
	A
	A
	B
	B
	A
	A
	B
	B
	A
	A
	B
	B
	A
	B
	A
	B
	B
	A
	B
	A
	B
	A
	A
	B
	B
	A
	B
	A

Ariflo/157

Randomization Code Listing

Randomization Number	Period 1
[redacted]	A
	B
	B
	A
	A
	B
	A
	B
	A
	B
	B
	A
	B
	A
	A
	B
	B
	A
	B
	A
	B
	A
	B
	A
	A
	A
	B
	B
	B
	A
	A
	B
	B
	A
	A
	B

Randomization Number	Period 1
[redacted]	B
	A
	B
	A
	A
	B
	B
	A
	A
	B
	A
	B
	B
	A
	A
	B
	A
	A
	B
	B
	A
	B
	A
	B
	B
	B
	A
	A
	B
	B
	A
	A
	A
	B
	B
	A

Ariflo/157

Randomization Code Listing

Randomization Number	Period 1
[redacted]	A
	B
	B
	A
	A
	B
	A
	B
	B
	A
	B
	A
	B
	A
	B
	A
	A
	B
	B
	A
	B
	A
	B
	A
	B
	A
	A
	B
	A
	A
	B
	B
	B
	A
	A
	B

Randomization Number	Period 1
[redacted]	B
	A
	B
	A
	B
	A
	A
	B
	A
	B
	A
	B
	A
	B
	A
	B
	A
	B
	B
	A
	B
	B
	A
	A
	A
	A
	B
	B
	A
	A
	B
	B
	B
	A
	B
	A

Randomization Number	Period 1
[redacted]	B
	A
	A
	B
	B
	A
	B
	A
	A
	A
	B
	B
	B
	A
	A
	B
	A
	B
	A
	B
	A
	B
	A
	B
	A
	B
	A
	B
	A
	B
	A
	B
	B
	A
	A
	B

Randomization Number	Period 1
[redacted]	B
	A
	A
	B
	B
	B
	A
	A
	A
	A
	B
	B
	A
	A
	B
	B
	B
	A
	B
	A
	A
	B
	B
	B
	A
	B
	B
	A
	A
	B
	B
	A
	A
	A
	B
	A
	B

Ariflo/157

Randomization Code Listing

Randomization Number	Period 1
[redacted]	A
	B
	B
	A
	A
	B
	B
	A
	A
	A
	B
	B
	A
	B
	B
	A
	A
	B
	A
	B
	B
	A
	B
	A
	B
	B
	A
	A
	B
	A
	A
	B
	A
	A
	B
	B

Randomization Number	Period 1
[redacted]	A
	B
	B
	A
	B
	A
	A
	B
	B
	A
	A
	B
	A
	A
	B
	B
	B
	B
	A
	A
	A
	B
	A
	B
	B
	B
	A
	A
	B
	A
	A
	B
	A
	B
	A
	B

Ariflo/157

Randomization Code Listing

Randomization Number	Period 1
[redacted]	A
	B
	A
	B
	A
	B
	B
	A
	A
	A
	B
	B
	A
	A
	B
	B
	B
	A
	A
	B
	B
	A
	A
	B
	A
	B
	A
	B
	A
	B
	B
	A
	B
	A
	B
	A

Randomization Number	Period 1
[redacted]	A
	B
	A
	B
	A
	B
	B
	A
	B
	A
	A
	B
	B
	B
	A
	A
	B
	A
	B
	A
	B
	B
	A
	A
	A
	B
	A
	B
	B
	B
	A
	A
	A
	B
	A
	B

Randomization Number	Period 1
[redacted]	A
	B
	A
	B
	A
	B
	A
	B
	B
	A
	A
	B
	A
	A
	B
	B
	B
	A
	A
	B
	B
	B
	A
	A
	A
	B
	B
	A
	A
	B
	B
	A
	A
	A
	B
	B

Randomization Number	Period 1
[redacted]	B
	B
	A
	A
	B
	A
	B
	A
	B
	B
	A
	A
	B
	A
	B
	A
	A
	A
	B
	B
	B
	A
	A
	B
	B
	A
	A
	B
	A
	B
	A
	B
	A
	B
	A
	B

Ariflo/157

Randomization Code Listing

Randomization Number	Period 1
[redacted]	A
	B
	A
	B
	B
	A
	A
	B
	B
	A
	A
	B
	B
	A
	A
	B
	A
	B
	A
	B
	A
	B
	A
	B
	B
	A
	B
	B
	A
	A
	B
	A
	B
	A
	B
	B
	A
	A

Ariflo/157

Randomization Code Listing

Randomization Number	Period 1
[redacted]	B
	A
	A
	B
	B
	A
	B
	A
	A
	B
	A
	B
	B
	A
	A
	B
	A
	A
	B
	B
	A
	A
	B
	B
	B
	B
	A
	A
	B
	B
	A
	A
	A
	B
	A
	B

Randomization Number	Period 1
[redacted]	A
	A
	B
	B
	B
	A
	B
	A
	A
	B
	B
	A
	A
	B
	B
	A
	A
	B
	A
	B
	A
	A
	B
	B
	A
	B
	B
	A
	A
	B
	B
	A
	A
	A
	B
	B

Randomization Number	Period 1
[redacted]	A
	B
	A
	B
	B
	B
	A
	A
	A
	A
	B
	B
	A
	B
	B
	A
	B
	B
	A
	A
	A
	B
	A
	B
	B
	A
	B
	A
	B
	A
	B
	A
	B
	A
	B
	B
	A
	A

Ariflo/157

Randomization Code Listing

Randomization Number	Period 1
[redacted]	B
	A
	B
	A
	A
	B
	A
	B
	A
	B
	A
	B
	B
	A
	B
	A
	B
	A
	B
	A
	B
	A
	A
	B
	B
	A
	B
	A
	B
	B
	A
	A
	B
	A
	B
	A

Ariflo/157

Randomization Code Listing

Randomization Number	Period 1
[redacted]	A
	B
	A
	B
	B
	B
	A
	A
	B
	A
	A
	B
	A
	B
	B
	A
	B
	A
	A
	B
	B
	A
	A
	B
	B
	A
	B
	A
	A
	B
	A
	B

Randomization Number	Period 1
[redacted]	B
	A
	B
	A
	A
	A
	B
	B
	A
	A
	B
	B
	B
	A
	B
	A
	B
	B
	A
	A
	A
	B
	A
	B
	A
	B
	B
	A
	B
	A
	B
	A
	A
	A
	B
	B

Randomization Number	Period 1
[redacted]	B
	A
	B
	A
	A
	B
	B
	A
	B
	B
	A
	A
	B
	B
	A
	A
	A
	B
	B
	A
	A
	A
	B
	B
	B
	A
	A
	B
	A
	B
	B
	A
	A
	B
	A
	B

Ariflo/157

Randomization Code Listing

Randomization Number	Period 1
[redacted]	B
	B
	A
	A
	B
	A
	B
	A
	A
	B
	B
	A
	A
	B
	B
	A
	B
	A
	A
	B
	A
	A
	B
	B
	A
	B
	B
	A
	B
	A
	B
	A
	A
	B
	B
	A

Randomization Number	Period 1
[redacted]	B
	A
	A
	B
	B
	A
	B
	A
	A
	B
	B
	A
	A
	B
	B
	A
	B
	A
	A
	B
	A
	A
	B
	B
	B
	B
	A
	A
	B
	A
	A
	B
	B
	B
	A
	A

