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Division:	New Product Development	**Document Number:**	SB-207499/RSD-101MFC/1
Document Type:	Clinical Study Report	**Study Identifier:**	SB 207499/156
Site of Issue:	RTP		
Classification:	Level 2	**Document Date:**	12 November 2002

Title:

A Randomized, 24-week, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy, Safety and Tolerability of Ariflo (15mg BID) in Patients with Chronic Obstructive Pulmonary Disease (COPD)

Abstract: (For Internal Use Only)

This was a randomized, 24-week, double-blind, placebo-controlled, parallel-group study in patients with COPD. Male and female patients were randomized in a 1:1 ratio to receive SB 207499 (15mg twice daily) or placebo. The objectives were to demonstrate the clinical efficacy of SB 207499 versus placebo using multiple pulmonary function tests, to examine the risk of COPD exacerbations, and to further define the clinical safety and tolerability of SB 207499. SB 207499 was shown to have a statistically significant ($p = 0.024$) effect on the co-primary endpoint of FEV_1, with a difference between the treatment groups of 24mL in the mean change from baseline for trough FEV_1 averaged over 24 weeks. The total score of the SGRQ co-primary endpoint demonstrated statistically significant improvements for SB 207499-treated patients over patients who received placebo (1.9 points; $p = 0.017$, CI -3.5 through -0.3). In general, there were numerical advantages favoring SB 207499 in pulmonary function (PEFR, FEF_{25-75}, and change from baseline in trough FVC), COPD symptoms (overall breathlessness and use of rescue medication), quality of life measurements (activities score of SGRQ), post-exercise oxygen saturation, and exercise performance. The overall incidence of AEs was comparable in the two treatment groups (placebo, 83.3%; SB 207499, 87.1%), and the majority of AEs were mild to moderate in intensity. The three most frequently reported AEs were chronic obstructive airways disease (placebo, 30.7%; SB 207499, 27.3%), nausea (placebo, 6.6%; SB 207499, 26.1%), and diarrhea (placebo, 10.8%; SB 207499, 19.6%). In general, GI intolerance (characterized by nausea/vomiting, diarrhea, abdominal pain, etc.) occurred in a higher percentage of SB 207499-treated versus placebo-treated patients and was generally reported at a higher rate during the first 4 weeks of therapy compared to the remainder of the study. The GI adverse event assessments, including fecal occult blood testing, assessment of orthostatic changes in vital signs, and laboratory assessments showed no untoward risk of hypovolemic events associated with these adverse events. Similarly, extensive cardiac monitoring confirmed the absence of cardiovascular safety concerns for SB 207499.

Authors: [redacted]

Compound Numbers/Keywords (if applicable):
SB 207499, Cilomilast, ARIFLO, COPD, PDE4 Inhibitor

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Sponsor Signatory Signature Page

STUDY TITLE: A Randomized, 24-week, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy, Safety and Tolerability of Ariflo (15mg BID) in Patients with Chronic Obstructive Pulmonary Disease (COPD)

Study: SB207499/156 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 Clinical Development and Medical Affairs, GlaxoSmithKline

Signature: _____

Date: _____

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A Randomized, 24-week, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy, Safety and Tolerability of Ariflo (15mg BID) in Patients with Chronic Obstructive Pulmonary Disease (COPD)

Clinical Study Report for Study 156 (Development Phase III)

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Indication Studied: Chronic obstructive pulmonary disorder

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Sponsor Signatory: [redacted] MD
(and Medical Officer) Vice President, Respiratory Clinical Development and Medical Affairs, GlaxoSmithKline

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

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Synopsis

Document Number: SB-207499/RSD-101MFC/1

Study Number: SB 207499/156

Title: A Randomized, 24-week, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy, Safety and Tolerability of Ariflo (15mg BID) in Patients with Chronic Obstructive Pulmonary Disease (COPD)	
Investigator(s): The study was conducted at 132 centers in the United States and Canada. Patients were randomized in 126 of these centers.	
Study center(s): This was a multicenter study (See Appendix A for Investigator information)	
Publication(s): No publication to date.	
Study period: The first dose of single-blind medication was taken on 12 December 2000. The first and last doses of double-blind medication were administered on 11 January 2001 and 16 July 2002, respectively.	Phase of Development: III
Objectives: The primary objective of the study was to demonstrate the clinical efficacy of SB 207499 (15mg BID) versus placebo by assessment of forced expiratory volume in 1 second (FEV_1) at trough drug levels and the quality of life improvement based on total score of the St. George's Respiratory Questionnaire (SGRQ) over 24 weeks in patients with COPD. The secondary objectives of the study were to examine risk of exacerbations and to compare the clinical efficacy of SB 207499 versus placebo on additional pulmonary function tests (clinic trough measurements) and other clinical evaluations (e.g., breathlessness). An additional objective of the study was to further define the clinical safety and tolerability of SB 207499 through the assessment of adverse events, vital signs, clinical laboratory tests, and electrocardiograms (ECGs).	
Study Design: This was a randomized, double-blind, placebo-controlled, parallel-group, study in patients with COPD. After a 4-week, single-blind, placebo run-in period, eligible patients were randomized in a ratio of 1:1 to receive SB 207499 (15mg twice daily) or placebo for 24 weeks. There was a 1-week (7 ± 3 days) safety follow-up period for patients who completed the study or who withdrew before the end of Week 24.	
Number of subjects: A total of 1252 patients met eligibility criteria and entered the single-blind phase of the study at 132 centers in the United States and Canada. Of the 1252 patients who were enrolled, 427 patients (34.1%) were withdrawn prior to randomization and 825 patients (65.9%) were randomized to placebo (407 patients) or SB 207499 (418 patients) treatment groups.	

Diagnosis and Main Criteria for Inclusion: Male and female patients between 40 and 80 years of age (inclusive) with COPD (by American Thoracic Society [ATS] Guidelines), and a cigarette-smoking history of ≥10 pack years were eligible. Additional inclusion criteria were pre-albuterol FEV_1 to FVC ratio ≤0.7, post-albuterol reversibility ≤15% or ≤200mL (or both), and post-albuterol FEV_1 ≥30% and ≤70% of predicted normal for height, age, and sex.

Treatment administration: One yellow, round, convex tablet containing 15mg of SB 207499 (Batch [redacted] or matching placebo (Batch [redacted] was taken in the morning and one in the evening, after a meal.

Criteria for Evaluation:

Efficacy Parameters: The primary efficacy variables were changes from baseline in trough pre-bronchodilator FEV_1 and in total score of the SGRQ averaged over 24 weeks. Secondary measures of efficacy were changes from baseline in clinic trough FVC and post-exercise breathlessness (modified Borg Scale) and time to first COPD exacerbation and to first Level 2 or Level 3 COPD exacerbation. Tertiary efficacy variables were use of "as needed" albuterol, clinic trough PEFR, first and last dose effects on pulmonary function, post-bronchodilator effects on pulmonary function, overall breathlessness during usual activity, exertional (post-exercise) breathlessness, SF-36 subscales, health economic endpoints, SGRQ subscales, global patient and investigator assessments, exercise performance, post-exercise and resting SaO_2 (in patients with FEV_1 <40% of prediction at Screening based on age, height, and sex), arterial blood gases in patients with FEV_1 of <40% who lived at high altitudes or who had a resting SaO_2 <88%, clinic trough FEF_{25-75}, cough assessment, and sputum assessment.

Safety Parameters: Safety was evaluated by monitoring adverse events (AEs), including a structured assessment of GIAEs of concern, laboratory data, electrocardiogram parameters, and vital signs.

Pharmacokinetics: Plasma samples for the population pharmacokinetic analysis of SB 207499 and the metabolite SB 217493 were collected from all randomized patients pre-dose and/or at various times post-dose at Weeks 0, 4, 12, and 24, and when practical, from patients who had a gastrointestinal AE of concern or any serious AE. The population pharmacokinetic evaluation of SB 207499 and SB 217493 is reported separately [18].

Pharmacoeconomics: Data on lost workdays due to COPD exacerbations and COPD-related symptoms were collected. Data were also collected on restrictions to leisure activities and paid or unpaid assistance with daily activities due to COPD-related symptoms.

Statistical Methods:

Summary: The planned sample size was 830 patients to obtain 550 completed patients. The primary endpoints were analyzed using a repeated measures model to compare the average change over 24 weeks. Additional comparisons were made at individual time points. Continuous secondary and tertiary variables were analyzed analogously. Exacerbation-free survival at 24 weeks was estimated using the Kaplan-Meier product limit. Analyses were performed for the intent-to-treat (ITT) population, composed of all patients who received at least one dose of double-blind medication and had a baseline and at least one on-therapy efficacy assessment, and for the per-protocol (PP) population, composed of all patients in the ITT population who did not significantly violate the protocol. COPD exacerbations were analyzed for randomized patients. Descriptive statistics were provided for safety parameters.

Data Sets: All analyses were performed for the ITT population. Analyses for the PP population were limited to FEV_1 (including first and last dose effects on FEV_1), SGRQ total score, FVC, post-exercise breathlessness, and exercise performance.

Patient Disposition and Key Demographic Data: The two treatment groups in the randomized patient population were well matched for demographic characteristics and for baseline characteristics of COPD. The treatment groups were similar with respect to pulmonary function at screening, except that the placebo group had a mean FEV_1 that was 50mL greater than the SB 207499 treatment group (1.45L placebo vs. 1.40L SB 207499). This difference in FEV_1 is likely due to a gender effect since a higher number of female patients were enrolled in the SB 207499 treatment group (43.8%) compared to the placebo treatment group (38.1%). However, the % predicted FEV_1 for the patients randomized to placebo (50.0%) and SB 207499 (50.3%) were nearly identical. Overall, the patients were representative of a moderate COPD population. At screening, patients who were ultimately randomized to placebo and SB 207499 both had a mean FEV_1/FVC ratio of 0.53, poor reversibility to albuterol of 8.6%, and percent predicted DLCO of approximately 55%. In the placebo and SB 207499 treatment groups there were 33.7% and 32.3% of patients, respectively, with a current medical condition at screening of of chronic bronchitis. The most common current medical conditions in both groups (excluding respiratory disease) were hypertension (42.0% placebo vs. 39.2% SB 207499) and allergic rhinitis (20.9% placebo vs. 25.4% SB 207499). At entry, 45.9% and 46.7% of patients in the placebo and SB 207499 treatment groups, respectively, were current smokers, with few patients in either group changing smoking status during the study; the mean pack year smoking history was 61.8 and 58.9 years at screening for the placebo and SB 207499 treatment groups, respectively. The characteristics of the per protocol population were similar to those of the randomized population.

Patients were provided with albuterol metered dose inhalers for use on an 'as-needed' basis and were permitted to continue inhaled anticholinergic medication and mucolytics at a stable dose throughout the study; no other COPD medications were allowed except for the short-term treatment of exacerbations. The addition of new mucolytics was also not allowed. The use of albuterol was similar in both treatment groups (100% for placebo and 99.8% for SB 207499) and 30.7% and 32.8% of patients in the placebo and SB 207499 treatment groups, respectively, continued with a stable dose of ipratropium bromide during the study. Compliance with study medication was good as 95.3% of placebo-treated and 89.6% of SB 207499-treated patients were between 80% and 120% compliant at each week of double-blind treatment.

Efficacy Results:

Primary Efficacy Variables: SB 207499 was shown to have a statistically significant ($p = 0.024$) effect on pulmonary function, preventing the decline in FEV_1 observed in the placebo treatment group over a six-month period. The mean change from baseline averaged over the 24 weeks of treatment for trough FEV_1 was significantly greater compared to placebo; the difference in the mean change from baseline in trough FEV_1 was 24mL. Progressive improvement over time in FEV_1 was observed for SB 207499 compared to placebo with differences in FEV_1 at Week 16 (Δ=0.05L, $p = 0.001$), Week 20 (Δ=0.04L, $p = 0.028$), Week 24 (Δ=0.03L, $p = 0.047$), and at Endpoint (Δ=0.04L, $p = 0.013$). The total score of the SGRQ co-primary endpoint demonstrated statistically significant improvements for SB 207499-treated patients over patients who received placebo (1.9 points; $p = 0.017$, CI –3.5 through -0.3).

Secondary Variables: The secondary efficacy endpoint of change from baseline in trough FVC was improved in SB 207499 patients compared to placebo patients. The SB 207499 treatment group showed an increase over baseline in trough FVC from Week 8 through Week 24 and at endpoint, ranging from 10mL to 50mL, while the placebo treatment group showed a decrease or no change from baseline in trough FVC at these time points.Exacerbation-free survival at 24 weeks and post-exercise breathlessness was comparable between the two treatment groups.

Tertiary Variables: The tertiary endpoints showed a numerical advantage favoring SB 207499 in pulmonary function (PEFR and FEF_{25-75}), COPD symptoms (overall breathlessness and use of rescue medication), quality of life measurements (activities score of SGRQ), post-exercise oxygen saturation, and exercise performance.

Safety Results:

Extent of Exposure: The mean duration of exposure to study medication was 143.6 days for patients who received placebo and 128.2 days for patients who received SB 207499.

Adverse Experiences: The number of adverse events in the SB 207499 treatment group was not unexpected for a PDE4 inhibitor and was consistent with the known pharmacological profile of the drug. The overall incidence of AEs was comparable in the two treatment groups (placebo, 83.3%; SB 207499, 87.1%). The majority of AEs were mild to moderate in intensity with 12.8% of patients in the placebo treatment group and 16.3% of patients in the SB 207499 treatment group reporting severe AEs. A similar percentage of patients receiving placebo (30.7%) reported chronic obstructive airways disease compared with SB 207499-treated patients (27.3%). As shown in the following table, the percentages of patients with the gastrointestinal AEs of nausea, diarrhea, abdominal pain, dyspepsia, and vomiting were higher in the SB 207499 treatment group compared to placebo. Of note, AEs of upper respiratory tract infection, coughing, and dyspnea were reported in 15.0%, 8.4%, and 7.1% of placebo-treated patients compared with 11.0%, 5.0%, and 3.6% of SB 207499-treated patients, respectively.