Randomization Number	Period 1
[redacted]	B
	A
	A
	B
	B
	B
	A
	A
	B
	A
	B
	A
	A
	B
	B
	A
	B
	A
	B
	A
	B
	A
	A
	B
	B
	A
	B
	A
	A
	B
	B
	A
	A
	B
	B
	A

Ariflo/157

Randomization Code Listing

Randomization Number	Period 1
[redacted]	B
	A
	A
	B
	B
	B
	A
	A
	B
	A
	B
	A
	A
	B
	A
	B
	B
	A
	B
	A
	B
	A
	B
	A
	B
	A
	A
	B
	A
	B
	B
	A
	B
	A
	B
	A

Randomization Number	Period 1
[redacted]	A
	B
	B
	A
	B
	A
	B
	A
	A
	B
	A
	B
	A
	A
	B
	B
	A
	B
	B
	A
	B
	A
	B
	A
	B
	A
	A
	A
	B
	B
	A
	B
	A
	B

Randomization Number	Period 1
[redacted]	B
	B
	A
	A
	B
	B
	A
	A
	B
	A
	B
	A
	B
	A
	B
	A
	B
	A
	B
	A
	B
	A
	B
	A
	A
	B
	B
	A
	B
	B
	A
	A
	B
	B
	A
	A

Randomization Number	Period 1
[redacted]	B
	B
	A
	A
	A
	B
	A
	B
	B
	A
	B
	A
	A
	B
	A
	B
	B
	A
	A
	B
	B
	A
	B
	A
	B
	B
	A
	A
	A
	B
	B
	A
	B
	A
	B
	A

Randomization Number	Period 1
[redacted]	A
	B
	B
	A
	A
	B
	A
	B
	A
	A
	B
	B
	A
	A
	B
	B
	B
	A
	A
	B
	B
	A
	A
	B
	B
	A
	A
	B
	A
	A
	B
	B
	A
	A
	B
	B

Ariflo/157

Randomization Code Listing

Randomization Number	Period 1
[redacted]	A
	B
	A
	B
	B
	A
	A
	B
	B
	B
	A
	A
	B
	A
	B
	A
	A
	A
	B
	B
	A
	A
	B
	B
	B
	A
	A
	B
	A
	B
	A
	B
	A
	A
	B
	B

Randomization Number	Period 1
[redacted]	A
	A
	B
	B
	B
	B
	A
	A
	A
	A
	B
	B
	A
	A
	B
	B
	A
	A
	B
	B
	A
	A
	B
	B
	B
	A
	B
	A
	A
	A
	B
	B
	B
	A
	B
	A

Randomization Number	Period 1
[redacted]	A
	A
	B
	B
	B
	B
	A
	A
	A
	B
	B
	A
	B
	A
	A
	B
	B
	B
	A
	A
	B
	A
	B
	A
	B
	A
	B
	A
	B
	B
	A
	A
	B
	A
	A
	B

Randomization Number	Period 1
[redacted]	B
	A
	B
	A
	A
	B
	A
	B
	B
	B
	A
	A
	A
	B
	A
	B
	A
	A
	B
	B
	A
	B
	A
	B
	B
	A
	A
	B
	B
	A
	B
	A
	B
	A
	A
	B

Ariflo/157

Randomization Code Listing

Randomization Number	Period 1
[redacted]	B
	A
	A
	B
	B
	A
	A
	B
	A
	A
	B
	B
	A
	B
	A
	B
	A
	B
	A
	B
	A
	B
	A
	B
	B
	A
	B
	A
	B
	A
	B
	A
	B
	A
	A
	B

Randomization Number	Period 1
[redacted]	A
	A
	B
	B
	A
	A
	B
	B
	A
	A
	B
	B
	A
	B
	B
	A
	B
	B
	A
	A
	A
	A
	B
	B
	B
	A
	B
	A
	A
	B
	B
	A
	B
	A
	A
	B

Ariflo/157

Randomization Code Listing

Randomization Number	Period 1
[redacted]	B
	A
	B
	A
	B
	A
	B
	A
	A
	B
	B
	A
	A
	B
	B
	A
	B
	B
	A
	A
	A
	B
	B
	A
	A
	A
	B
	B
	B
	A
	A
	B
	B
	A
	B
	A

Randomization Number	Period 1
[redacted]	B
	A
	B
	A
	A
	A
	B
	B
	A
	B
	A
	B
	A
	B
	B
	A
	A
	B
	A
	B
	B
	A
	B
	A
	B
	B
	A
	A
	B
	A
	A
	B
	A
	B
	A
	B

Randomization Number	Period 1
[redacted]	A
	B
	B
	A
	A
	B
	B
	A
	A
	B
	A
	B
	B
	A
	A
	B
	A
	B
	B
	A
	A
	A
	B
	B
	B
	A
	B
	A
	A
	B
	B
	A
	A
	B
	B
	A

Randomization Number	Period 1
[redacted]	B
	A
	A
	B
	A
	B
	B
	A
	A
	A
	B
	B
	A
	B
	A
	B
	B
	B
	A
	A
	A
	A
	B
	B
	A
	A
	B
	B
	A
	B
	A
	B
	B
	A
	B
	A

Randomization Number	Period 1
[redacted]	A
	B
	B
	A
	A
	B
	B
	A
	B
	B
	A
	A
	A
	B
	B
	A
	B
	B
	A
	A
	B
	B
	A
	A
	A
	B
	B
	A
	A
	B
	A
	B
	A
	B
	B
	A

Ariflo/157

Randomization Code Listing

Randomization Number	Period 1
[redacted]	B
	B
	A
	A
	B
	B
	A
	A
	B
	A
	A
	B
	A
	A
	B
	B
	B
	A
	B
	A
	B
	A
	B
	A
	A
	B
	B
	A
	B
	A
	B
	A
	A
	B
	B
	A

Randomization Number	Period 1
[redacted]	A
	B
	B
	A
	A
	B
	B
	A
	B
	B
	A
	A
	A
	B
	A
	B
	A
	A
	B
	B
	A
	B
	A
	B
	B
	A
	B
	A
	B
	A
	B
	A
	B
	A
	A
	B
	B
	A

Randomization Number	Period 1
[redacted]	B
	B
	A
	A
	A
	A
	B
	B
	B
	A
	B
	A
	B
	A
	A
	B
	B
	A
	B
	A
	B
	A
	A
	B
	A
	B
	A
	B
	A
	A
	B
	B
	B
	A
	B
	A

Randomization Number	Period 1
[redacted]	B
	B
	A
	A
	A
	B
	B
	A
	B
	B
	A
	A
	B
	A
	A
	B
	B
	B
	A
	A
	B
	A
	B
	A
	A
	B
	A
	B
	A
	A
	B
	B
	B
	B
	A
	A

Randomization Number	Period 1
[redacted]	B
	A
	B
	A
	B
	B
	A
	A
	A
	B
	A
	B
	B
	A
	A
	B
	A
	B
	A
	B
	A
	B
	B
	A
	B
	A
	A
	B
	A
	B
	B
	A
	B
	B
	A
	A

Randomization Number	Period 1
[redacted]	B
	A
	A
	B
	B
	A
	A
	B
	A
	B
	B
	A
	B
	A
	B
	A
	B
	B
	A
	A
	B
	A
	A
	B
	B
	A
	B
	A
	A
	A
	B
	B
	A
	B
	A
	B