Most Common On-therapy Adverse Events:

Adverse Event (Preferred Term)	Treatment Group: Placebo (N=407) N (%)		Treatment Group: SB 207499 15mg BID (N=418) n (%)	
Total[a]	339	(83.3)	364	(87.1)
Chronic Obstructive Airways Disease	125	(30.7)	114	(27.3)
Nausea	27	(6.6)	109	(26.1)
Diarrhea	44	(10.8)	82	(19.6)
Abdominal Pain	38	(9.3)	52	(12.4)
Headache	33	(8.1)	46	(11.0)
Upper Respiratory Tract Infection	61	(15.0)	46	(11.0)
Dyspepsia	10	(2.5)	38	(9.1)
Vomiting	11	(2.7)	33	(7.9)
Injury	28	(6.9)	31	(7.4)
Sinusitis	34	(8.4)	30	(7.2)
Dizziness	22	(5.4)	24	(5.7)
Arthralgia	18	(4.4)	22	(5.3)
Coughing	34	(8.4)	21	(5.0)
Back Pain	24	(5.9)	16	(3.8)
Dyspnea	29	(7.1)	15	(3.6)

a. Total represents total number of patients reporting at least one adverse event.
Data Source: Section 15, Table 15.2A.

Gastrointestinal AEs of Concern: During the double-blind treatment period, 18 of 407 (4.4%) patients in the placebo treatment group and 51 of 418 (12.2%) patients in the SB 207499 treatment group had GIAEs of concern (i.e., bloody or black stool, abdominal discomfort such as pain or cramps, diarrhea, or vomiting that concerned the patient or interfered with daily activities, including eating or sleeping). The most common of these were nausea, diarrhea, abdominal pain, and vomiting. All GIAEs of concern, with the exception of feces discolored, hemorrhage rectum, hemorrhoids, and diverticulitis, were reported with greater frequency in the SB 207499 treatment group compared with the placebo treatment group. In general, early onset gastrointestinal intolerance was not unexpected and seen at a higher rate in SB 207499-treated patients during the first 4 weeks of therapy compared to placebo; however, incidences of GI intolerance were comparable between the two groups during the remainder of the study. Analysis of the initial time of onset of nausea, abdominal pain, diarrhea, and vomiting showed an overall gradual increase in incidence over the course of the double-blind treatment period in the placebo treatment group compared to a higher incidence during the first 4 weeks of treatment in the SB 207499 treatment group. Differences between the groups were apparent within the first week of double-blind treatment. GIAEs of concern led to the withdrawal of 1.0% of placebo-treated patients and 4.8% of SB 207499-treated patients. [redacted]

In the SB 207499 treatment group, 7 of the 51 patients who experienced on-therapy GIAEs of concern had positive fecal occult blood results during the double-blind or post-study periods, and 3 of the 51 patients who experienced on-therapy GIAEs of concern had orthostatic changes in vital signs of concern at the GIAE assessment. No SB 207499-treated patients who had GIAEs of concern had low hemoglobin or hematocrit values of clinical concern. Overall, 12 patients had colonoscopies performed as a result of events that occurred during the study, including 5 placebo-treated and 7 SB 207499-treated patients. A total of 7 patients (3 placebo-treated and 4 SB 207499-treated patients) who experienced one or more GIAEs of concern had a colonoscopy performed. Three SB 207499-treated and 2 placebo-treated patients with AEs of the gastrointestinal system that were not considered GIAEs of concern also had colonoscopies performed. The colonoscopies did not identify any SB 207499 related safety concerns.

Deaths/Serious Adverse Experiences: No patients died during the double-blind period or within 30 days following the last dose of study medication. A total of 3 patients died during the placebo run-in period. Serious non-fatal AEs were reported on-therapy for 38 of 407 (9.3%) placebo-treated patients and 25 of 418 (6.0%) SB 207499-treated patients. [redacted] No serious adverse events were reported that were considered to have a probable relationship to study medication.

Withdrawals Due to Adverse Events: Overall, a higher percentage of patients experienced AEs leading to withdrawal in the SB 207499 treatment group (17.9%) compared with the placebo treatment group (9.8%). The most common AE leading to withdrawal in the placebo treatment group was chronic obstructive airways disease (placebo, 2.2%; SB 207499, 2.6%). The most common AEs leading to withdrawal in the SB 207499 treatment group were associated with GI intolerance, including nausea (0.7% placebo vs. 8.4% SB 207499), diarrhea (0.5% placebo vs. 3.8% SB 207499), and abdominal pain (0.7% placebo vs. 2.6% SB 207499).

Laboratory Tests: Mean changes from baseline in clinical laboratory parameters were small and comparable between the treatment groups. The percentages of patients with transitions from normal range at baseline to outside the normal range and to a level of clinical concern were similar for all laboratory parameters in the two treatment groups. The most common AE related to a laboratory result was hyperglycemia with a higher incidence in the placebo treatment group (2.9%) compared with SB 207499 (2.6%).

Electrocardiograms: Mean changes from baseline for 12-lead ECGs values performed at trough and C_{max} were similar between the placebo and SB 207499 treatment groups. There were few differences in either the incidence or pattern of new onset ECG abnormalities observed on-therapy between treatment groups. Multifocal PVCs (1.7% vs. 0.7%), right atrial hypertrophy (4.0% vs. 1.8%) and sinus bradycardia (17.4% vs. 13.8%) were reported at a slightly higher rate in the SB 207499 treatment group compared with the placebo treatment group. Left anterior hemiblock (4.3% vs. 2.7%), left axis deviation (5.9% vs. 2.7%), old anterior myocardial infarction (3.4% vs. 0.8%), old septal myocardial infarction (3.3% vs. 1.3%), unifocal PVCs (16.8% vs. 12.8%), sinus tachycardia (5.3% vs. 3.4%), flat T-waves (2.7% vs. 0.7%) and T-wave inversion (2.0% vs. 0.7%) were reported at a slightly higher rate in the placebo treatment group versus the SB 207499 treatment group. The number of patients having ECG abnormalities reported as adverse events was similar in the two treatment groups. Overall, there was no difference between the treatment groups in the percentage of patients having transitions in QRS axis or QTc (absolute value) from within the normal range to a level of concern. Among patients with <120msec QRS interval at baseline, QRS axis transitions from normal at baseline to on-therapy high concern were comparable between the SB 207499 (12.5%) and placebo (13.1%) treatment groups. There were no marked differences in transitions from normal range at baseline to clinical concern for other trough ECG values on-therapy or C_{max} ECG values on Day 1 and Week 24.
Other Safety Tests: A total of 564 of 825 patients (68.4%) had a fecal occult blood test during the double-blind period of the study. Only 11 of the 564 patients (3 placebo- and 8 SB 207499-treated patients) had at least one positive FOB result during double-blind therapy. The mean changes from baseline in sitting vital sign parameters were small with no clinically meaningful differences between treatment groups. Treatment groups were also comparable for transitions from baseline in sitting vital sign parameters with the exception of a slightly higher incidence of on-therapy orthostatic changes in systolic blood pressure above the normal range (but not of clinical concern) in the SB 207499 treatment group (7.8%) compared with the placebo treatment group (7.1%) among patients in the normal range at baseline.
Pharmacokinetic Results: The pharmacokinetic analysis is presented separately [18].
Pharmacoeconomic Results: Measures of health economics were comparable between treatment groups.

Conclusions:

This study provides evidence of efficacy for SB 207499 15mg twice daily over a 24-week treatment period in patients with COPD. SB 207499 was shown to have statistically significant effects on both primary endpoints of FEV_1 and SGRQ. The decline in FEV_1 observed in the placebo treatment group was not seen in the SB 207499 treatment group and an improvement in quality of life was seen in the SB 207499 treatment group compared with placebo. Other measures confirming the treatment benefits of SB 207499 were noted in PEFR, FEF_{25-75}, overall breathlessness, use of rescue medication, post-exercise oxygen saturation, exercise performance, activities score of SGRQ, and change from baseline in trough FVC.

Based on the known pharmacology of the compound, gastrointestinal adverse events were not unexpected and occurred particularly early in treatment. However, these adverse events were generally mild or moderate in intensity. The gastrointestinal adverse event assessments, including fecal occult blood testing, assessment of orthostatic changes in vital signs, and laboratory assessments showed no untoward risk of hypovolemic events associated with these adverse events. Similarly, extensive cardiac monitoring confirmed the absence of cardiovascular safety concerns for SB 207499.

Date of Report: November 2002

TABLE OF CONTENTS

PAGE

1. ETHICS 25
1.1. Independent Ethics Committee (IEC) or Institutional Review Board (IRB) 25
1.2. Ethical Conduct of the Study 25
1.3. Subject Information and Consent 25

2. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE 25

3. INTRODUCTION 26

4. STUDY OBJECTIVE(S) 28
4.1. Primary Objectives 28
4.2. Secondary Objectives 28

5. METHODOLOGY 29
5.1. Study Design 29
5.1.1. Protocol Amendments 32
5.2. Investigators 33
5.3. Eligibility Criteria 33
5.3.1. Inclusion Criteria 33
5.3.2. Exclusion Criteria 34
5.4. Study Medication and Administration 35
5.4.1. Study Medication 35
5.4.2. Dosages and Administration 36
5.4.3. Methods of Blinding 36
5.4.4. Other Protocol-Specified Therapy 37
5.5. Compliance With Study Medication 37
5.6. Prior and Concomitant Medications and Non-Drug Therapies 37
5.6.1. Prior Medication 37
5.6.2. Allowed Medications 38
5.6.3. Prohibited Medications 38
5.7. Study Procedures 38
5.7.1. Schedule of Assessments 39
5.7.2. Screening Visit 42
5.7.3. Single-Blind Run-In Phase 42
5.7.4. Baseline Visit 43
5.7.5. Treatment Phase 44
5.7.5.1. Additional Assessments Performed During the Treatment Phase 45
5.7.5.2. Early Withdrawal Visit 46
5.7.6. Safety Follow-up Visit 46
5.7.7. Subject Completion and Withdrawal 46
5.8. Efficacy Assessment 47
5.8.1. Primary Efficacy Parameters 47
5.8.2. Secondary Efficacy Endpoint(s) 47

5.8.3. Tertiary Efficacy Parameters....47
5.8.4. Methodology....48
5.8.4.1. Pulmonary Function Tests....48
5.8.4.2. St. George's Respiratory Questionnaire....49
5.8.4.3. Other Clinical Assessments....50
5.9. Safety Assessments....53
5.9.1. Adverse Events....53
5.9.1.1. Serious Adverse Events....54
5.9.1.2. COPD Exacerbations....55
5.9.1.3. Gastrointestinal Adverse Events of Concern....55
5.9.2. Physical Examination....56
5.9.3. Vital Signs....56
5.9.4. Electrocardiogram....56
5.9.5. Laboratory Testing....57
5.10. Pharmacokinetic Assessments....58
5.10.1. Sampling Times....58
5.10.1.1. Baseline....58
5.10.1.2. Week 4....58
5.10.1.3. Week 12....58
5.10.1.4. Week 24....58
5.10.1.5. Unscheduled Samples....59
5.10.2. Specimen Preparation....59
5.10.3. Assay Methods....59
5.10.4. Population Pharmacokinetic Analysis....59
5.11. Medical Care Utilization....59
5.12. Data Quality Assurance....60
5.13. Statistical Evaluation....60
5.13.1. Target Sample Size....60
5.13.2. Method of Randomization....61
5.13.3. Planned Efficacy Evaluations....61
5.13.3.1. Primary Efficacy Variables....61
5.13.3.2. Secondary Efficacy Variables....61
5.13.3.3. Tertiary Efficacy Variables....61
5.13.4. Methods of Analysis....62
5.13.4.1. Data Analysis Conventions and Data Deviations....62
5.13.4.2. Comparisons of Interest....63
5.13.4.3. Efficacy Analysis....64
5.13.5. Populations to be Evaluated....66
5.13.6. Safety Evaluation....66

6. STUDY POPULATION....67
6.1. Study Dates....67
6.2. Patient Disposition....67
6.2.1. Number and Distribution of Patients....67
6.2.2. Number of Patients Present at Each Week....68
6.2.3. Withdrawal Reasons....69
6.3. Protocol Violations....71
6.3.1. Protocol Violations That Led to Exclusion From the Per-Protocol Analysis....73
6.3.2. Conduct of Study Deviations....75
6.4. Demographic and Baseline Characteristics....75

6.4.1. Demographic Characteristics 75
6.4.2. Baseline Characteristics 77
6.5. Presenting Conditions and Medical History 79
6.6. Baseline Signs and Symptoms 80
6.7. Prior and Concomitant Medications 81
6.7.1. Prior Medications 81
6.7.2. Concomitant Medications 83
6.7.3. Medications for COPD Exacerbations 85
6.8. Treatment Compliance 85

7. EFFICACY RESULTS 86
7.1. Efficacy Evaluation 86
7.1.1. Data Sets Analyzed 86
7.2. Primary Efficacy Parameters 87
7.2.1. Trough FEV_1 (L) 87
7.2.2. SGRQ 91
7.3. Secondary Efficacy Parameters 94
7.3.1. Pulmonary Function Tests – Clinic Trough FVC 94
7.3.2. Post-Exercise Breathlessness 97
7.3.3. Time to First COPD Exacerbation 100
7.3.4. Time to First Level 2 and 3 COPD Exacerbations 101
7.4. Tertiary Efficacy Parameters 102
7.4.1. Pulmonary Function 102
7.4.1.1. Clinic Trough PEFR 102
7.4.1.2. Clinic Trough FEF_{25-75} 102
7.4.1.3. First-Dose Effect on Pulmonary Function 103
7.4.1.4. Last-Dose Effects on Pulmonary Function 105
7.4.1.5. Post-Albuterol Pulmonary Function 106
7.4.2. Symptoms of COPD 106
7.4.2.1. Overall Breathlessness 106
7.4.2.2. Cough and Sputum Assessments 107
7.4.2.3. Use of Rescue Medication 107
7.4.3. Quality of Life Assessments 107
7.4.3.1. Subscales of the SGRQ 107
7.4.3.2. Subscales of the SF-36 111
7.4.4. Oxygen Saturation at Rest and Arterial Blood Gases 112
7.4.5. Post-exercise Oxygen Saturation 112
7.4.6. Global Investigator and Patient Assessments 112
7.4.7. Exercise Performance 113
7.4.8. Health Economic Endpoints 114
7.4.8.1. Summary of COPD-related Healthcare Utilization Prior to Study Entry by Treatment Group 114
7.4.8.2. COPD-related Healthcare Utilization-free Survival 115
7.4.8.3. Summary of Poisson Regression of Utilization Rates by Types of Utilization 117
7.4.8.4. Summary of the Time In Hospital and ICU, Restricted Leisure Activity, Percent of Days Lost From Work, and Paid and Unpaid Assistance 117

8. SAFETY RESULTS 118
8.1. Extent of Exposure 118
8.2. Adverse Events 118
8.2.1. Incidence of On-therapy Adverse Events 119
8.2.2. Adverse Events by Relationship to Study Medication 120
8.2.3. Adverse Events by Intensity 121
8.2.4. Adverse Events by Time of First Occurrence 123
8.3. Adverse Events Requiring Corrective Treatment 131
8.4. Deaths 132
8.5. Serious Adverse Events 133
8.6. Withdrawals Due to Adverse Events 139
8.7. Gastrointestinal Adverse Events of Concern 145
8.7.1. Incidence of On-therapy Gastrointestinal Adverse Events of Concern 145
8.7.2. Gastrointestinal Adverse Events of Concern by Intensity 154
8.7.2.1. Patients With Severe GI Adverse Events of Concern Who Received Placebo 154
8.7.2.2. Patients with Severe GI Adverse Events of Concern Who Received SB 207499 154
8.7.3. Gastrointestinal Adverse Events of Concern by Relationship 156
8.7.4. Gastrointestinal Adverse Events of Concern by Time of Initial Onset 156
8.7.5. Gastrointestinal Adverse Events of Concern That Led to Withdrawal 157
8.7.6. Fecal Occult Blood Tests in Patients With On-therapy Gastrointestinal Adverse Events of Concern 157
8.7.7. Adverse Events of Gastrointestinal Bleeding 158
8.7.7.1. Placebo-treated Patients with Adverse Events of Gastrointestinal Bleeding Not Reported As GIAEs of Concern 159
8.7.7.2. SB 207499-treated Patients with Adverse Events of Gastrointestinal Bleeding Not Reported As GIAEs of Concern 159
8.7.8. Colonoscopy Results 160
8.7.8.1. Colonoscopy Results in Patients with Gastrointestinal Adverse Events of Concern who Received Placebo 160
8.7.8.2. Colonoscopy Results in Patients with Gastrointestinal Adverse Events of Concern who Received SB 207499 161
8.7.8.3. Colonoscopies and other GI procedures in patients with AEs in the GI body system that were not considered GIAEs of Concern 163
8.7.9. Orthostatic Vital Signs in Patients With Gastrointestinal Adverse Events of Concern 164
8.7.10. Hemoglobin and Hematocrit Levels in Patients With Gastrointestinal Adverse Events of Concern 166
8.7.11. Gastrointestinal Adverse Events of Concern During Run-in and Post-therapy 166
8.8. Fecal Occult Blood Testing (All Patients) 166
8.9. Vital Signs 169

8.10. Electrocardiographic Data 180
8.10.1. ECG Assessments 180
8.11. Laboratory Tests 192

9. PHARMACOKINETIC EVALUATION 199

10. PHARMACODYNAMIC EVALUATION 199

11. DISCUSSION/CONCLUSIONS 199
11.1. Discussion 199
11.2. Conclusions 205

12. REFERENCES 205

13. SOURCE TABLES: STUDY POPULATION 208

14. SOURCE TABLES: EFFICACY RESULTS 209

15. SOURCE TABLES: SAFETY RESULTS 220

16. SOURCE TABLES: POPULATION PHARMACOKINETIC 222

17. SOURCE TABLES: PHARMACODYNAMICS 222

18. SOURCE TABLES: PHARMACOECONOMICS 222

19. SOURCE FIGURES 223

20. APPENDICES 227

LIST OF TABLES

PAGE

Table 1 Treatment Differences for SB 207499 Phase III Placebo-Controlled Studies in Primary and Secondary Parameters (Intent-to-Treat Population)[a] 27

Table 2 Overall Incidence of Most Commonly Reported (>5% of Patients in Either Treatment Group) On-therapy Adverse Events in SB 207499 Phase III Placebo-Controlled Studies 28

Table 3 Appearance, Formulation, and Batch Numbers of Study Medication 35

Table 4 Outline of Study Procedures 40

Table 5 Disposition of Patients 68

Table 6 Distribution of Randomized Patients by Week 69

Table 7 Number (%) of Randomized Patients Who Completed the Study or Were Withdrawn by Reason for Withdrawal 70

Table 8 Cumulative Percentage of Patients Withdrawn by Time of Withdrawal and Reason for Withdrawal 71

Table 9 Summary of Protocol Violations Resulting in Exclusion From Per-protocol Analysis by Treatment Group 74

Table 10 Summary of Demographic Characteristics at Screening (All Randomized Patients) 76

Table 11 Descriptive Statistics for Smoking History, Alcohol Intake, and Duration of COPD by Treatment Group (All Randomized Patients) 77

Table 12 Descriptive Statistics for Pulmonary Function Parameters and % Predicted DLCO at Screening (All Randomized Patients) 78

Table 13 Summary of Most Common (≥10% of Patients in Either Treatment Group) Current/Active Medical Conditions at Screening (All Randomized Patients) 80

Table 14 Summary of Most Common (≥2% of Patients in Either Treatment Group) Baseline Signs and Symptoms (All Randomized Patients) 81

Table 15 Summary of Most Common (≥5% of Patients in Either Treatment Group) Prior Medications (All Randomized Patients) 82

Table 16 Summary of Most Common (≥5% of Patients in Either Treatment Group) Concomitant Medications (All Randomized Patients) 84

Table 17 Summary of Most Common (≥2% of Patients in Either Treatment Group) Medications for Treatment of COPD Exacerbations During Double-blind Treatment (All Randomized Patients) 85

Table 18 Overall Compliance With Double-blind Medication (All Randomized Patients) 86

Table 19 Change From Baseline in Trough FEV_1 (L) Averaged Over 24 Weeks (Repeated Measures Analysis) - ITT 87

Table 20 Mean Change From Baseline in Trough FEV_1 (L) – ITT 88

Table 21 Change From Baseline in SGRQ (Total Score) Averaged Over 24 Weeks (Repeated Measures Analysis) - ITT 91

Table 22 Mean Change from Baseline in SGRQ (Total Score) - ITT 92

Table 23 Change From Baseline in Clinic Trough FVC (L) Averaged Over 24 Weeks (Repeated Measures Analysis) - ITT 94

Table 24 Mean Change From Baseline in Clinic Trough FVC (L) - ITT 96

Table 25 Change From Baseline in Post-exercise Dyspnea Averaged Over 24 Weeks (Repeated Measures Analysis) - ITT 98

Table 26 Mean Change From Baseline in Post-Exercise Dyspnea - ITT 99

Table 27 Exacerbation-Free Survival at 24 Weeks– ITT 101

Table 28 Level 2/Level 3 Exacerbation-Free Survival at 24 Weeks– ITT 101

Table 29 Change From Baseline in Clinic Trough FEF_{25-75} (L/sec) Averaged Over 24 Weeks (Repeated Measures Analysis) - ITT 102

Table 30 Change From Baseline in Symptoms, Impacts, and Activities Scores of the SGRQ Averaged Over 24 Weeks (Repeated Measures Analysis) - ITT 108

Table 31 Change From Baseline in Distance Walked (Meters) Averaged Over 24 Weeks (Repeated Measures Analysis) - ITT 113

Table 32 Summary of COPD-related Healthcare Utilization Prior to Study Entry 115

Table 33 Summary of Utilization-Free Survival and Total Number of Utilizations – ITT 116

Table 34 Duration of Exposure 118

Table 35 Summary of Most Frequently Reported (≥2% of Patients in Either Treatment Group) On-therapy Adverse Events 119

Table 36 Summary of Most Frequently Reported (≥2% of Patients in Either Treatment Group) Adverse Events Considered Related to Study Medication 121

Table 37 Number (%) of Patients with On-therapy Adverse Events by Intensity..... 122

Table 38 Summary of Most Frequently Reported (≥1% of Patients in Either Treatment Group) Severe Adverse Events..... 122

Table 39 Summary of Most Frequently Reported (≥2% of Patients in Either Treatment Group) On-therapy Adverse Events by Initial Time of Onset: Placebo Treatment Group..... 124

Table 40 Summary of Most Frequently Reported (≥2% of Patients in Either Treatment Group) On-therapy Adverse Events by Initial Time of Onset: SB 207499 Treatment Group..... 126

Table 41 Summary of Most Frequently Reported (≥2% of Patients in Either Treatment Group) On-therapy Adverse Events That Required Corrective Therapy 132

Table 42 Deaths 133

Table 43 Summary of Most Frequently Reported (>1 Patient in Either Treatment Group) On-therapy Serious Adverse Events 134

Table 44 Non-fatal Serious Adverse Events..... 135

Table 45 Incidence of On-therapy Adverse Events Leading to Withdrawal in More Than One Patient in Either Treatment Group..... 140

Table 46 Withdrawals Due to Adverse Events..... 141

Table 47 Incidence of On-therapy Gastrointestinal Adverse Events of Concern..... 146

Table 48 Listing of Patients Who Experienced GIAEs of Concern 147

Table 49 Summary of Fecal Occult Blood Tests..... 157

Table 50 Summary of Patients with Gastrointestinal Bleeding..... 158

Table 51 Listing of Patients Receiving SB 207499 Who Experienced GIAEs of Concern and Orthostatic Changes in Vital Signs of Clinical Concern at the GIAE Assessment..... 165

Table 52 Summary of Fecal Occult Blood Tests at Study End 167

Table 53 Listing of Patients With a Positive Fecal Occult Blood Test Result During the Double-blind Treatment Period 168

Table 54 Summary of Mean Change in Vital Sign Values..... 170

Table 55 Vital Sign Levels of Clinical Concern..... 171

Table 56 Transitions from Normal Range at Baseline for Sitting Vital Signs - Time Point: On-therapy..... 172

Table 57 Transitions from Normal Range at Baseline for Orthostatic Vital Signs - Time Point: On-therapy..... 173

Table 58 Patients Receiving SB 207499 Who Had On-therapy Orthostatic Vital Sign Changes of High Clinical Concern..... 174

Table 59 Listing of Patients with Vital Signs Reported as On-therapy Adverse Events.. 179

Table 60 Summary of Mean Change in 12-lead ECG Values at Trough 181

Table 61 Summary of Mean Change in 12-lead ECG Values at C_{max} at Day 1 and Week 24 182

Table 62 New-Onset ECG Abnormalities Occurring in $\geq$1% of Patients in Either Treatment Group..... 184

Table 63 Electrocardiographic Values of Clinical Concern 185

Table 64 Transitions from Normal Range at Baseline for Trough ECG Parameters - Time Point: On-therapy 187

Table 65 Transitions from Normal Range at Baseline for ECG Parameters - Time Point: Post-dose (C_{max}) 189

Table 66 Listing of Patients With ECG Abnormalities Reported as On-therapy Adverse Events 191

Table 67 Summary of Mean Change in Selected Clinical Laboratory Parameters 193

Table 68 Laboratory Values of Clinical Concern..... 195

Table 69 Transitions from Normal Range at Baseline for Hematology Laboratory Values - Time Point: On-therapy..... 196

Table 70 Transitions from Normal Range at Baseline for Clinical Chemistry Laboratory Values - Time Point: On-therapy..... 197

Table 71 On-therapy Adverse Events Related to Laboratory Results Reported in at Least 2 Patients in Either Treatment Group 199

LIST OF FIGURES

PAGE

Figure 1 Schematic Representation of Study Design 30
Figure 2 Mean (SEM) Change from Baseline in Trough FEV1 - ITT 89
Figure 3 Mean (SEM) Change From Baseline in Total Score of the SGRQ – ITT 93
Figure 4 Mean (SEM) Change From Baseline in Trough FVC – ITT 97
Figure 5 Mean (SEM) Change From Baseline in Post-Exercise Dyspnea – ITT 100
Figure 6 Mean (SEM) Change From Baseline in Trough FEF25-75 – ITT 103
Figure 7 Mean (SEM) Change From Baseline in FEV1 (L) After First Dose of Double-Blind Study Medication - ITT 104
Figure 8 Mean (SEM) Change From Week 24 Trough in FEV1 After the Last Dose of Double-blind Study Medication - ITT 105
Figure 9 Mean (SEM) Change From Baseline in Symptoms Score of the SGRQ – ITT 109
Figure 10 Mean (SEM) Change From Baseline in Impacts Score of the SGRQ - ITT 110
Figure 11 Mean (SEM) Change From Baseline in Activities Score of the SGRQ - ITT 111
Figure 12 Mean (SEM) Change From Baseline in Distance Walked – ITT 114
Figure 13 Cumulative incidence of Nausea 129
Figure 14 Cumulative incidence of Abdominal Pain 129
Figure 15 Cumulative incidence of Diarrhea 130
Figure 16 Cumulative incidence of Vomiting 130
Figure 17 Cumulative Incidence of Gastrointestinal Adverse Events of Concern by Time of Initial Onset 156

LIST OF APPENDICES

		PAGE
Appendix A	Final Protocol, Sample (Blank) CRF, CVs of Investigators, Randomization Code, Certificates of Analysis, References, Audited Investigator Sites	228
Appendix B	Patient Data Listings of Demographic and Baseline Characteristics	229
Appendix C	Patient Data Listings of Efficacy	230
Appendix D	Patient Data Listings of Safety	231
Appendix E	Patient Data Listings of Vital Signs and Electrocardiograms	233
Appendix F	Patient Data Listings of Laboratory Values	234
Appendix G	CRFs and DRQs for GI Adverse Events of Concern, Non-fatal Serious Adverse Events, Withdrawals for Adverse Events and Death	235
Appendix H	CRF Tabulations by Patient ID	236
Appendix I	Statistical Report Listings	237

Abbreviations

AE	adverse event
AIVR	accelerated idioventricular rhythm
ALP	alkaline phosphatase
ALAT (SGPT)	alanine aminotransferase
ANOVA	analysis of variance
ASAT (SGOT)	aspartate aminotransferase
ATS	American Thoracic Society
BID	twice daily
BP	blood pressure
Bpm	Beats per minute
BTPS	Body temperature pressure saturated
BUN	blood urea nitrogen
cyclic AMP	cyclic adenosine monophosphate
CI	confidence interval
Cm	Centimeter
CO	carbon monoxide
COPD	chronic obstructive pulmonary disease
CRF	case report form
CRO	contract research organization
DL	Deciliter
DLCO	carbon monoxide diffusing capacity
DMPK	Drug metabolism and pharmacokinetics
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
ER	emergency room
FDA	Food and Drug Administration
FEF_{25-75}	forced expiratory flow at 25-75% vital capacity
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
G	Gram
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GI	Gastrointestinal
GIAE	Gastrointestinal adverse event
GSK	GlaxoSmithKline
HCG	human chorionic gonadotropin
HR	Heart rate
ICU	intensive care unit
IL	Interleukin
ITT	intent-to-treat
IU	international unit
IUD	intrauterine device
IVR	Idioventricular rhythm
Kg	Kilogram

L	Liter
LLN	lower limit of normal
LPS	Lipopolysaccharide
LTOT	long-term oxygen therapy
M	Meter
MAR	missing at random
Max	Maximum
Mcg	Microgram
MDI	metered dose inhaler
MEq	Milliequivalent
Mg	Milligram
Min	Minimum
ML	Milliliter
MmHg	millimeters of mercury
Mmol	Millimole
Msec	Millisecond
NA	not applicable
PCO_2	arterial carbon dioxide tension
PDE4	Phosphodiesterase 4
PEFR	Peak expiratory flow rate
PFT	pulmonary function test
PK	Pharmacokinetic
PO_2	arterial oxygen tension
PP	per-protocol
PRN	pro re nata (as needed)
PRP	pulmonary rehabilitation program
PV	protocol violation
RAMOS	Registration and Medication Ordering System
R&D	research and development
REML	restricted maximum likelihood
SaO_2	Transcutaneous oxygen saturation
SB	SmithKline Beecham
SD	standard deviation
SEM	standard error of the mean
SF-36	Short form survey 36
SGRQ	St. George's Respiratory Questionnaire
SI	standard international
SNOMED	Systematized Nomenclature of Human (and Veterinary) Medicine
Trt	Treatment
ULN	upper limit of normal
Umol	Micromole
WBC	white blood cell count
y/yrs	Years

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 unfavorable 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 untoward medical occurrence which fulfills the definition for an AE (as defined above) and in addition, is any experience which is fatal, life-threatening, disabling or incapacitating or results in hospitalization, prolongs a hospital stay or is associated with pregnancy, a congenital abnormality, cancer, or overdose (either accidental or intentional). In addition, an SAE was any important medical occurrence which the Investigator regarded as serious based on appropriate medical judgment.
Gastrointestinal adverse event of concern	Gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhea, vomiting) which cause the patient concern or interfere with usual activity (including eating and sleeping).
COPD diagnosis	Diagnosis was based on patient history (smoking, coughing, wheezing, and dyspnea.), physical examination (airflow obstruction, emphysema, and characteristic breathing abnormalities), and laboratory results (spirometry, lung volumes, and arterial blood gases).