Randomization Number	Period 1
[redacted]	B
	A
	B
	A
	B
	B
	A
	A
	A
	B
	A
	B
	B
	A
	B
	A
	B
	B
	A
	A
	A
	B
	B
	B
	A
	B
	B
	A
	A
	A
	B
	B
	A
	B
	A
	B
	A

Ariflo/157

Randomization Code Listing

Randomization Number	Period 1
[redacted]	A
	B
	A
	B
	B
	B
	A
	A
	A
	B
	B
	A
	A
	A
	B
	B
	B
	A
	A
	B
	B
	A
	A
	B
	B
	A
	A
	B
	B
	B
	B
	A
	A

Randomization Number	Period 1
[redacted]	A
	B
	A
	B
	A
	B
	A
	B
	A
	A
	B
	B
	B
	A
	A
	B
	A
	A
	B
	B
	B
	A
	B
	A
	B
	A
	B
	A
	B
	A
	B
	A
	B
	A
	B
	A

Ariflo/157

Randomization Code Listing

Randomization Number	Period 1
[redacted]	A
	A
	B
	B
	A
	A
	B
	B
	A
	A
	B
	B
	A
	A
	B
	B
	A
	B
	A
	B
	A
	A
	B
	B
	A
	B
	B
	A
	A
	B
	B
	A
	B
	A
	A
	B

Ariflo/157

Randomization Code Listing

Randomization Number	Period 1
[redacted]	A
	A
	B
	B
	A
	B
	A
	B
	B
	B
	A
	A
	A
	B
	B
	A
	B
	B
	A
	A
	B
	B
	A
	A
	B
	B
	A
	B
	A
	A
	B
	A
	B
	A
	B

Ariflo/157

Randomization Code Listing

Randomization Number	Period 1
[redacted]	A
	B
	A
	B

Certificate of Registration

Quality Management System

This is to certify that:

Quest Diagnostics Limited
Unit B1, Parkway West
Cranford Lane
Heston
Middlesex
United Kingdom
TW5 9QA

Hold Certificate No: **FS 41524**

and operate a Quality Management System which complies with the requirements of **BS EN ISO 9001:1994** *for the following scope:*

The provision of central laboratory services for the management of pharmaceutical clinical trials.

For and on behalf of BSI:

[redacted]

Certification Manager, Systems Assessment

Originally registered: **12 Feb 1999** *Latest issue:* **9 Mar 2001** *Page:* 1 of 2

UKAS QUALITY MANAGEMENT
003

Accredited by the Dutch Accreditation Council - RvA

This licence remains the property of BSI and shall be returned immediately upon request.
This certificate does not expire.
To check its validity telephone [redacted] *or visit www.bsi-global.com/BusinessPartners*

The British Standards Institution is incorporated by Royal Charter.
Group Headquarters: 389 Chiswick High Road, London W4 4AL, UK.

MC4401/ISSUE 1/SA/0010/UK/DP

Certificate of Registration

Quality Management System

Certificate No: **FS 41524**

Location	*Registered Activities*
Quest Diagnostics Limited Heston Middlesex United Kingdom TW5 9QA	The provision of central laboratory services for the management of pharmaceutical clinical trials.
Quest Diagnostics Limited Clinical Trials Les Collines de Wavre 8G, Avenue Einstein 1300 Wavre Belgium	The provision of central laboratory services for the management of pharmaceutical clinical trials.
Quest Diagnostics Clinical Trials Immeuble Petra B-BP 64 Rue Albert Caquot F-06902 Sophia Antipolis Cedex France	The provision of central laboratory services for the management of pharmaceutical clinical trials.

Originally registered: **12 Feb 1999** *Latest issue:* **9 Mar 2001** *Page:* 2 of 2

This licence remains the property of BSI and shall be returned immediately upon request.
This certificate does not expire.
To check its validity telephone [redacted] *or visit www.bsi-global.com/BusinessPartners*

The British Standards Institution is incorporated by Royal Charter.
Group Headquarters: 389 Chiswick High Road, London W4 4AL, UK.

MC4401/ISSUE 1/SA/0010/UK/DP

Advancing Excellence

Accredited Laboratory

The College of American Pathologists

certifies that the laboratory named below

Quest Diagnostics Clinical Laboratories, Inc.

[redacted] ***MD***

LAP Number: 6798801
AU-ID: 1191244

has met all applicable standards for accreditation and is hereby fully accredited by the College of American Pathologists' Laboratory Accreditation Program. Reinspection should occur within 30 days prior to November 10, 2003 to maintain accreditation.

Accreditation does not automatically survive a change in director, ownership, or location and assumes that all interim requirements are met.

[redacted]
Chair, Commission on Laboratory Accreditation

[redacted]
President, College of American Pathologists

CONFIDENTIAL

College of American Pathologists
325 Waukegan Road, Northfield, Illinois 60093-2750
[redacted] • http://www.cap.org

Advancing Excellence

LAP#: 6798801
AU-ID: 1191244
March 21, 2002

[redacted] MD
Quest Diagnostics Clinical Laboratories, Inc.
Unit B1, Parkway West
Middlesex TW5 9QA
United Kingdom

Dear Dr. [redacted]:

The Commission on Laboratory Accreditation of the College of American Pathologists (CAP) is pleased to advise you that the medical laboratory you direct, Quest Diagnostics Clinical Laboratories, Inc., Middlesex, United Kingdom, successfully met the Laboratory Accreditation Program (LAP) Standards for Accreditation in the area(s) listed on the attached sheet. **Please retain this letter and list of accredited services in your records, as this is your official notification of accreditation.**

Your Certificate of Accreditation is enclosed. Accreditation is valid for a two-year period and may be maintained on a continuous basis *provided the following requirements are met:*

1. Provide an inspection team of a size and composition similar to that required for your inspection and perform at least one inspection during the two-year accreditation cycle, if asked to do so by your Commissioner;
2. Submit an application for reinspection in sufficient time that the reinspection may be accomplished prior to your anniversary date. Application materials will automatically be sent to you to be completed and must be returned within 35 days of date sent;
3. Successfully participate in the CAP Surveys or a CAP-approved alternative proficiency testing program;
4. Notify the Commission of changes in location, ownership, or directorship of the laboratory. Accreditation does not automatically survive such changes. Documentation, including a copy of the new director's curriculum vitae and an organizational chart, will be requested for evaluation of the accreditation status;
5. Notify the Commission whenever the laboratory finds itself the subject of an investigation by a state or federal agency or adverse media attention related to laboratory performance;
6. Submit a completed Self-Evaluation Verification Form in the interim year.

The Commission congratulates you on the accreditation of the laboratory under your direction and the excellence of the services being provided. Please be reminded that CAP accreditation is not a substitute for the continuous in-depth monitoring by the laboratory and its personnel. Only such monitoring can produce a safe and properly functioning laboratory.

Sincerely,

[redacted] MD
Chair, Commission on Laboratory Accreditation

cc: [redacted] MD

Ref: LAPACCLTR

Quest Diagnostics Clinical Laboratories, Inc.

LAP Number: 6798801
AU ID: 1191244

The above Laboratory is accredited by the College of American Pathologists Laboratory Accreditation Program for the following services:

Bacteriology
Chemistry
Cytopathology
Flow Cytometry
Hematology
Laboratory General
Molecular Pathology
Mycobacteriology
Mycology
Non-Syphilis Serology
Parasitology
Special Chemistry
Surgical Pathology
Toxicology
Urinalysis

This accreditation is valid for the period ending November 10, 2003.