1. ETHICS

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

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 center ethics committee or institutional review board.

1.2. Ethical Conduct of the Study

The study was conducted in accordance with Good Clinical Practices[1], the World Medical Association Declaration of Helsinki as amended in the Republic of South Africa (1996), and the US 21 CFR parts 50 (Protection of Human Subjects) and 56 (Institutional Review Boards). The protocol and statement of informed consent were approved by an Institutional Review Board (or Ethics Committee) prior to each center's initiation. Written informed consent [2] was obtained from each patient prior to entry into the study. Case report forms (CRF) were provided for each patient's data to be recorded (Appendix A).

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 listing of the Investigators and their affiliations is provided in Section 13, Table 13.0, and the curriculum vitae of each Principal Investigator is provided in Appendix A. The Investigators were selected because of their interest in the study, their ability to conduct the study according to GCP standards, and their ability to enroll patients. A total of 132 centers in 2 countries participated in this study.

[1] As stated in US 21 CRF.

[2] Appendix A contains the protocol and the sample informed consent is an Appendix to the protocol.

3. INTRODUCTION

COPD is a disorder characterized by reduced maximum expiratory flow and slow forced emptying of the lungs, features which do not change markedly over several months. [1] It is a major cause of morbidity and mortality. Fixed airflow limitation in COPD is due to three conditions: chronic bronchitis, emphysema, and small airways disease, which frequently co-exist in individual patients. [1]

Chronic Bronchitis is defined by the presence of chronic or recurrent increases in bronchial secretions sufficient to cause expectoration. [1] Cough is present for a minimum of 3 months a year, for at least two successive years, and cannot be attributed to other pulmonary or cardiac causes. The site of most of the mucus hypersecretion is the large airways. Histological studies show enlargement of tracheobronchial submucosal glands and hyperplasia of tracheobronchial surface mucous (goblet) cells. Emphysema is defined as abnormal permanent enlargement of the air spaces distal to the terminal bronchioles, accompanied by destruction of their walls, and without obvious fibrosis. Airflow obstruction in COPD patients is progressive in nature, mostly irreversible and may be accompanied by airway hyperreactivity.

Recent data suggest that airway inflammation is a key feature of COPD, even in the early stages of the disease. It is characterized by the accumulation of increased numbers of mononuclear cells in the sub-mucosa and neutrophils in the airway lumen.[2]

The main risk factor for COPD is inhalation of tobacco smoke. Current treatment modalities for COPD include smoking cessation, symptomatic pharmacological therapies for dyspnea and cough, and long-term oxygen therapy (LTOT). [1,3] Presently, drug therapies can treat only the symptoms of COPD and not the underlying condition.

SB 207499 (Ariflo) is a potent and selective phosphodiesterase type 4 (PDE4) inhibitor currently under development for the treatment of asthma and 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-hydrolyzing isozyme in these cells. [4]

Preclinical data suggest that SB 207499 may have anti-inflammatory, bronchodilatory and neuromodulatory activities. Furthermore, the ability of SB 207499 to inhibit airway smooth muscle cell proliferation suggests potential effects on airway remodeling. This unique combination of activities gives rise to the possibility that SB 207499 may represent a new modality for the treatment of COPD, in that they may elicit short and long term benefits in the treatment of this disorder. [5]

Three Phase III randomized, double-blind, placebo-controlled studies (039, 042, and 091) have recently completed. Study 039 was conducted in North America, 091 in Europe, and 042 Internationally. Patients with COPD were characterized by a post-bronchodilator % predicted FEV_1 of ≥30% and ≤70%, a pre-bronchodilator FEV_1/FVC of ≤0.7, and fixed airway obstruction defined by ≤15% reversibility following

administration of a $beta_2$-agonist. In each of the Phase III, placebo-controlled studies, patients with COPD entered a 4-week single-blind run-in phase and then were randomized to receive SB 207499 15mg BID or placebo in a ratio of 2 to 1. A total of 1374 patients were treated with SB 207499 15mg BID. Efficacy data from the three Phase III studies are presented in Table 1.

Table 1 Treatment Differences for SB 207499 Phase III Placebo-Controlled Studies in Primary and Secondary Parameters (Intent-to-Treat Population)[a]

Randomized Patients	039 N=638	042 N=700	091 N=711
FEV_1 (trough)[b]	40mL (0.002) [0.01, 0.06]	30mL (0.044) [0.00, 0.06]	30mL (0.055) [-0.00, 0.06]
SGRQ[b,c]	-4.1 (<0.001) [-6.0, -2.2]	0.7 (0.473) [-1.2, 2.6]	-0.4 (0.711) [-2.4, 1.6]
FVC (trough)	50mL (0.049) [0.00, 0.10]	50mL (0.047) [0.00, 0.09]	20mL (0.515) [-0.03, 0.06]
Dyspnea	-0.24 (0.029) [-0.45, -0.02]	-0.20 (0.068) [-0.41, 0.01]	-0.16 (0.114) [-0.36, 0.04]
All Level Exacerbations Relative Risk[d]	0.61 (0.002) [0.45, 0.83]	1.07 (0.589) [0.83, 1.40]	0.70 (0.005) [0.55, 0.90]

a. 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
b. Primary Endpoint; alpha = 0.025.
c. St. Georges Respiratory Questionnaire.
d. SB 207499 relative to placebo.

Table 2 displays the most common on-therapy adverse events reported in more than 5% of patients in order of decreasing frequency. Exacerbation of chronic obstructive pulmonary disease was more frequent in patients who received placebo, while diarrhea, nausea, abdominal pain, dyspepsia and vomiting were reported more frequently in patients who received SB 207499. The majority of the events were considered mild or moderate in severity by the Investigators. The gastrointestinal adverse events, reported more frequently in patients who received SB 207499, were generally mild and expected side effects of the known pharmacology of the drug. Most of these gastrointestinal adverse events were self-limited and occurred during the initial period of treatment. Few of the events were considered serious.

Table 2 Overall Incidence of Most Commonly Reported (>5% of Patients in Either Treatment Group) On-therapy Adverse Events in SB 207499 Phase III Placebo-Controlled Studies

	All Randomized Patients			
	Placebo		SB 207499	
Adverse Event	(N=681)		(N=1368)	
(Preferred Term)	n	(%)	n	(%)
Chronic obstructive airways disease	265	(38.9)	421	(30.8)
Diarrhea	41	(6.0)	175	(12.8)
Nausea	28	(4.1)	170	(12.4)
Abdominal pain	39	(5.7)	155	(11.3)
Upper respiratory tract infection	51	(7.5)	111	(8.1)
Headache	43	(6.3)	101	(7.4)
Dyspepsia	17	(2.5)	83	(6.1)
Vomiting	7	(1.0)	76	(5.6)

There was no greater incidence of serious adverse events in patients who received SB 207499 15mg BID when compared with patients who received placebo. 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. [5]

Study 156 was being conducted as a pivotal Phase III study to assess the efficacy and safety of SB 207499 versus placebo in patients with COPD. The study was designed to detect a 50mL treatment difference on FEV_1 and confirm the effects observed in Study 039 on health status. The study design of Study 156 was similar to that of Studies 039, 042, and 091.

4. STUDY OBJECTIVE(S)

4.1. Primary Objectives

- To demonstrate the clinical efficacy of SB 207499 (15mg BID) versus placebo by assessment of FEV_1 at trough drug levels over 24 weeks in patients with COPD.
- To demonstrate clinical efficacy of SB 207499 (15mg BID) versus placebo in the total score of the SGRQ over 24 weeks in patients with COPD.

4.2. Secondary Objectives

- To compare the clinical efficacy of SB 207499 versus placebo on additional pulmonary function tests (clinic trough measurements) and other clinical evaluations (e.g., breathlessness).
- To examine the risk of COPD exacerbations.

An additional objective of the study was to further define the clinical safety and tolerability of SB 207499 through the assessment of adverse events (AEs), vital signs, clinical laboratory tests, and electrocardiograms (ECGs).

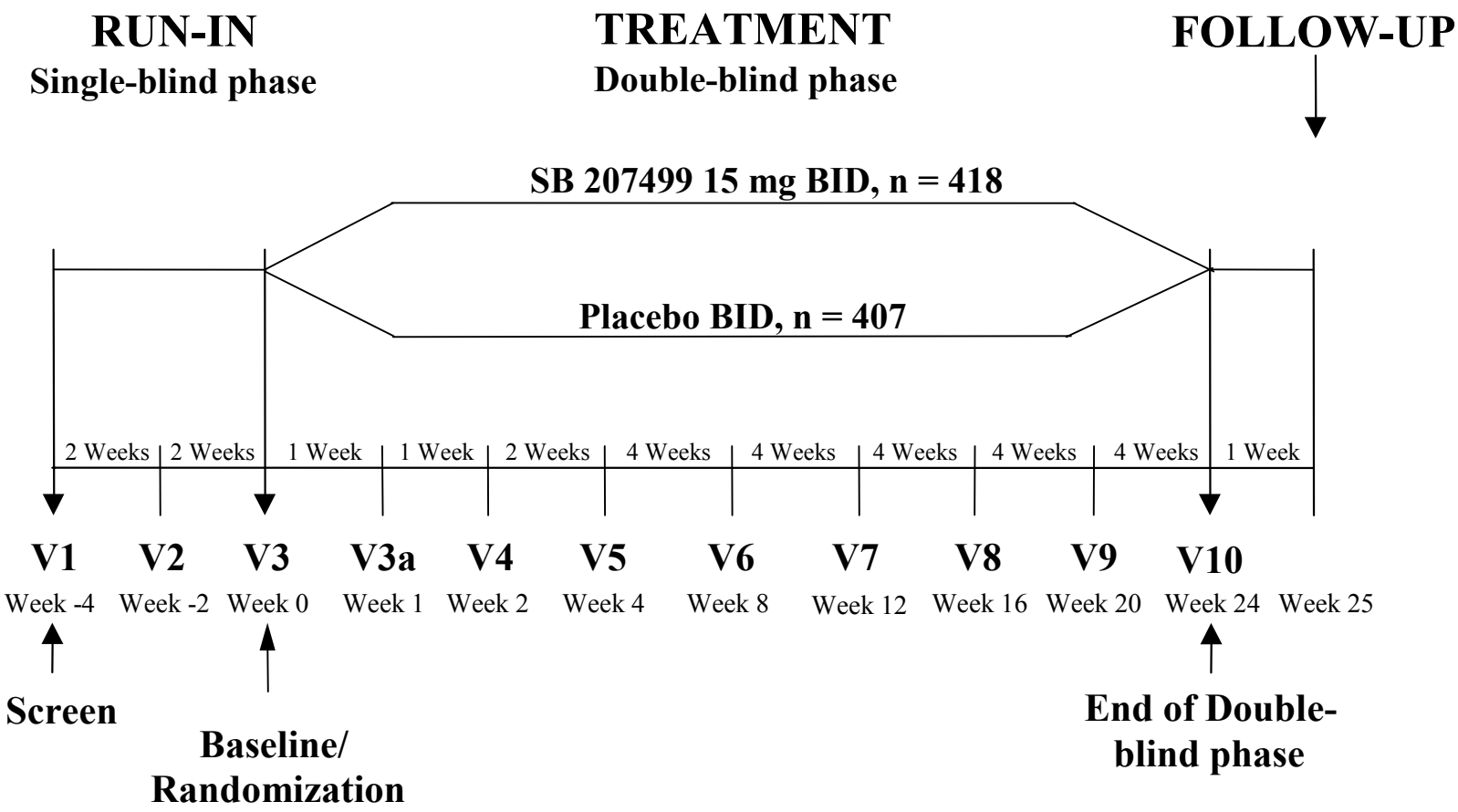
5. METHODOLOGY

5.1. Study Design

The study was a Phase III, randomized, double-blind, placebo-controlled, parallel group study in patients with COPD (as defined by American Thoracic Society [ATS] guidelines) involving 12 visits over a 29-week period (Week -4 [Screening] through Week 25 [Safety Follow-up]). One tablet of SB 207499 (15mg) or matched placebo was taken twice daily, immediately after breakfast and after the evening meal (previous clinical pharmacology studies have shown that SB 207499 is better tolerated when administered in the fed state).