PLEASE RETAIN THIS DOCUMENT IN YOUR RECORDS.

CPA

Clinical Pathology Accreditation (UK) Ltd.
Company Registration No. 2675095

Certificate of Accreditation

Clinical Pathology Accreditation (UK) Ltd. certifies that the

Department of Clinical Biochemistry
Quest Diagnostics
Cranford Lane
Heston

has been inspected, and has met the appropriate CPA standards

for its clinical pathology services

CPA Reference: [redacted]

This certificate is only valid
if the department holds a current letter
of approval from CPA (UK) Ltd.

[redacted] (CHAIRMAN CPA)

(DIRECTOR CPA)

DATE October 2001

The Association of Clinical Biochemists

Institute of Healthcare Management

INDEPENDENT HEALTHCARE ASSOCIATION

45 Rutland Park
Botanical Gardens
Sheffield
S10 2PB

Tel [redacted]
Fax

e-mail: [redacted]
website: www.cpa-uk.co.uk

Clinical Pathology Accreditation (UK) Ltd.
Company Registration No. 2675095

CPA Ref No: [redacted]

Dear Dr. [redacted]

Following your recent application for accreditation and subsequent visit by CPA Inspectors, I am pleased to inform you that the Specialist Advisory Committee have recommended that:

Department of Clinical Biochemistry
Quest Diagnostics
Unit B1 Parkway West
Cranford Lane
Heston

be granted:

Unconditional Accreditation

This decision has been endorsed by the CPA Board of Directors. Attached is the CPA certificate.

Accreditation is valid for a four year period from the date of registration and may be maintained on a continuous basis provided that you meet with the following requirements:

Submit a completed registration form annually, and return to CPA Central Office together with the annual registration fee. The annual registration form and invoice will be issued by CPA 60 days prior to this date each year.

Since accreditation does not automatically survive major changes in staffing, structure, repertoire or facilities, CPA Central Office must be informed immediately such changes occur.

Annual Registration Date: 1st March

Submit an application for re-registration on a four yearly cycle. Application forms will be issued by CPA Central Office at least six months in advance.

The accreditation certificate is only valid when accompanied by a current letter of accreditation. Please keep these documents in your files.

Signed on behalf of CPA (UK) Ltd:

[redacted]

Designation: [redacted]
Executive Manager

Date: 10/10/2001

CPA

Clinical Pathology Accreditation (UK) Ltd.
Company Registration No. 2675095

Certificate of Accreditation

Clinical Pathology Accreditation (UK) Ltd. certifies that the

Department of Haematology/Blood Transfusion
Quest Diagnostics
Cranford Lane
Heston

has been inspected, and has met the appropriate CPA standards

for its clinical pathology services

CPA Reference: [redacted]

This certificate is only valid
if the department holds a current letter
of approval from CPA (UK) Ltd.

[redacted] (CHAIRMAN CPA)

[redacted] (DIRECTOR CPA)

DATE October 2001

The Association of Clinical Biochemists

Institute of Healthcare Management

INDEPENDENT HEALTHCARE ASSOCIATION

CONFIDENTIAL

45 Rutland Park
Botanical Gardens
Sheffield
S10 2PB

Tel [redacted]
Fax

e-mail: [redacted]
website: www.cpa-uk.co.uk

Clinical Pathology Accreditation (UK) Ltd.
Company Registration No. 2675095

CPA Ref No: 1384

Dear Dr. [redacted]

Following your recent application for accreditation and subsequent visit by CPA Inspectors, I am pleased to inform you that the Specialist Advisory Committee have recommended that:

Department of Haematology/Blood Transfusion
Quest Diagnostics
Unit B1 Parkway West
Cranford Lane
Heston

be granted:

Unconditional Accreditation

This decision has been endorsed by the CPA Board of Directors. Attached is the CPA certificate.

Accreditation is valid for a four year period from the date of registration and may be maintained on a continuous basis provided that you meet with the following requirements:

Submit a completed registration form annually, and return to CPA Central Office together with the annual registration fee. The annual registration form and invoice will be issued by CPA 60 days prior to this date each year.

Since accreditation does not automatically survive major changes in staffing, structure, repertoire or facilities, CPA Central Office must be informed immediately such changes occur.

Annual Registration Date: 1st January

Submit an application for re-registration on a four yearly cycle. Application forms will be issued by CPA Central Office at least six months in advance.

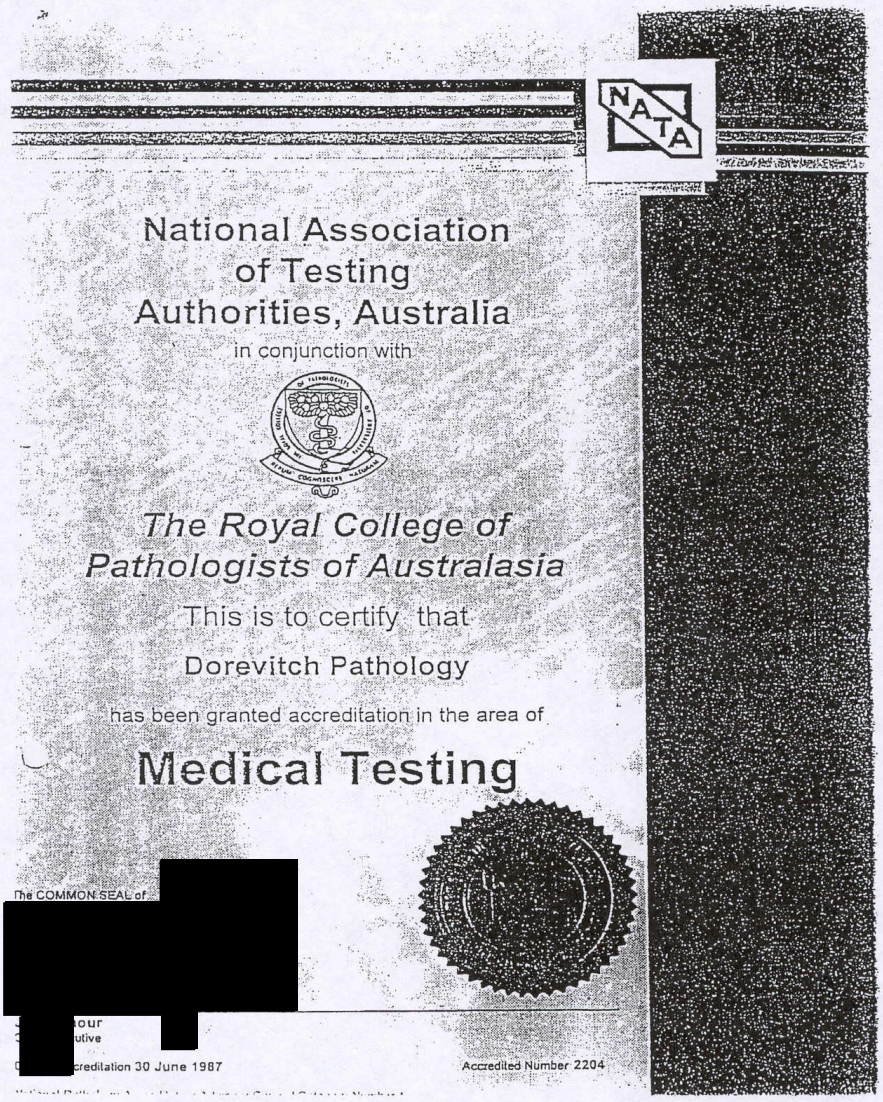
The accreditation certificate is only valid when accompanied by a current letter of accreditation. Please keep these documents in your files.