The study commenced with a 4-week, single-blind, placebo run-in phase, after which eligible patients were randomized in a double-blind manner to either 15mg SB 207499 or matching placebo in a ratio of 1:1 for 24 weeks. Patients were 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



Pulmonary function tests (PFTs) were performed at all visits (with the exception of one safety-only visit at Week 1). At the screening visit (Week -4), pulmonary function (FEV_1, FVC, forced expiratory flow at 25-75% vital capacity [FEF_{25-75}] and PEFR) was assessed before and after a standard dose of albuterol (180mcg). At subsequent visits, pulmonary function was measured at trough levels of study drug, in the absence of albuterol. In addition, the acute first and last dose (Visits 3 and 10, respectively) effects of SB 207499 (post-albuterol) on lung function were assessed by hourly testing for a period of four hours. To ensure consistency and standardization of pulmonary function data, spirometry equipment and interpretation was standardized and centrally monitored.

Symptom-based assessments, such as exercise tolerance and breathlessness (modified Borg scale) were also performed at clinic visits.

The impact of COPD on patient health status was assessed using the SGRQ at baseline, Week 12 and Week 24 and the SF-36 (health survey questionnaire) at baseline and Week 24. Investigator and Patient Global Assessments were completed at Week 24.

Safety assessments included adverse events, vital signs, ECGs, and clinical laboratory tests. As a prompt for reporting adverse events at clinic visits, patients were asked to record in a diary if they felt differently since starting the study medication. Additional monitoring was provided for gastrointestinal adverse events. Gastrointestinal adverse events of concern were defined as symptoms (i.e., bloody or black stool, abdominal discomfort such as pain or cramps, diarrhea, 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 standardized clinical and laboratory assessment was completed, and patients were followed daily until resolution of the adverse event. Any patient who had a gastrointestinal adverse event of concern and a positive fecal occult blood test or melena during the randomized treatment phase of the study was referred to a gastroenterologist for a complete colonoscopy. The colonoscopy emphasized visualization of the transverse colon with reporting of positive or negative findings, irrespective of other identified pathology or causes for gastrointestinal bleeding. Biopsies were taken if appropriate.

A stable dose of anticholinergic medication via a metered dose inhaler (MDI), albuterol (on an "as needed" basis) via MDI with or without a spacer (according to the patient's usual practice) and mucolytics were the only COPD medications permitted during the study (i.e., between Visits 1 and 10), with the exception of additional medication allowed for the treatment of exacerbations as outlined below. Combination products (e.g., a combined albuterol and ipratropium bromide formulation) were not permitted. Patients using a combined anticholinergic-$beta_2$-agonist were required to be changed to separate single therapies prior to or at Visit 1, and patients were requested to maintain equivalent doses of the component bronchodilators.

If clinically indicated, inhaled/oral steroids or antibiotics were allowed to be administered for a short course (<14 days) for the treatment of an exacerbation of COPD. COPD exacerbations were categorized as Level 1, 2, or 3, based on the treatment received by the patient for the exacerbation (Section 5.8.4.3). If a patient experienced more than three Level 2 or Level 3 exacerbations during the double-blind treatment period, the

Investigator was advised to contact the GSK Medical Monitor regarding the continuation of the patient in the study. Patients who used any corticosteroids or antibiotics for the treatment of a COPD exacerbation during the run-in phase were withdrawn from the study prior to randomization (Section 5.7.3).

At all visits, the following restrictions applied: patients should not have smoked for 2 hours or taken inhaler therapy (i.e., albuterol and/or anticholinergic agent) for a minimum of 4 hours prior to presentation to the clinic. If this time period was not observed, 4 hours was required to elapse before pulmonary function tests were performed.

5.1.1. Protocol Amendments

The protocol, initially approved on 20 October 2000, was amended on 01 March 2001, 24 August 2001, and 08 November 2001 and modified on 22 March 2002. The protocol, amendments, and modification are described briefly below and provided in Appendix A.

Amendment #1, 01 March 2001

- A requirement for performing colonoscopies was added for patients with GIAEs of concern and a positive fecal occult blood test or melena during the randomized treatment phase of the study.
- Instructions for performing and evaluating fecal occult blood tests were clarified.
- A statement that albuterol use was recorded in the diary was deleted.
- The telephone number to be used for reporting gastrointestinal symptoms if the patient is unable to contact the Investigator was clarified.
- Study contact and medical monitor information was changed.
- The informed consent form was modified to reflect changes made to the protocol.
- Procedures for reporting the results of additional tests performed by the Investigator were added.
- Reference citations omitted in error were added.

Amendment #2, 24 August 2001

- A requirement was added that patients must be supplied with a Fecal Occult Blood test kit to use at home in the event that they experience a GIAE of concern during the study.
- Assessments of patients reporting GIAEs of concern and monitoring requirements for GIAEs of concern were modified.
- The informed consent form was modified to reflect changes made to the protocol.

Amendment #3, 08 November 2001

- The number of patients expected to be randomized and the overall number of study centers were increased. Therefore, study enrollment was re-initiated to increase the number of randomized patients.
- The informed consent form was modified to reflect changes made to the protocol.

Modification #1, 22 March 2002

- Study contact and medical monitor information was changed.

5.2. Investigators

The study was performed at 132 centers in the United States and Canada. A listing of the Investigators and their affiliations are provided in Section 13, Table 13.0, and the curriculum vitae of each principal Investigator are provided in Appendix A. The Investigators were selected because of their interest in the study, their ability to conduct the study according to Good Clinical Practice (GCP) standards, and their ability to enroll patients.

5.3. Eligibility Criteria

Each Investigator maintained and submitted a log of all patients who were considered for the study. To exclude systematic bias in selecting patients, data on reason for exclusion were collected for patients who were considered but who did not enter screening.

5.3.1. Inclusion Criteria

Only Patients who fulfilled all of the following criteria were eligible for inclusion in the study:

1. Male or female adults between 40 and 80 years of age (inclusive).

   Note: Women of childbearing potential were required to have used 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 to continue using the same contraceptive measure during the study.
2. Patients with a clinical diagnosis of COPD, as defined by American Thoracic Society Guidelines. [3]
3. Patients with a cigarette smoking history of ≥10 pack years (1 pack year = 20 cigarettes smoked per day for 1 year or the equivalent). Both current smokers and ex-smokers were eligible.

4. Patients with a pre-albuterol FEV_1 to FVC ratio (FEV_1:FVC) ≤0.7 at Visit 1 (Screening).
5. Patients with fixed airway obstruction, defined by ≤15% **or** ≤200mL (or both) increase in FEV_1 after the administration of albuterol 180mcg via MDI with a spacer at Visit 1 (Screening).
6. Patients with a post-albuterol FEV_1 between ≥30% and ≤70% of predicted normal for height, age and gender at Visit 1 (Screening). Patients were assessed 15 to 30 (± 5) minutes after receiving albuterol 180mcg via MDI with a spacer.
7. Patients who gave their signed written informed consent to participate.

5.3.2. Exclusion Criteria

Patients who fulfilled **any** of the following criteria were not eligible for the study.

1. Women who were pregnant or lactating.
2. Patients with asthma as the main component of their obstructive airways disease.
3. Patients with poorly controlled COPD, defined as the occurrence of any of the following in the 2 weeks prior to Visit 1 (Screening): acute worsening of COPD that was managed by the patient at home by self-treatment with corticosteroids or antibiotics, that required treatment prescribed by a physician, or for which the patient was hospitalized.
4. Patients with active tuberculosis, lung cancer, or clinically overt bronchiectasis.
5. Patients with clinically significant cardiovascular, neurological, renal, endocrine, or hematological abnormalities that were uncontrolled on permitted therapy.
6. Patients with clinically significant gastrointestinal or hepatic abnormalities.
7. Patients with a positive fecal occult blood test result between Visits 1 and 3 (Screening and Baseline).
8. Patients with clinically significant orthostatic changes in blood pressure or heart rate at Visit 1 (Screening) or 3 (Baseline) (Section 5.9.3).
9. Patients with a history of hypersensitivity to PDE4 inhibitors.
10. Patients with a history (or suspected history) of alcohol misuse or any other recreational substance abuse.
11. Patients who required treatment with inhaled cromolyn sodium or nedocromil, inhaled long-acting $beta_2$-agonists, oral $beta_2$-agonists, nebulized $beta_2$-agonists, nebulized anticholinergics, xanthines, leukotriene modifiers or oral/inhaled corticosteroids beyond Visit 1 (Screening). All COPD medications except anticholinergic medication or albuterol via MDI were withdrawn prior to or at Visit 1 (Screening) (Section 5.6).
12. Patients receiving treatment with long-term oxygen therapy (LTOT), patients who required supplemental oxygen more often than on an occasional (PRN) basis, or patients who required nocturnal positive pressure for sleep apnea.

13. Patients who had participated in a Pulmonary Rehabilitation Program within 4 weeks prior to Visit 1 (Screening) or who planned to enter a Pulmonary Rehabilitation Program during the study.
14. Patients who had received an investigational drug within 30 days of entry into this study, or within 5 drug half-lives of the investigational drug (whichever was longer).
15. Patients who had previously participated in a SB 207499 study and who received randomized study medication.
16. Patients unable to comply with study procedures (including completion of the health status questionnaires).

5.4. Study Medication and Administration

5.4.1. Study Medication

SB 207499 was provided as a yellow, round, convex tablets containing 15mg of SB 207499. Placebo tablets, identical in appearance to the active medication, were provided for the single-blind placebo run-in phase and for the placebo arm of the double-blind phase of the study. The appearance, formulation, and batch numbers of the study medication are presented in Table 3.

Table 3 Appearance, Formulation, and Batch Numbers of Study Medication

Study Drug	Appearance	Formulation	Dose Unit	Batch Numbers
SB 207499	Yellow, round, convex	tablet	15mg	[redacted]
Placebo	Yellow, round, convex	tablet	-	[redacted]

Appendix A contains the Certificates of Analysis

For the single-blind placebo run-in phase, SB 207499-matched placebo tablets were supplied in bottles containing 20 tablets (a 10-day supply). Therefore, two bottles of run-in medication (a 20-day supply) were dispensed to eligible patients at both Visits 1 and 2 to allow for some flexibility in the interval between visits. Study medication for the 24-week double-blind treatment period was dispensed to patients in bottles containing 20 (a 10-day supply) or 70 tablets (a 35-day supply) of SB 207499 (15mg) or matching placebo. One 20-tablet bottle of SB 207499 or placebo was dispensed at both Visits 3 and 3a where the interval to the next visit was one week. Similarly, patients received two 20-tablet bottles of SB 207499 or placebo at Visit 4, which was separated by an interval of two weeks from the next scheduled visit. Seventy-tablet bottles were dispensed at visits scheduled 4 weeks apart (Visits 5-9). An excess of tablets was included in each bottle to allow for flexibility in the interval between visits.

A 2-panel label consisting of a fixed portion and a tear-off portion was attached to the medication bottles. The Investigator (or designate) removed the tear-off portion of the label from the bottle at the time of dispensing and attached it to the appropriate page in the CRF.

Labels for the double-blind study medication contained:

- 6-digit container number (the same number that appears on the patient packer label)
- Fill count
- Blinded disclosure panel (on tear-off portion only)
- Space to enter patient initials, date dispensed, and visit number on fixed portion of the label
- Protocol number
- Dosing directions
- Storage conditions
- Appropriate caution statements
- Company Address

Labels for the single-blind run-in medication had similar information as listed on the double-blind labels but also included the packaging job number and batch number (tear-off portion only).

Prior to dispensing, all study medication was kept safely locked, in a dry place at room temperature (20-25ºC or 68-77ºF).

5.4.2. Dosages and Administration

The first dose of SB 207499 run-in medication was taken during the Screening Visit at Week -4 and the first dose of double-blind medication was taken at the Baseline Visit (Week 0).

During the run-in phase, patients took one SB 207499-matched placebo tablet twice daily, in the morning immediately after breakfast and in the evening immediately after a meal. Patients who fulfilled the Randomization Criteria entered a 24-week double-blind treatment phase. Patients were randomized to receive either SB 207499 15mg or matching placebo in a 1:1 ratio. One tablet of study medication was taken twice daily, in the morning immediately after breakfast and in the evening immediately after a meal. Throughout the study, patients did not take the morning dose of study medication before attending morning clinic visits. If an afternoon visit was scheduled, patients were instructed to take the morning dose of study medication after breakfast, which was at least 8 hours before their clinic visit. On the day of clinic visits, the first dose of study medication was administered in the clinic with food after completion of efficacy and safety assessments.

5.4.3. Methods of Blinding

This was a double-blind, placebo-controlled, randomized study. During the run-in period, the study medication was blinded only to the patient. The double-blind

medication drug labels identified the randomization number. The patient's randomization number was provided during the randomization call to RAMOS (Registration and Medication Ordering System). Labels on all double-blind bottles were coded. The blind was maintained by GlaxoSmithKline who maintained an updated copy of the master randomization code. Neither the patient, nor the Investigator, nor any GlaxoSmithKline personnel directly involved in the monitoring of the study or reviewing the data knew which treatment had been allocated until the code was broken and the data analyzed.

5.4.4. Other Protocol-Specified Therapy

The use of albuterol 90mcg/actuation, 200 actuations per canister (MDI with or without a spacer) on an "as-needed" (PRN) basis was permitted throughout the study. Albuterol was provided as Proventil® for patient use during the study. Between Visits 1 and 10, patients were instructed not to use any additional bronchodilators that they possess at home, with the exception of a stable dose of anticholinergic medication by MDI if prescribed for the patient.

If the patient experienced symptoms which did not respond adequately to rescue medication (e.g., albuterol, 2 actuations every 4 hours), the patient was instructed to contact the Investigator. If a patient occasionally used albuterol at an interval of less than every 4 hours (did not exceed twice a day at the reduced interval), the patient remained in the trial at the discretion of the Investigator.

5.5. Compliance With Study Medication

Counts of tablets returned were made at the beginning of Visits 2 through 10. Percent

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

compliance was calculated by using the formula below and entered in the CRF:

If a patient had <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. If a patient had <80% or >120% compliance at 2 consecutive visits, the patient was withdrawn from the study after consultation with the GSK Medical Monitor.

5.6. Prior and Concomitant Medications and Non-Drug Therapies

5.6.1. Prior Medication

All medication for COPD, including inhalers, taken during the 3 months preceding the Screening Visit was recorded, together with all other medications taken within 2 weeks of the visit. Prohibited respiratory medications (Section 5.6.3) were discontinued prior to or at the Screening Visit. Combination therapies (beta$_2$-agonist anticholinergic mix) were

changed to separate single therapy inhalers with equivalent doses, prior to or at Screening.

5.6.2. Allowed Medications

All concomitant medication taken during the study was recorded in the CRF with the indication, dose, frequency and dates of administration. In addition to albuterol, provided as rescue medication (Section 5.4.4), stable doses of anticholinergic medication by MDI and mucolytics were also permitted during the study. Patients were not allowed to start a new mucolytic treatment regime during the study; however, mucolytic therapy started prior to the Visit 1 was allowed to continue at a stable dose throughout the study.

5.6.3. Prohibited Medications

The following medications were prohibited throughout the study (between Visits 1 and 10) except for the short-term (<2 weeks) management of COPD exacerbations: corticosteroids (inhaled or oral), xanthines, inhaled cromolyn sodium or nedocromil, inhaled long-acting $beta_2$-agonists, inhaled short-acting $beta_2$-agonists other than albuterol, oral or nebulized $beta_2$-agonists, nebulized anticholinergics, and/or leukotriene modifiers. All medications prescribed for the treatment of COPD exacerbations were recorded in a separate section of the CRF. Combination $beta_2$-agonist/anticholinergic therapy was not permitted during the study, but changed to separate, single-therapy inhalers prior to or at Screening. Theophylline and the use of combined $beta_2$-agonist/ipratropium therapy (e.g., Combivent®) were not permitted at any time during the study.

Any patient who used prohibited medications other than for the management of an exacerbation of COPD between Visits 1 and 10 was withdrawn from the study after consultation with the GSK Medical Monitor.

5.7. Study Procedures

For each scheduled study visit, patients were required to attend the clinic in the morning, at the same time and after breakfast. Clinic visits were scheduled at 10:00 a.m. ± 2 hours. Smoking and the use of albuterol and anticholinergic treatment were avoided during the 2-hour and 4-hour periods, respectively, preceding the pulmonary function tests of each visit and during the clinic stay if at all possible. Patients did not take their morning doses of study medication before attending morning clinic visits.

In exceptional circumstances, a patient was allowed afternoon appointments at Visit 1 or for Visits 2, 3, 3a, 4, 6, 8, 9, and 10 only if ≥8 hours elapsed since the last dose of study medication and the Investigator was capable of completing all visit assessments. If an afternoon visit was scheduled, patients were instructed to take the morning dose of study medication after breakfast (at least 8 hours before their clinic visit). If the Baseline Visit was done in the afternoon, all subsequent visits were done at this time with the exception of Visits 5 and 7. Because of post-dose pharmacokinetic (PK) assessments, only morning appointments were permitted for the visits scheduled at Visits 5 and 7.

5.7.1. Schedule of Assessments

The outline of study procedures is presented in Table 4.

Table 4 Outline of Study Procedures

Visit	1 Screen	2	3 Baseline	3a	4	5	6	7	8	9	10 End Double-blind	Early With-drawal[a]	Final Safety Follow-up
Time relative to baseline (weeks)	-4	-2	0	+1	+2	+4	+8	+12	+16	+20	+24		+25
Signed written informed consent	x												
Medical & surgical history	x												
Physical examination[b]	x		x								x	x	x[c]
Pulmonary history & symptoms	x												
Postero-anterior chest radiograph[d]	x												
Exacerbation assessment/resource use	x	x	x	x	x	x	x	x	x	x	x	x	x
Medication history	x												
Overall breathlessness (modified Borg)	x	x	x	x	x	x	x	x	x	x	x	x	
Resting 12-lead ECG	x		x	x	x	x	x	x	x	x	x	x	x[c]
Vital signs (BP, HR)	x[e]	x	x[e]	x	x	x	x	x	x	x	x[e]	x[e]	x
Exercise Tolerance (6-Minute walk)	x	x	x			x	x	x	x	x	x	x	
Post-exercise SaO_2 & breathlessness	x	x	x			x	x	x	x	x	x	x	
CO Diffusing Capacity (DLCO)[f]	x												
Albuterol reversibility[g]	x												
Laboratory tests	x		x[h]	x	x	x	x	x	x[i]	x[i]	x[h]	x[h]	x[c,i]
Dispense single-blind medication	x	x											
Albuterol Use		x	x	x	x	x	x	x	x	x	x		
Concomitant medication/medical procedures		x	x	x	x	x	x	x	x	x	x	x	x
PFTs (in absence of albuterol)[j]		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	
Baseline signs and symptoms/AEs[k]		x	x	x	x	x	x	x	x	x	x	x	x
Health status assessment: SGRQ			x					x			x	x	
Quality of life assessment: SF-36			x								x	x	

Visit	1 Screen	2	3 Baseline	3a	4	5	6	7	8	9	10 End Double-blind	Early With-drawal[a]	Final Safety Follow-up
Time relative to baseline (weeks)	-4	-2	0	+1	+2	+4	+8	+12	+16	+20	+24		+25
Cough and sputum assessments			x					x			x	x	
Pharmacokinetic evaluations[l]			x			x		x			x		
Arterial blood gas/SaO_2[m]			x								x		
Hourly PFTs for 4 hrs post first/last dose [n]			x								x		
Dispense double-blind medication			x	x	x	x	x	x	x	x			
Investigator/Patient global assessment											x	x	
Study conclusion record												x	x

a. Patients who stop taking study medication between clinic visits will attend the clinic within 24 hours for an early withdrawal visit.
b. To include a respiratory examination.
c. If abnormalities at previous visit for patients who complete Visit 10 or withdraw from the study.
d. Postero-anterior chest X-ray must be performed at Visit 1 unless the film from a chest X-ray within the 12 weeks prior to Visit 1 is available to the Investigator.
e. Including Orthostatic vital signs.
f. DLCO should be done between Visit 1 and Visit 3 if not performed during the previous 24 weeks or if the results are unavailable.
g. Before and 15 to 30 (± 5) minutes after administration of 180mcg albuterol via a MDI with a spacer to determine % predicted FEV_1, FVC, FEF_{25-75}, PEFR, and FEV_1: FVC.
h. In addition to usual laboratory tests, three fecal occult blood tests will be performed between Visits 1 and 3, between Visits 9 and 10, and at early withdrawal; amylase will be measured at Visit 3.
i. Urinary beta-HCG tests will be performed in females of childbearing potential. No other laboratory samples will be collected at Visits 8 and 9.
j. Includes FEV_1, FVC, FEF_{25-75}, PEFR, and FEV_1:FVC measured by centralized spirometry by the same person at each visit.
k. A diary will be used to record if patients feel different since starting study medication.
l. Visit 3: 3 hours post-dose. Visit 5: trough and 0.5-3 hours post-dose. Visit 7: trough and 3-10 hours post-dose. Visit 10: trough only.
m. In patients with <40% of predicted FEV_1 at Visit 1 and resting SaO2 <88% or if the patient lives at a high altitude.
n. Pulmonary function tests 30 (± 5) minutes after albuterol followed by 4-hour post double-blind drug assessments at Visits 3 and 10.

5.7.2. Screening Visit

Patients were not eligible for the study if they experienced a Level 2 or 3 COPD exacerbation in the 2 weeks prior to the Screening Visit. Additionally, patients experiencing any level of COPD exacerbation that was managed by self-treatment with corticosteroids or antibiotics in the 2 weeks prior to the Screening Visit were not eligible to participate in this study.

At the Screening Visit, patients signed informed consent and discontinued prohibited respiratory medications. Eligibility for the study was determined from assessments that included a full medical and surgical history (including alcohol consumption and pulmonary history and symptoms); medication history (including all COPD medication and all other medications taken during 3 months and 2 weeks, respectively, preceding the Screening Visit); cigarette smoking history; physical examination (including respiratory examination); a chest X-ray if not performed in the previous 12 weeks; an assessment of COPD exacerbations; overall breathlessness (modified Borg scale); and hematology and clinical chemistry laboratory tests, including serum human beta-chorionic gonadotropin (hCG) pregnancy tests for women of childbearing potential. A standard 12-lead electrocardiogram (ECG); sitting and orthostatic blood pressure and heart rate; pulmonary function tests before and after a standard dose of albuterol; exercise tolerance as assessed by a 6-minute walk test; post-exercise breathlessness (modified Borg scale), transcutaneous oxygen saturation (SaO_2), and heart rate; and carbon monoxide diffusing capacity (DLCO) were also measured at least 4 hours after the patient's last albuterol administration.

The Investigator dispensed single-blind study medication, a diary card, a fecal occult blood test kit, and a spacer and albuterol MDI for as-needed use to patients who satisfied all entry criteria. The first dose of study medication was taken in the clinic with food, and patients were reminded to take one tablet in the morning immediately after breakfast and a second tablet immediately after the evening meal; not to take their morning doses of study medication before attending morning clinic visits; not to smoke or use albuterol or anticholinergic treatment during the 2-hour and 4-hour periods, respectively, preceding each visit; to return the diary card and any unused study medication (including medication containers and albuterol inhaler and spacer); and to continue taking anticholinergic medication, if prescribed, at a constant dose. Patients were asked to return to the clinic in 14 (± 3) days for the next visit.

5.7.3. Single-Blind Run-In Phase

At this visit in the single-blind run-in phase, the Investigator documented in the CRF albuterol or anticholinergic use; smoking during the 2 hours immediately preceding the visit; any changes or additions to the patient's concomitant medication, smoking status, or participation in a pulmonary rehabilitation program; compliance in taking study medication; and any adverse events, including COPD exacerbations. Patients who took corticosteroids or antibiotics for the treatment of a COPD exacerbation during the run-in period were withdrawn from the study. The diary card was also reviewed with the patient.

At Week -2, the following assessments were made: overall breathlessness; sitting blood pressure and heart rate; an exercise tolerance test; post-exercise breathlessness, SaO_2, and heart rate; and pulmonary function tests in the absence of albuterol. Patients whose clinic trough FEV_1 increased or decreased by more than 20% between Screening and Week –2 were withdrawn from the study. Additionally, patients with positive fecal occult blood tests or orthostatic vital sign results of clinical concern during the run-in period were withdrawn from the study.

The Investigator dispensed single-blind study medication and a diary card. The first dose of study medication was taken in the clinic with food, and patients were asked to return to the clinic in 14 (± 3) days for the Baseline Visit.

5.7.4. Baseline Visit

Two quality of life questionnaires, the SGRQ and SF-36, were completed by the patient before any other assessments. Patients who did not complete the SGRQ were withdrawn from the study.

The following assessments were made at baseline: a physical examination, including a respiratory examination; overall breathlessness; a 12-lead ECG; sitting and orthostatic blood pressure and heart rate; an exercise tolerance test; COPD exacerbations between Visits 2 and 3; post-exercise breathlessness, SaO_2, and heart rate; health economic factors; cough and sputum production; and pulmonary function tests in the absence of albuterol. The Investigator documented in the CRF albuterol or anticholinergic use; smoking during the 2 hours immediately preceding the visit; any changes or additions to the patient's concomitant medication, smoking status, participation in a pulmonary rehabilitation program; and compliance in taking study medication. The diary card was also collected and reviewed with the patient. Patients with clinically significant orthostatic changes in blood pressure or heart rate, defined as a decrease in systolic or diastolic blood pressure of ≥20mmHg or ≥10mmHg, respectively, or an increase in heart rate of ≥10 beats per minute (bpm), were withdrawn from the study. Patients who had a positive fecal occult blood test between Screening and the Baseline Visit were also withdrawn.

In order to be randomized, patients were required to meet the following criteria:

- Stability in pulmonary function: Clinic trough FEV_1 (absolute value) in the absence of albuterol did not increase or decrease by >20% between Screening and Baseline.
- Medication Compliance: Patients demonstrated ≥80% and ≤120% compliance since the previous visit in taking single-blind study medication.

Patients who did not meet the randomization criteria were withdrawn from the study.

The following assessments were made for patients eligible to be randomized: hematological, biochemical, and urinalysis testing (including beta-HCG for women of childbearing potential) and resting SaO_2 in patients with FEV_1 <40% of prediction at Screening. Arterial blood gases were measured in patients with FEV_1 of <40% living at high altitudes or having a resting SaO_2 <88%. Following completion of these procedures,

patients were assigned the next available randomization number. Patients were also assigned, in approximately equal numbers, to either of two pharmacokinetic sampling groups, designated 'Early' and 'Late' (see Section 5.10).

After the initial pulmonary function tests (PFTs #1), 180mcg of albuterol (via MDI with spacer) was administered in the clinic and PFTs #2 were performed 30 (±5) minutes later. The first dose of double-blind study medication was then taken in the clinic with food, and the time of administration was recorded in the CRF. For the next 4 hours, the patient was observed and underwent post dose pulmonary function testing every hour (PFTs #3 through #6). During the observation period, patients avoided using albuterol or anticholinergic inhalers and refrained from smoking if at all possible. If a patient used albuterol or anticholinergic inhalers, all remaining pulmonary function tests were abandoned. Prior to PFTs #5 (3 hours post double-blind dose), a 12-lead ECG was performed and a blood sample was collected for pharmacokinetic analysis.

After pulmonary function testing was completed, patients were issued a new diary card, a 10-day supply of double-blind study medication, a new albuterol inhaler and a fecal occult blood kit (if necessary). The procedure for reporting gastrointestinal symptoms was reviewed and patients were instructed to return to the clinic in 7 (± 2) days for the safety visit (Visit 3a), and in 14 (± 3) days for Visit 4. Patients were also reminded of the study procedures as outlined in Section 5.7.2. If results of any assessment made at baseline were not available at the time of randomization and subsequently precluded continuation in the study, the patient was withdrawn immediately and a Safety Follow-up Visit scheduled.

5.7.5. Treatment Phase

At each visit during the double-blind treatment phase, the diary card was reviewed with the patient. The Investigator assessed health economic factors and documented in the CRF albuterol or anticholinergic use; smoking during the 2 hours immediately preceding the visit; any changes or additions to the patient's concomitant medication, smoking status, or participation in a pulmonary rehabilitation program; compliance in taking study medication; and any adverse events, including COPD exacerbations. Patients who were <80% or >120% compliant in taking study medication on two consecutive visits or who had more than three Level 2 or Level 3 COPD exacerbations (see Section 5.8.4.3) during the double-blind treatment period were withdrawn from the study.

For patients eligible to continue in the study, vital signs and ECGs were measured at every visit; pulmonary function in the absence of albuterol and overall breathlessness were determined at every visit except Week 1; exercise tolerance and post-exercise SaO_2 and breathlessness were measured at every visit except Weeks 1 and 2; and hematology, clinical chemistry, and urinalysis (including serum beta-HCG for women of childbearing potential) tests were performed at all visits except Weeks 16 and 20. Urinary beta-HCG was measured at Weeks 16 and 20 in women of childbearing potential. Additional assessments performed at specific visits are described in Section 5.7.5.1.