Signed on behalf of CPA (UK) Ltd:

[redacted]

Designati[redacted]
Executive Manager

Date: 10/10/2001



National Association
of Testing
Authorities, Australia
in conjunction with

The Royal College of Pathologists of Australasia

This is to certify that

Dorevitch Pathology

has been granted accreditation in the area of

Medical Testing

The COMMON SEAL of [redacted]

[redacted]

Accreditation 30 June 1987

Accredited Number 2204

DOREVITCH PATHOLOGY ACCREDITATION CERTIFICATE BY THE NATIONAL ASSOCIATION OF TESTING AUTHORITIES, AUSTRALIA

SENT BY:QUEST ; 2-27- 1 ; 9:08AM ; CLINICAL TRIALS CTR- [redacted]

National Association of Testing Authorities, Australia
ACN 004 379 748
71-73 Flemington Road, North Melbourne, Victoria 3051 Australia
Telephone: [redacted] International: [redacted]
Fax: [redacted] International: [redacted]

22 January 1999

[redacted]
Dorevitch Pathology
691 Burke Road
CAMBERWELL VIC 3124

Dear [redacted]

NATA/RCPA ACCREDITATION NO 2204
DOREVITCH PATHOLOGY
Fairfield Laboratory

I would like to confirm that your Fairfield laboratory currently holds accreditation with NATA/RCPA.

The scope of accreditation is attached.

I would also like to confirm that the certificate of accreditation is current. NATA/RCPA do not annually reissue this certificate and it remains current until the accreditation is withdrawn.

Please let me know if I can be of any further assistance at this time.

Yours sincerely

[redacted]

[redacted]
SENIOR SCIENTIFIC OFFICER, MEDICAL TESTING

jhs790.doc

[redacted] P.02/04

NATIONAL ASSOCIATION OF TESTING AUTHORITIES, AUSTRALIA

ACCREDITATION NUMBER : 2204

Dorevitch Pathology

582 Heidelberg Road
FAIRFIELD VIC 3078

CONTACT : [redacted]
Phone : [redacted] Fax : [redacted]
FACILITIES : NPAAC Category 1

10.10 Microbiology

10.11 Bacteriology
- .01 Preparation of films for microscopic examination
- .02 Inoculation of cultures
- .03 Microscopic examination of clinical specimens
- .04 Identification of organisms including antibiotic sensitivity testing
- .06 Detection of bacterial antigens

10.12 Parasitology
- .01 Detection and provisional identification of parasites
- .02 Definitive identification of parasites

10.13 Virology
- .01 Non-cultural methods of detection
- .02 Isolation of viruses
- .03 Definitive identification of viruses
  Herpes simplex and Varicella zoster viruses only

10.14 Mycology
- .01 Microscopic examination of clinical specimens
- .02 Culture of specimens
- .04 Definitive identification of isolates

10.15 Mycobacteriology
- .01 Microscopic examination of clinical specimens
- .02 Culture for isolation of mycobacteria

10.16 Serology of infection
- .02 General serological testing

10.19 Miscellaneous
- .01 General clinical microscopy
- .02 Semen analysis (Screening Test)

10.20 Immunohaematology
- .01 Blood grouping including ABO, Rh(D)
- .03 Blood group antibody screen
- .05 Determination of compatibility of donor units using appropriate techniques including the investigation of transfusion reactions
- .10 Storage and distribution of blood and blood components
- .13 Collection and storage of blood for autologous transfusions

NATIONAL ASSOCIATION OF TESTING AUTHORITIES, AUSTRALIA

10.30 Haematology
- .01 Blood counts
- .02 Visual examination of blood films
- .03 Erythrocyte sedimentation rate
- .05 Automated differential leucocyte counts
- .08 Blood film examinations involving special staining procedures
- .20 Bone marrow examination
- .30 Tests for haemoglobin variants and thalassaemia
- .35 Tests to investigate haemolysis
- .40 Limited haemostasis related tests
- .41 General haemostasis related tests
- .45 Tests of platelet function
- .57 Screening test for infectious mononucleosis

10.40 Immunology
- .01 Quantitative investigation of immunoglobulins G, A, M and D in body fluids
- .02 Qualitative investigation of immunoglobulins G, A, M and D in body fluids
- .03 Total IgE
- .04 Allergen-specific IgE
- .06 Investigation of complement
- .10 Rheumatoid factor - quantitative assays
- .12 Detection of autoantibodies in body fluids and biopsy material
- .36 Cell markers
- .40 Tissue typing
  HLA - B27 only

10.50 Anatomical pathology

10.51 Histopathology
- .01 Histopathology of biopsy material
- .02 Immediate frozen section diagnosis
- .03 Immunohistochemical investigation

10.52 Cytopathology
- .01 Gynaecological (cervical)
- .02 Non-gynaecological
- .03 Fine needle aspiration biopsy specimens
- .04 Gynaecological (other than cervical)

10.60 Chemical pathology
- .01 Analytes in general use in cardiac, liver function, lipid, renal and other profiles and metabolic studies
- .02 Proteins, quantitative analysis
- .03 Proteins, qualitative and semiquantitative analysis
- .09 Trace elements
- .10 Drugs for therapeutic monitoring
- .15 Drugs for toxicological purposes
- .20 Hormones
- .30 Catecholamines and related metabolites
- .33 Amniotic fluid analytes
- .35 Assays of neonatal specimens
- .40 Iron studies
- .50 Vitamin B_{12} and folate
- .65 Pregnancy tests - qualitative
- .66 Glycohaemoglobin
- .68 Faecal fats

.69 Carcinoembryonic antigen
.70 Vitamin assays
.71 Occult blood
.73 5-Hydroxyindole acetic acid
.99 Miscellaneous tests
Ammonia; bromide; calculi; xylose

Data change date 13/11/98

TOTAL P. 04

GlaxoSmithKline

Pharmaceutical Development
USE-BY DATE CERTIFICATE

Protocol number: 207499/157

Job number: WH001

Country(ies): Belgium, Czech Republic, Denmark, Finland, France, Germany, Italy, Netherlands, Poland, Russia, Slovakia, Spain, United Kingdom, Australia, New Zealand, South Africa.

The use-by date for the above supplies is:

Primary pack description	**Use-by date:**
60cc HDPE bottles with 33mm IIIS CR Caps.	31 Aug 2005

at the following storage conditions:

Store at 20 – 25°C.

Approved by: [redacted] 10 Oct 2001
Clinical Trial Supplies

New Frontiers Science Park, Third Avenue, Harlow, Essex. CM19 5AW
Telephone: [redacted] Fax: [redacted]

PDRU [redacted]49

GlaxoSmithKline
Pharmaceutical Development

[redacted]

Drug Product Certificate of Analysis PDRU-02449

Product:	SB-207499	Product Code:	AW
Batch Number:	[redacted]	Strength/ Dose Form:	15 mg/tablet
Date of Manufacture:	10Sept2001	Analytical Ref. No.:	0100322
Site of Manufacture:	GSK Cidra, PR		

Test	Results
Appearance	Pale yellow, round, convex, film coated tablet – Passes
Identification (HPLC)	The retention time of the major elution peak must correspond to that of the Reference Standard, similarly prepared and measured – Passes
Identification (UV)	The ultraviolet spectrum of the sample must correspond to that of the Reference Standard, similarly prepared and measured – Passes
SB-207499 Content (HPLC)	15.0mg/tablet, 15.2mg/tablet, 15.2mg/tablet, 14.9mg/tablet, 15.0 mg/tablet, 15.1 mg/tablet; Average: 15.1 mg/tablet; 0.73% RSD, N=6 – Passes
Dissolution	Rate at 30 Min: Average = 89%, Range: 85-94%, RSD = 2.7%, N = 18 – Passes
Uniformity of Dosage Units	Average = 98.1%, Range: 95.3-100.0%, RSD = 1.59% – Passes

This material conforms with Specification PDSU-0782/01

Approved by: [redacted] Date: 03 OCT 2001

PDRU[redacted]449 *Page 2 of 2*

This material was manufactured and tested in accordance with current Good Manufacturing Practices.

Approved by: [redacted] Date: 05 Oct 2001

Quality Assurance

GlaxoSmithKline
Pharmaceutical Technologies
USE-BY DATE CERTIFICATE

Protocol number: 207499/157

Job number: WH002

Country(ies): SWEDEN & TAIWAN

The use-by date for the above supplies is:

Primary pack description	**Use-by date:**
60cc HDPE Bottles with 33mm CR IHS Caps	31 Aug 2005

at the following storage conditions:

Store at 20 - 25°C.

Approved by: [redacted] Date: 20 MAR 2001.

Clinical Trial Supplies

New Frontiers Science Park, Third Avenue, Harlow, Essex, CM19 5AW
Telephone: [redacted] Fax: [redacted]

PDRU-02448 2449 [redacted]

GlaxoSmithKline
Pharmaceutical Development

Drug Product Certificate of Analysis PDRU-02448 2449 [redacted]

Product:	SB-207499	Product Code:	SS
Batch Number:	[redacted]	Strength/ Dose Form:	Placebo tablet
Date of Manufacture:	10Sept2001	Analytical Ref. No.:	0100321
Site of Manufacture:	GSK Upper Providence, PA, USA		

Test	Results	
General Appearance	Pale Yellow, film-coated, convex, round tablet	Passes
Identification (HPLC)	Absence of the major elution peak at the retention time corresponding to that of the Reference Standard, similarly prepared and measured or absence of active as defined in the method.	Passes

This material conforms with Specification PDSU-0676/01

Approved by: [redacted] Date: 03 Oct 2001

This material was manufactured and tested in accordance with current Good Manufacturing Practices.

Approved by: [redacted] Date: 04 Oct 2001 [redacted]
18 Oct 2001
[redacted]ity Assurance

GlaxoSmithKline

Pharmaceutical Development
USE-BY DATE CERTIFICATE

Protocol number: 207499/157

Job number: WH003

Country(ies) **Belgium, Czech Republic, Denmark, Finland, France, Germany, Italy, Netherlands, Poland, Russia, Slovakia, Spain, United Kingdom, Australia, New Zealand, South Africa.**

The use-by date for the above supplies is:

Primary pack description	**Use-by date:**
60cc HDPE bottle with 33mm CR IHS caps	29th February 2004

at the following storage conditions:

Store at 20-25°C

Approved by: [redacted] Date 17 Jun 2002
Clinical Trial Supplies

New Frontiers Science Park, Third Avenue, Harlow, Essex, CM19 5AW
Telephone: [redacted] Fax: [redacted]

Certificate of Analysis

GlaxoSmithKline

Product Name	Placebo to match SB-207499 tablets.
Strength	Placebo tablet.
Product Code	SS
Batch Number	[redacted]
Analytical Reference	9900132
Date of Manufacture	09 Mar 1999

GlaxoSmithKline Research & Development Limited
New Frontiers Science Park
Third Avenue
Harlow
Essex
CM19 5AW
Tel. [redacted]
Fax.
www.gsk.com

Test	Result
Description	Pale Yellow, film-coated, convex, round tablet. Passes.
Identification (HPLC)	Absence of the major elution peak at the retention time corresponding to that of the Reference Standard, similarly prepared and measured or absence of the active as defined in the method. Passes.

This product conforms with Release Specification Number, PDSU-0676/01, and has been manufactured and tested in accordance with Good Manufacturing Practice.

Approved b[redacted] on 13 June 2002
[redacted] BSc, MRPharmS 13 June 2002
Director European Pharmaceutical Development QA.

[redacted] 12/06/2002

Registered in England & Wales
No 895139
Registered office
980 Great West Road
Brentford, Middlesex. TW8 9GS

GlaxoSmithKline

Pharmaceutical Development
USE-BY DATE CERTIFICATE

Protocol number:	207499/157
Job number:	WH004
Country(ies):	Czech Republic, Belgium, Denmark, Spain, Finland, France, Germany, Poland, Russia, Slovakia, Italy, Netherlands, Australia, New Zealand, South Africa & United Kingdom.

The use-by date for the above supplies is:

Primary pack description	**Use-by date:**
60cc HDPE bottles with	31-Jul-2006
33mm CR Induction seal caps	
at the following storage conditions:	
Store at 20 - 25°C	

Approved by: [redacted] Date 16-Aug-2002

Clinical Trial Supplies

New Frontiers Science Park, Third Avenue, Harlow, Essex, CM19 5AW
Telephone: [redacted] Fax: [redacted]

Certificate of Analysis

GlaxoSmithKline

Product Name	SB-207499
Strength	Placebo tablet
Product Code	SS
Batch Number	[redacted]
Analytical Reference	0100321
Date of Manufacture	10 September 2001

New Frontiers Science Park
Third Avenue
Harlow
Essex
CM19 5AW
Tel. [redacted]
Fax [redacted]
www.gsk.com

Test	Results
General Apparance	Pale Yellow, film-coated, convex, round tablet. Passes
Identification (HPLC)	Absence of the major elution peak at the retention time corresponding to that of the Reference Standard, similarly prepared and measured or absence of active as defined in the method. Passes

This product conforms with Release Specification PDSU-0676/01 and has been manufactured and tested in accordance with Good Manufacturing Practice.