After completion of assessments at all visits except Week 24, diary cards, albuterol inhalers, FOB kits, and double-blind medication were dispensed, and the patient took the

first dose of the study medication in the clinic with food. During the treatment period, patients returned for clinic visits after 1, 2, 4, 8, 12, 16, 20, and 24 weeks of treatment. Visits were scheduled with an interval of 14 ± 3 days for the biweekly visits and 28 ± 6 days for the monthly visits.

5.7.5.1. Additional Assessments Performed During the Treatment Phase

At several visits during the during the treatment phase, additional visit specific assessments were performed as described below. There were no additional assessments for Week 8, 16, and 20 visits.

- Week 4

A blood sample was taken for pharmacokinetic analysis prior to administration of the morning dose of study medication in the clinic. A further sample was collected between 0.5 and 2 hours after dosing for the 'Early' group and 1.5 and 3 hours after dosing in the 'Late' group (see Section 5.10).

- Week 12

Prior to any other procedures at Week 12, patients completed the SGRQ, quality of life assessment. Cough and sputum assessments were performed and a blood sample was taken for pharmacokinetic analysis prior to administration of the morning dose of study medication in the clinic. A further sample was collected between 3 and 6 hours after dosing for the 'Early' group and 5 and 10 hours after dosing in the 'Late' group (see Section 5.10).

- Week 24

Prior to any other procedures at Week 24, patients completed the SGRQ and SF-36, quality of life assessments. Additional assessments included a physical examination including respiratory examination, Investigator and Patient global assessments, cough and sputum assessments, orthostatic vital signs, a fecal occult blood test between Weeks 20 and 24, pharmacokinetic analysis of a pre-dose blood sample, and resting SaO_2 in patients with FEV_1 <40% of prediction at Screening. Arterial blood gases were measured in patients with FEV_1 of <40% living at high altitudes or having a resting SaO_2 <88%.

Pulmonary function tests (PFTs #1) were performed prior to albuterol administration (180mcg via MDI with spacer) at Week 24 and PFTs #2 were performed 30 minutes after administration of albuterol. Double-blind study medication was then taken in the clinic with food, and the time of administration was recorded in the CRF. For the next 4 hours, the patient was observed and underwent post-dose pulmonary function testing every hour (PFTs #3 through #6). During the observation period, patients avoided using albuterol or anticholinergic inhalers and refrained from smoking if at all possible. If a patient used albuterol or anticholinergic inhalers, all remaining pulmonary function tests were abandoned. Prior to PFTs #5 (3 hours post double-blind dose), a 12-lead ECG was performed.

5.7.5.2. Early Withdrawal Visit

Patients who withdrew from the study at a scheduled visit completed the assessments scheduled at that visit (with the exception of any post-dose assessments). A physical examination, including a respiratory examination and orthostatic vital signs, and laboratory assessments, including fecal occult blood testing, were performed, and the SGRQ and SF-36 questionnaires, Investigator and Patient Global Assessments, and cough and sputum assessments were completed if not already included in the scheduled visit assessments. Pulmonary function tests (without albuterol) were performed if a patient withdrew from the study at Week 1.

Patients who withdrew from the study between scheduled clinic visits were instructed to return to the clinic within 24 hours of stopping study medication for withdrawal assessments. At this clinic visit, patients completed trough pulmonary function tests, exercise tolerance tests, the SGRQ and SF-36 questionnaires, Investigator and Patient Global Assessments, and cough and sputum assessments, and safety assessments (adverse events, COPD exacerbations, laboratory testing including fecal occult blood, ECG, physical examination, vital signs including orthostatic vital signs). Medication compliance, concomitant medications, medical procedures, entry into pulmonary rehabilitation programs, smoking status, and diary cards were also evaluated.

5.7.6. Safety Follow-up Visit

A Safety Follow-up visit was required for all patients, including patients who completed the end of the study (Visit 10) and any patients who withdrew from double-blind therapy prior to completion of Visit 10 (either at a scheduled visit or between visits). The Safety Follow-up visit occurred 7 ± 3 days after Visit 10 or withdrawal from the study. The Investigator documented in the CRF albuterol or anticholinergic use; smoking during the 2 hours immediately preceding the visit; any changes or additions to the patient's concomitant medication (including the resumption of any COPD medications) or smoking status; and any adverse events, including COPD exacerbations. The following assessments were made: a physical examination, including a respiratory examination, if there were abnormal findings at the previous visit; sitting blood pressure and heart rate; an ECG, if there were abnormal findings at the previous visit; urine pregnancy tests in women of child-bearing potential; laboratory tests, if there were abnormal findings at the previous visit; and pulmonary function tests in the absence of albuterol.

5.7.7. Subject Completion and Withdrawal

Patients who completed the assessments scheduled for Week 24 were defined as completing the study for the purpose 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 this definition was considered as a withdrawal, whether or not they received any study medication.

A patient could be discontinued prior to completion of the study for any of the following reasons:

- **Adverse event**: This included a deterioration in COPD or a COPD exacerbation. Every effort was made to follow patients who were withdrawn due to adverse events in order to determine the final outcome of the event.
- **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 a COPD exacerbation.
- **Protocol deviation**: This included lack of compliance (dosing, visit schedule, diary criteria).
- **Patient lost to follow-up**
- **Termination of the study by GSK**
- **Other**: The specific reason was documented in the CRF.

5.8. Efficacy Assessment

5.8.1. Primary Efficacy Parameters

The primary measures of efficacy were change from baseline in trough pre-bronchodilator FEV_1 and total score of the SGRQ averaged over 24 weeks.

5.8.2. Secondary Efficacy Endpoint(s)

- Change from baseline in post-exercise breathlessness (modified Borg scale)
- Change from baseline in clinic FVC at trough
- Time to first COPD exacerbation
- Time to first level 2 or 3 COPD exacerbation

5.8.3. Tertiary Efficacy Parameters

- Use of 'as needed' albuterol
- First and last dose effect on pulmonary function tests (FEV_1, PEFR, FVC, FEF_{25-75})
- Post-bronchodilator effect for FEV_1, PEFR, FVC, FEF_{25-75}
- Clinic PEFR at trough
- Clinic FEF_{25-75} at trough
- Subscales of the SGRQ (disease specific quality of life) including symptoms, impacts, and activities
- SF-36 (generic quality of life)
- Health economic endpoints (impact on activities, healthcare utilization)
- Global Investigator and Patient Assessments

- Exercise performance (distance walked) during the exercise tolerance test (6-minute walk with encouragement)
- Overall breathlessness during usual activity (modified Borg scale)
- Post-exercise SaO_2 and breathlessness
- SaO_2 at rest in patients with FEV_1 of <40% predicted for age, height, and sex at screening
- Arterial blood gases, PO_2 and PCO_2 in patients with FEV_1 of <40% living at high altitudes or having a resting SaO_2 <88%
- Cough and sputum assessments

5.8.4. Methodology

5.8.4.1. Pulmonary Function Tests

At all visits, except for Week 1 (Visit 3a), pulmonary function tests were conducted greater than 4 hours after the last dose of inhaled albuterol or anticholinergic agent. Patients were also asked to refrain from smoking in the 2 hours prior to PFTs.

FEV_1, FVC, PEFR, and FEF_{25-75}, were measured according to the body temperature pressure saturated (BTPS) convention using the Koko spirometer provided by GSK. Complete spirometry systems suitable for research purposes were provided by Biomedical Systems (St. Louis, Missouri, USA), and were calibrated and maintained to acceptable respiratory function laboratory standards. Customized spirometry software requirements were identified through a collaboration between GSK and Biomedical Systems personnel to meet protocol requirements. Agreed upon software customizations were sent to Pulmonary Data Service, Inc. (Louisville, Colorado USA) to be performed and validated. Additional software was developed by Biomedical Systems to provide enhanced password security and an edit log, to comply with the FDA Electronic Signatures and Electronic Records Guideline (August 1997). Software development and validation were performed in accordance with the vendors' standard operating procedures.

All PFTs were performed in accordance with the spirometry manual provided to each site, and the data were transmitted electronically via modem to a centralized data management facility (Biomedical Systems, St. Louis, Missouri, US). All site technicians were required to be certified by Biomedical Systems before they were allowed to enroll patients. Certification consisted of performing a number of spirometry tests to demonstrate familiarity with spirometry equipment, electronic data capture procedures and protocol requirements for obtaining quality spirometry tests.

At each assessment, PFTs were repeated up to eight times to obtain three acceptable readings according to ATS guidelines [7]. For each set of three FEV_1 measurements, one FEV_1 was required to be within 10% of the highest. The quality of the PFTs was assured by review of a representative sample from each site by a registered respiratory therapist employed at Biomedical Systems.

At all visits, PFTs were performed in the absence of albuterol and at trough (pre-dose) plasma levels of study medication. Additional PFTs were performed at Visits 1, 3 and 10.

At Screening (Visit 1), PFTs were conducted before and 15 to 30 (± 5) minutes after administration of 2 puffs (180mcg) of albuterol via MDI with a spacer. Albuterol reversibility was calculated by the spirometer software using the following formula:

$$\text{Reversibility} = \frac{\text{Highest post - albuterol } FEV_1 - \text{Highest pre - albuterol } FEV_1}{\text{Highest pre - albuterol } FEV_1} \times 100$$

Predicted FEV_1 for each patient was calculated by the spirometer software according to the Crapo equation [8]:

Females: Predicted $FEV_1(L) = 0.0342H – 0.0255A – 1.578$

Males: Predicted $FEV_1(L) = 0.0414H – 0.0244A – 2.190$

Where H = height in cm A = age in years

At Baseline and Week 24 (Visits 3 and 10), PFTs were first assessed prior to administration of albuterol (180mcg via MDI with a spacer), 30 (± 5) minutes after albuterol administration, and 1, 2, 3, and 4 hours after the dose of double-blind study medication.

5.8.4.2. St. George's Respiratory Questionnaire

The SGRQ was given to the patients to complete in the clinic at baseline, Week 12, and Week 24 prior to all other scheduled procedures. Any patient who withdrew from the study also completed the SGRQ at the time of withdrawal.

The SGRQ is a self-administered questionnaire designed to measure and quantify the impact of chronic respiratory disease on health-related quality of life and well-being. 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 8 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 contains 42 items and 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, stigmatization, 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 change in score was considered to be a clinically meaningful difference. [9, 10]

5.8.4.3. Other Clinical Assessments

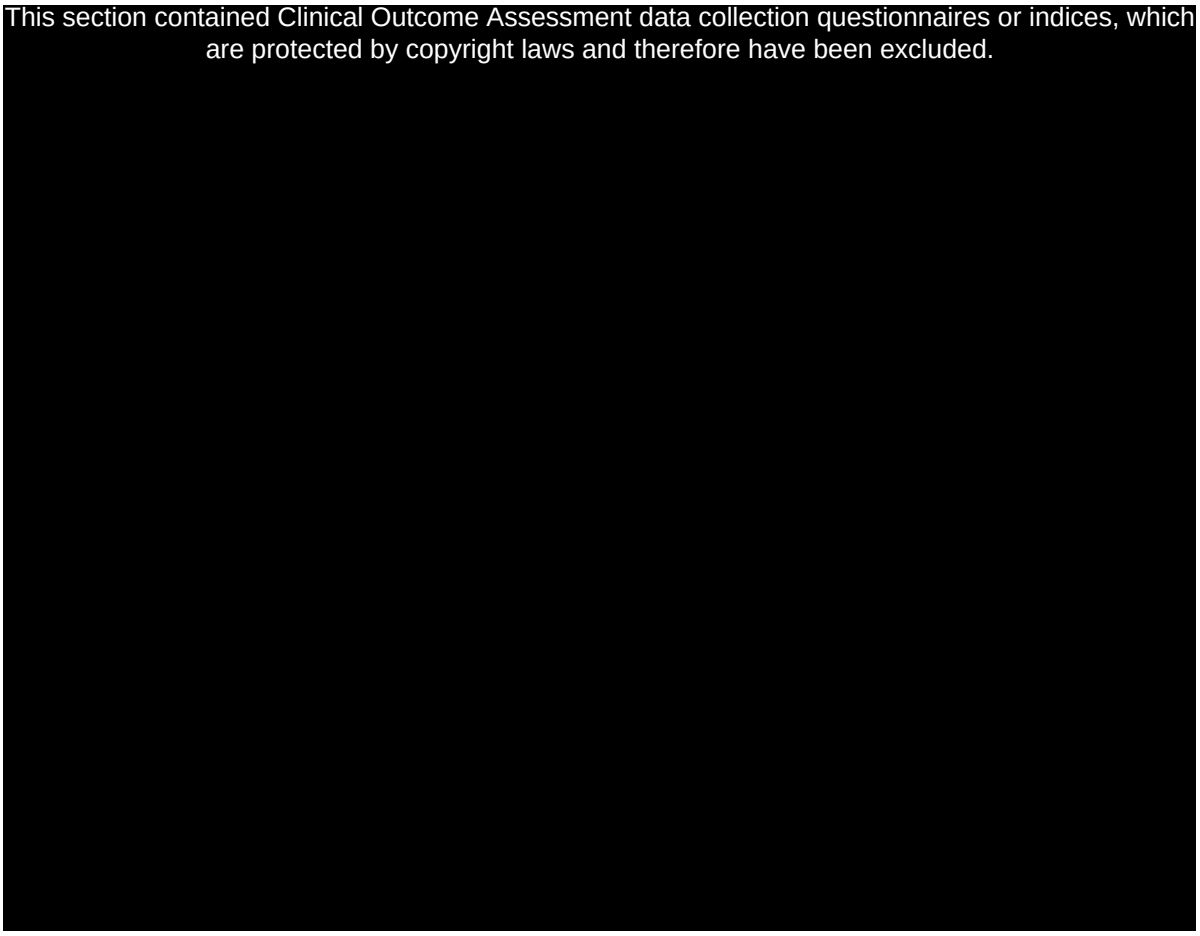
Exercise Tolerance Test

At all visits except Week 1, Week 2, and Safety Follow-up, a 6-minute walk test was used to assess the functional capacity of the patient. [11,12]

The 6-minute walk was conducted more than 4 hours after the patient's last albuterol administration. The patient was instructed and encouraged to walk from one end of a course to the other. The distance walked was measured and recorded on the CRF, even if the patient was unable to walk for the entire 6 minutes.

Breathlessness – Overall and Post-Exercise

At all visits except Safety Follow-up, overall breathlessness was assessed before exercise using the modified Borg scale [13]. The patient was asked the following question:



Diary Card Records

The diary also provided space for the patient to record if they felt differently since starting the study medication. At each visit, diaries were reviewed in the presence of the patient for legibility and compliance.