Approved by [redacted] on 23 Oct 2001
[redacted] BSc, MRPharmS 23 October 2001
[redacted]Director European Pharmaceutical Development QA

[redacted] 22/10/2001

SmithKline Beecham Pharmaceuticals
is a business name of SmithKline Beecham plc.
Registered in England & Wales
No. 2337959
Registered Office
New Horizons Court, Brentford, Middlesex TW8 9EP

gsk 0066

Other Data Listings - Part 1

Page

LISTING A.1 TREATMENT RANDOMIZATION WITH PATIENT NUMBER 3

LISTING A.2 SMOKING STATUS DISCREPANCY BETWEEN RAMOS AND CRF . 24

LISTING B.1 REASON FOR STUDY CONCLUSION, DAYS OF PARTICIPATING IN THE STUDY AND DEMOGRAPHICS BY PATIENT NUMBER 45

LISTING B.2A EXCLUSIONARY MEDICATIONS AND VISIT SPECIFIC PROTOCOL VIOLATIONS BY PATIENT NUMBER 87

LISTING B.2B VIOLATIONS OF ELIGIBILITY CRITERIA BY PATIENT NUMBER . 144

LISTING B.2C CONDUCT OF STUDY DEVIATIONS BY PATIENT NUMBER 147

LISTING B.3 PULMONARY FUNCTION PARAMETERS AT SCREENING BY PATIENT NUMBER 165

LISTING B.4 ALCOHOL CONSUMPTION AND CIGARETTE SMOKING HISTORY AT SCREENING BY PATIENT NUMBER 213

LISTING B.5 PRIOR MEDICAL CONDITIONS BY PATIENT NUMBER AND DISEASE CLASSIFICATION 255

LISTING B.6 CURRENT/ACTIVE MEDICAL CONDITIONS BY PATIENT NUMBER AND DISEASE CLASSIFICATION 328

LISTING B.7 PRIOR MEDICATIONS BY PATIENT NUMBER 489

LISTING B.8A CONCOMITANT MEDICATIONS BY PATIENT NUMBER 961

LISTING B.8B COPD EXACERBATION MEDICATIONS BY PATIENT NUMBER . . 1687

LISTING B.8C POST-THERAPY MEDICATIONS BY PATIENT NUMBER 1894

LISTING B.9 MEDICAL PROCEDURE DATA BY PATIENT NUMBER 2019

LISTING B.10 BASELINE SIGNS AND SYMPTOMS BY PATIENT NUMBER, MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND VERBATIM TERM 2050

LISTING B.11 STUDY MEDICATION COMPLIANCE BY PATIENT NUMBER 2107

LISTING B.12 STUDY MEDICATION RECORD BY PATIENT NUMBER 2351

LISTING B.13 SMOKING STATUS BY PATIENT NUMBER 2591

LISTING C.1 PULMONARY FUNCTION PARAMETERS BY PATIENT NUMBER . . 2837

LISTING C.2 SAINT GEORGES RESPIRATORY QUESTIONNAIRE BY PATIENT NUMBER 3306

LISTING C.3 GLOBAL SUBJECT ASSESSMENT, GLOBAL INVESTIGATOR ASSESSMENT, BLOOD CD4 +/CD8+RATIO AND SERUM C REACTIVE PROTEIN BY PATIENT NUMBER 3377

LISTING C.4 COPD EXACERBATIONS BY PATIENT NUMBER 3454

Other Data Listings - Part 2

Page

LISTING C.6 COPD SYMPTOM PARAMETERS BY PATIENT NUMBER 2

Other Data Listings - Part 3

Page

LISTING C.7A HEALTH CARE RESOURCE UTILIZATION BY PATIENT NUMBER 6

LISTING C.7B TIME OFF FROM WORK OR USUAL ACTIVITIES AND USE OF CAREGIVER ASSISTANCE BY PATIENT NUMBER 29

LISTING C.8 EQ-5D BY PATIENT NUMBER 358

LISTING C.9 MORNING PEF AND SYMPTOMS BY PATIENT NUMBER 431

LISTING D.1 ON-THERAPY ADVERSE EXPERIENCES BY PATIENT NUMBER, MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND VERBATIM TERM 7012

LISTING D.2A ON-THERAPY ADVERSE EXPERIENCES POSSIBLY OR PROBABLY RELATED TO TREATMENT BY PATIENT NUMBER, MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND VERBATIM TERM 7508

LISTING D.2B ON-THERAPY ADVERSE EXPERIENCES UNLIKELY OR NOT RELATED TO TREATMENT BY PATIENT NUMBER, MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND VERBATIM TERM 7559

LISTING D.3 ON-THERAPY ADVERSE EXPERIENCES THAT LED TO DOSE INTERRUPTION BY PATIENT NUMBER, MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND VERBATIM TERM 8007

LISTING D.4 ON-THERAPY ADVERSE EXPERIENCES THAT REQUIRED CORRECTIVE THERAPY BY PATIENT NUMBER, MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND VERBATIM TERM 8023

LISTING D.5A RUN-IN SERIOUS ADVERSE EXPERIENCES BY PATIENT NUMBER, MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND VERBATIM TERM. 8314

LISTING D.5B ON-THERAPY SERIOUS ADVERSE EXPERIENCES BY PATIENT NUMBER, MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND VERBATIM TERM. 8318

LISTING D.5C POST-THERAPY SERIOUS ADVERSE EXPERIENCES BY PATIENT NUMBER, MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND VERBATIM TERM 8342

LISTING D.5D PATIENT FATALITIES BY PATIENT NUMBER 8347

LISTING D.6A ON-THERAPY ADVERSE EXPERIENCES THAT LED TO WITHDRAWAL BY PATIENT NUMBER, MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND VERBATIM TERM 8348

LISTING D.6B RUN-IN ADVERSE EXPERIENCES THAT LED TO WITHDRAWAL BY PATIENT NUMBER, MEDDRA SYSTEM ORGAN CLASS, PREFERRED TERM AND VERBATIM TERM 8374

LISTING D.7 POST-THERAPY ADVERSE EXPERIENCES BY PATIENT NUMBER, MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND VERBATIM TERM 8391

LISTING D.8 GASTROINTESTINAL ADVERSE EXPERIENCES OF CONCERN BY PATIENT NUMBER, MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND VERBATIM TERM 8432

LISTING D.8A RUN-IN GASTROINTESTINAL ADVERSE EXPERIENCES OF CONCERN BY PATIENT NUMBER, MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND VERBATIM TERM 8441

LISTING D.8B POST-THERAPY GASTROINTESTINAL ADVERSE EXPERIENCES OF CONCERN BY PATIENT NUMBER, MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND VERBATIM TERM 8442

LISTING D.9 GASTROINTESTINAL SYMPTOM ASSESSMENT BY PATIENT NUMBER 8443

LISTING D.10 ABDOMINAL PAIN ASSESSMENT BY PATIENT NUMBER 8448

LISTING D.11 STOOL ASSESSMENT BY PATIENT NUMBER 8451

LISTING D.12 PHYSICAL EXAMINATION FOR PATIENTS WITH GASTROINTESTINAL SYMPTOMS OF CONCERN BY PATIENT NUMBER . . 8453

LISTING D.13 FOB TEST RESULTS BY PATIENT NUMBER 8455

LISTING D.14 LISTING OF GASTRO-INTESTINAL ADVERSE EXPERIENCES OF CONCERN WITH ASSOCIATED FOB RESULTS AND COLONOSCOPY FINDINGS BY PATIENT NUMBER 8588

LISTING E.1A STANDARD VITAL SIGNS BY PATIENT NUMBER 8593

LISTING E.1B STANDARD VITAL SIGNS OF CLINICAL CONCERN BY PATIENT NUMBER 8857

LISTING E.1C ORTHOSTATIC VITAL SIGNS CHANGES BY PATIENT NUMBER . 8870

LISTING E.1D ORTHOSTATIC VITAL SIGNS CHANGES OF CLINICAL CONCERN BY PATIENT NUMBER 8990

LISTING E.2A ECG INTERVALS BY PATIENT NUMBER 9027

LISTING E.2B ECGS OF CLINICAL CONCERN BY PATIENT NUMBER 9139

LISTING E.2C ECG ABNORMALITIES BY PATIENT NUMBER 9179

LISTING F.1 LIST OF PATIENTS WITH LABORATORY VALUES OF CLINICAL CONCERN BY TREATMENT GROUP AND PATIENT NUMBER 9392

LISTING F.2 CLINICAL LABORATORY VALUES BY TREATMENT GROUP AND PATIENT NUMBER 9549

LISTING F.3 LOCAL LABORATORY VALUES BY TREATMENT GROUP AND PATIENT NUMBER 15816

LISTING I.1 REPEATED MEASURES ANALYSES OF COUNTRY AND TIME INTERACTIONS WITH TREATMENT FOR PRE-BD TROUGH FEV1 (L) - ITT (SAS OUTPUT ASSOCIATED WITH TABLE 14.1N) 15819

LISTING I.2 REPEATED MEASURES ANALYSIS OF PRE-BD TROUGH FEV1 (L) - ITT (SAS OUTPUT ASSOCIATED WITH TABLE 14.1A) 15832

LISTING I.3 ANALYSIS OF VARIANCE TEST FOR TREATMENT DIFFERENCES FOR PRE-BD TROUGH FEV1 (L) AT ENDPOINT - ITT (SAS OUTPUT ASSOCIATED WITH ENDPOINT ENTRY OF TABLE 14.1B) 15884

LISTING I.4A SUMMARY OF AVERAGE CHANGE FROM BASELINE OVER 52 WEEKS (REPEATED MEASURES ANALYSIS) OF PRE-BD TROUGH FEV1 (L) BY COMPLETION STATUS AND TREATMENT GROUP - ITT 15891

LISTING I.4B SUMMARY STATISTICS FOR PRE-BD TROUGH FEV1 (L) AT ENDPOINT BY COMPLETION STATUS AND TREATMENT GROUP - ITT . . . 15892

LISTING I.4C DESCRIPTIVE STATISTICS FOR PRE-BD TROUGH FEV1 (L) AT ENDPOINT BY COMPLETION STATUS AND TREATMENT GROUP - ITT . . . 15893

LISTING I.6 SENSITIVITY ANALYSIS OF ASSUMED COVARIANCE STRUCTURE ON TREATMENT DIFFERENCES FOR PRE-BD TROUGH FEV1 (L) - ITT 15894

LISTING I.7 REPEATED MEASURES ANALYSIS TEST FOR COVARIATE EFFECTS ON TREATMENT DIFFERENCES FOR PRE-BD TROUGH FEV1 (L) - ITT (SAS OUTPUT ASSOCIATED WITH TABLE 14.1O) 15895

LISTING I.8 REPEATED MEASURES ANALYSIS OF TREATMENT-WITHDRAWAL INTERACTION FOR PRE-BD TROUGH FEV1 (L) - ITT 15908

LISTING I.9 WEIGHTED ESTIMATE FOR TREATMENT EFFECT FROM PATTERN MIXTURE MODEL FOR PRE-BD TROUGH FEV1 (L) - ITT 15910

LISTING I.10A SUMMARY OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS FOR ALL WITHDRAWN PATIENTS 15911

LISTING I.10B SUMMARY OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS FOR COMPLETERS 15912

LISTING I.11A SUMMARY OF AVERAGE CHANGE FROM BASELINE OVER 52 WEEKS IN PRE-BD TROUGH FEV1 (L) - ITT (REPEATED MEASURES ANALYSIS ADJUSTED BY COUNTRY, TIME, AND TREATMENT-BY-TIME INTERACTION) 15913

LISTING I.11B SUMMARY OF AVERAGE CHANGE FROM BASELINE FROM WEEK 36 TO WEEK 52 (REPEATED MEASURES ANALYSIS) IN PRE-BD TROUGH FEV1 (L) - ITT 15914

LISTING I.11C SUMMARY OF AVERAGE CHANGE FROM BASELINE OVER 52 WEEKS (REPEATED MEASURES ANALYSIS) IN PRE-BD TROUGH FEV1 (L) - ITT -- ALL WITHDRAWALS IMPUTED WITH ITT ENDPOINT 15915

LISTING I.11D SUMMARY OF AVERAGE CHANGE FROM BASELINE OVER 52 WEEKS (REPEATED MEASURES ANALYSIS) IN PRE-BD TROUGH FEV1 (L) -ITT -- WHITDRAWLS DUE TO LACK OF EFFICACY IMPUTED WITH WORST FEV1 15916

LISTING I.11E SUMMARY OF AVERAGE CHANGE FROM BASELINE OVER 52 WEEKS (REPEATED MEASURES ANALYSIS) IN PRE-BD TROUGH FEV1 (L) - ITT -- INCLUDING ESSENTIAL VISITS 15917

LISTING I.12A SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN PRE-BD TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP -- ITT COMPLETERS 15918

LISTING I.12B SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP ITT WITHDRAWALS 15919

LISTING I.12D SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP INCLUING ESSENTIAL VISITS -- ITT WITHDRAWALS 15920

LISTING I.12E SUMMARY STATISTICS FOR CHANGE FROM BASELINE IN TROUGH FEV1 (L) BY WEEK AND TREATMENT GROUP INCLUDING ESSENTIAL VISITS -- ITT 15921

LISTING I.13A POISSON REGRESSION OF LEVEL II / III COPD EXACERBATIONS (SAS OUTPUT ASSOCIATED WITH TABLE 14.7A) 15922

LISTING I.13B POISSON REGRESSION OF ALL COPD EXACERATIONS (SAS OUTPUT ASSOCIATED WITH TABLE 14.7B) 15928

LISTING I.13C POISSON REGRESSION OF LEVEL II/ III COPD EXACERBATIONS DURING ON-THERAPY AND ESSENTIAL VISITS - ITT . . 15934

LISTING I.13D POISSON REGRESSION OF ALL COPD EXACERBATIONS DURING ON-THERAPY AND ESSENTIAL VISITS 15935

LISTING I.13E SUMMARY OF LEVEL II / III COPD EXACERBATION RATES PER PATIENT YEAR BY SMOKING STATUS AND TREATMENT GOUP - ALL RANDOMIZED PATIENTS INCLUDING ESSENTIAL ASSESSMENTS . . 15936

LISTING I.13F SUMMARY OF EXACERBATION RATES PER PATIENT YEAR BY SMOKING STATUS AND TREATMENT GOUP - ALL RANDOMIZED PATIENTS INCLUDING ESSENTIAL ASSESSMENTS 15937

LISTING I.14A SUMMARY OF LEVEL II/III EXACERBATION-FREE SURVIVAL DURING ON-THERAPY AND ESSENTIAL VISITS 15938

LISTING I.14B SUMMARY OF EXACERBATION-FREE SURVIVAL DURING ON-THERAPY AND ESSENTIAL VISITS 15939

LISTING I.15 SUMMARY OF DEMOGRAPHIC CHARACTERISTICS AT SCREENING BY TREATMENT GROUP - ITT 15940

This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the ***GSK Clinical Study Register****.*

Sponsor Signatory Signature Page

STUDY TITLE: A Randomised, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy, Safety and Tolerability of Oral Cilomilast (15 mg bd) When Given as Maintenance Treatment for 12 Months to Subjects with Chronic Obstructive Pulmonary Disease (COPD)

Study: SB-207499/157 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], MD

Title of Sponsor Signatory: Vice President, Respiratory & Immunoinflammation Medicine Development Centre, Clinical

Signature: [redacted]

Date: 11-FEB-2009