COPD Exacerbation Definitions

COPD exacerbations, defined as a worsening of COPD symptoms requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids, and other bronchodilator therapy were recorded throughout the study in a COPD exacerbation section in the CRF (see Section 5.9.1.2). COPD exacerbations were categorized as Level 1, 2, or 3, based on the treatment received by the patient. The levels of exacerbation were defined as follows:

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

Level 2 Exacerbation: Acute worsening of COPD that requires additional treatment (e.g., a short course of oral steroids, antibiotics, etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

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

SF-36

The Short-Form 36 (SF-36) is a generic quality-of-life assessment tool used to evaluate the physical, mental, and general health status of patients. It contains 36 questions/statements and one multi-item scale measuring limitations in physical activities because of health problems, limitations in social activities because of physical or emotional problems, limitations in usual role activities because of physical health problems, pain, general mental health, limitations in usual role activities because of emotional problems, vitality (energy and fatigue), and general health perceptions. [14,15] The SF-36 was given to the patients to complete in the clinic at Baseline and at Week 24. Any patient who withdrew from the study also completed the SF-36 at the time of withdrawal. The SF-36 was scored using the standard scoring methodology described in the SF-36 reference manual. [15]

Carbon monoxide diffusing capacity (DLCO)

DLCO was measured between Screen and Baseline (Visit 3) if not performed during the previous 24 weeks or if the results were unavailable.

Cough and Sputum Assessments

Cough and sputum assessments were conducted at Baseline and Weeks 12 and 24. Cough and sputum production was rated according to the following scales:

COUGH

	"How troubled have you been by cough today?"
0	No symptoms at all
1	Some symptoms, but hardly noticeable
2	Symptoms noticeable and a little uncomfortable
3	Symptoms definitely noticeable and uncomfortable
4	Symptoms very bad and extremely uncomfortable

SPUTUM PRODUCTION

	"How much sputum have you produced today?"
0	No sputum at all
1	Some sputum, but not as much as usual
2	As much as usual
3	More than usual
4	A lot more than usual

Global Investigator and Patient Assessments

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

Oxygen Saturation

Resting Oxygen Saturation

Resting oxygen saturation (SaO_2) was measured by pulse oximetry at Baseline and at Week 24 for patients with severe COPD (i.e., those with an FEV_1 <40% of predicted at Screening).

Post-Exercise Oxygen Saturation

At all visits except Week 1, Week 2, and Safety Follow-up, SaO_2 (measured by ear or finger oximetry) and heart rate were measured immediately at the end of the 6-minute exercise test.

Arterial Blood Gases

Arterial blood gases were performed at Baseline and at Week 24 in patients with FEV_1 of <40% living at high altitudes or having a resting SaO2 <88%. PO_2, PCO_2, pH, and bicarbonate were measured from whole arterial blood by an arterial blood gas analyzer, properly calibrated and maintained to acceptable laboratory standards.

5.9. Safety Assessments

Safety was evaluated by monitoring adverse events, physical examinations, vital signs, laboratory parameters, and 12-lead ECGs.

5.9.1. Adverse Events

An adverse event 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 adverse event can therefore be any unfavorable 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.

Any pre-existing conditions or signs and/or symptoms present in a patient prior to the start of the study were recorded on the Medical/Surgical history form within the patient's CRF. Adverse events that occurred after informed consent was obtained, but prior to starting double-blind treatment, were documented on the "Baseline Signs and Symptoms" section in the CRF. All adverse events occurring after administration of the first dose of double-blind medication were reported on the "Adverse Event" pages in the CRF. Exacerbations of COPD were recorded as adverse events in a separate section of the CRF.

At each visit, AEs were elicited by the Investigator asking the patient a non-leading question such as ***"Do you feel differently in any way since starting the new treatment/or since the last visit?"*** In order to help the patient to remember and to answer this question accurately, the diary provided space in which the patient could record if they felt different since starting the study medication. If the patient responded "Yes", details of the treatment-emergent AE and its severity **(*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; or ***Severe*****,** an AE which prevents normal everyday activities) including any change in study drug administration, Investigator attribution to study drug, any corrective therapy given, and outcome status were documented on the case report form. Attribution or relationship to study drug was judged by the Investigator to be *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), or *probable* (there is a probable direct cause and effect relationship between the AE and the study drug). All adverse events were coded from the verbatim term according to the WHO Adverse Reaction Terminology dictionary by body system and preferred term.

Adverse events already documented in the CRF (i.e., at a previous visit) and designated as "ongoing" were reviewed at subsequent visits as necessary. If these had resolved, the documentation in the CRF was completed. If an adverse event increased in frequency or severity during a study period, a new record of the experience was started. Patients with adverse events were to be monitored by the Investigator until the event had subsided or the condition had stabilized.

5.9.1.1. Serious Adverse Events

A serious adverse event was defined as any untoward medical occurrence which fulfills the definition for an AE (defined in Section 5.9.1) and in addition, is any experience which is fatal, life-threatening, disabling or incapacitating or results in hospitalization, prolongs a hospital stay or is associated with pregnancy, a congenital abnormality, cancer, or overdose (either accidental or intentional). In addition, an SAE was any important medical occurrence which the Investigator regarded as serious based on appropriate medical judgment.

Serious adverse events that occurred at any time during the study or within 30 days of receiving the last dose of double-blind study medication, whether or not related to study drug, were required to be reported to the Medical Monitor within 24 hours and followed by a written report. Any serious AEs that occurred 30 days post-therapy and which were brought to the attention of the Investigator were recorded and reported to the Medical Monitor if the event was assessed as possibly drug related.

Serious AEs related to pre-existing conditions and which occurred prior to the start of the study (i.e., before informed consent) were reported on the Medical/Surgical History forms and not as serious AEs. Serious AEs that occurred after informed consent was obtained but prior to starting active or randomized treatment were documented in 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 were recorded and reported to the Medical Monitor. This included any serious AEs which occurred after informed consent was obtained but prior to study drug administration. In this case, the event was recorded on the Serious AE form and reported in the same time scale as for other serious AEs.

After the initial serious AE report the Investigator was required proactively to provide further information regarding the patient’s condition. Investigators followed patients with serious AEs until the events subsided (or disappeared), their conditions stabilized, the patients were lost to follow-up, or the events was otherwise explained. All follow-up information was forwarded to the Medical Monitor within 24 hours of receipt.

5.9.1.2. COPD Exacerbations

COPD exacerbations and levels of exacerbation are defined in Section 5.8.4.3. Exacerbations of COPD were recorded as adverse events, or serious adverse events if appropriate, in a separate section of the patient's CRF.

Patients who took any corticosteroids or antibiotics for the treatment of a COPD exacerbation during the run-in phase were not eligible to be randomized to the double-blind phase of the study. If more than three Level 2 or Level 3 COPD exacerbations occurred during the double-blind phase, patients were withdrawn from the study. If a patient had an exacerbation of COPD that was longer than 2 weeks in duration during the double-blind phase, the Investigator contacted the GSK Medical Monitor regarding the patient's continuation in the study. If clinically indicated, short-term (<2 weeks) treatment with inhaled/oral corticosteroids or antibiotics could have been prescribed for COPD exacerbations.

5.9.1.3. Gastrointestinal Adverse Events of Concern

Adverse events related to the gastrointestinal tract were closely monitored during this study. Patients were instructed to call the Investigator to report any gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhea, or vomiting) which caused them concern or interfered with their daily activities (including eating and sleeping). The Investigator completed a clinical assessment of the gastrointestinal adverse event(s) within 24 hours of occurrence. The patient had a fecal occult blood test kit available at home to obtain a fecal sample prior to reporting to the clinic for evaluation of a gastrointestinal AE of concern. When the patient reported a GIAE of concern, the Investigator instructed the patient to use the FOB test kit dispensed for this purpose. The patient was scheduled for a clinic visit within 24 hours and instructed to return the FOB test. The assessment at the clinic included 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; an assessment of orthostatic changes in heart rate and blood pressure; and a review of the fecal occult blood test results. 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 fecal occult blood test. When the fecal occult blood test samples were analyzed, the Investigator questioned the patient to determine if the results may have been affected by menstruation, bleeding hemorrhoids, blood in the urine, medications, vitamins, or foods. Whenever the patient could not provide a fecal sample prior to or at the clinic visit, the Investigator obtained a sample by digital rectal exam. Patients were provided with replacement fecal occult blood test kits whenever the blank kits were used. If a fecal occult blood test was positive or if the patient reported melena during the randomized treatment phase of the study, the patient was referred to a gastroenterologist for a complete colonoscopy as soon as possible within 10 to 14 days of the clinic visit. The colonoscopy emphasized visualization of the transverse colon with reporting of positive or negative findings, irrespective of other identified pathology or causes for gastrointestinal bleeding. Biopsies were taken if appropriate. A blood sample was also collected for pharmacokinetic (PK/PD) analysis of SB-207499 and SB-217493 plasma

concentrations. If indicated, additional testing was performed at the discretion of the Investigator and reports were faxed to the Sponsor as soon as possible.

Within 24 hours of the first assessment, the Investigator reported these gastrointestinal adverse events to the Medical Monitor.

Follow-up assessments of fecal occult blood, complete blood count, and orthostatic changes in blood pressure were conducted until the gastrointestinal symptoms were resolved. These daily assessments were performed by a qualified health care provider at the patient's home or during daily clinic visits. Any deterioration in the patient's condition since the previous assessment discovered by a health care provider was reported to the Investigator by telephone immediately; all results were forwarded to the Investigator by the end of the work day. If the patient experienced symptoms that were severe or persistent and considered by the Investigator to be study-drug related, withdrawal of the patient was considered. Detailed guidelines for the assessment of gastrointestinal adverse events are presented in Appendix H of the protocol (Appendix A).

5.9.2. Physical Examination

A complete physical examination (including respiratory examination) was performed at the Screening Visit. Physical examinations were also performed at Baseline, Week 24 or upon early withdrawal, at Safety Follow-up (if abnormal at the previous visit), and at visits required within 24 hours of the occurrence of gastrointestinal adverse events of concern. Any clinically significant worsenings were documented as Baseline Signs or Symptoms or as adverse events.

5.9.3. Vital Signs

Vital signs (blood pressure and heart rate) were measured at all visits after the patient had been sitting for 5 minutes and more than 4 hours after the patient's last albuterol administration. Vital sign values of clinical concern were identified and tabulated.

At Screening, Baseline, Week 24, early withdrawal, and at visits associated with gastrointestinal adverse events of concern, heart rate and blood pressure were obtained after the patient had been supine for 5 minutes and then after the patient sat up with legs dependent for 1 minute. Any patient who experienced a decrease in systolic or diastolic blood pressure of ≥20mmHg or ≥10mmHg, respectively, or an increase in heart rate of ≥10 bpm at Screening or Baseline was not eligible to participate in the study.

5.9.4. Electrocardiogram

Standardized 12-lead ECG equipment (MAC-PC machine manufactured by Marquette) and a procedures manual were provided to all sites. A 12-lead ECG was performed at least 4 hours after the last albuterol dose during the run-in (except for Week -2) and double-blind treatment periods, upon early withdrawal, and at Safety Follow-up (if abnormal at the previous visit) after the patient had been semisupine for 5 minutes. At Baseline and Week 24, an ECG was also recorded 3 hours after administration of study

medication during the 4.5-hour PFTs. The ECGs were transmitted electronically via modem to a centralized facility (Biomedical Systems, St. Louis) for interpretation by a Board-certified cardiologist and data processing. Clinically significant changes were recorded by the Investigator as adverse events. ECG values of clinical concern were identified and tabulated.

5.9.5. Laboratory Testing

Blood and urine samples for clinical laboratory testing were collected at all visits during the run-in and double-blind periods of the study (with the exception of Weeks -2, 16, and 20). Patients who withdrew from the study had blood and urine samples collected at the Safety Follow-up Visit, only if abnormalities were observed at their previous visit.

The following variables were measured:

Hematology: Hemoglobin concentration, hematocrit, red cell count, white cell count with differential, platelet count.

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 was measured at baseline and for patients who had gastrointestinal adverse events that were of concern

Feces: Fecal occult blood tests between Screening and Baseline, between Weeks 20 and 24, at early withdrawal, and in patients who had gastrointestinal adverse events of concern.

Urinalysis: Blood, glucose, protein, ketones.

Pregnancy: Serum beta-HCG for women of child-bearing potential at Screening, Baseline, and Weeks 4, 8, 12, and 24.

Urinary beta-HCG (performed at site) for women of child-bearing potential at Weeks 16 and 20 and the Safety Follow-up Visit.

Additional laboratory tests were performed where indicated for patients who reported gastrointestinal adverse events that were of concern.

A central laboratory, Quest Laboratories (Van Nuys, California), was used for the routine hematological and biochemical assessments. Urinalysis was initially performed at the site using a dipstick. If abnormalities were found, full microscopy was performed by the central or local laboratories.

Clinically significant worsenings in laboratory findings were recorded in the Baseline Signs and Symptoms or Adverse Events section of the CRF. If a positive fecal occult

blood test was found between Screening and Baseline, the patient was withdrawn from the study. Laboratory values of clinical concern were identified and tabulated.

5.10. Pharmacokinetic Assessments

Six blood samples for the pharmacokinetic analysis of plasma concentrations of SB 207499 and the metabolite SB 217493 were collected from all randomized patients. Following randomization, patients were assigned (in approximately equal numbers at each center) to either the "Early" or "Late" sampling group. These designations defined post-dose time intervals during which a blood sample was to be drawn at Weeks 4 and 12.

5.10.1. Sampling Times

At each of the following visits, the time and date of the study medication dose administered in the clinic, along with the previous two doses (except baseline visit), were recorded in the CRF. The exact time and date of each pharmacokinetic blood sample were also documented in the CRF.

5.10.1.1. Baseline

A blood sample was collected after the first dose of double-blind study medication, during the 4.5-hour post-dose PFTs. The blood was drawn immediately after the ECG procedures, and prior to the 3-hour PFTs.

5.10.1.2. Week 4

A blood sample was taken prior to administration of the morning dose of study medication. A second, post-dose blood sample was collected, either between 0.5 and 2 hours after the morning dose (for patients assigned to the "Early" sampling group) or between 1.5 and 3 hours after this dose (for patients in the "Late" group).

5.10.1.3. Week 12

A blood sample was taken prior to administration of the morning dose of study medication. A second, post-dose blood sample was collected, either between 3 and 6 hours after the morning dose (for patients assigned to the "Early" sampling group) or between 5 and 10 hours after this dose (for patients in the "Late" group).

5.10.1.4. Week 24

A blood sample was taken prior to administration of the morning dose of study medication.

5.10.1.5. Unscheduled Samples

Where feasible, a blood sample was collected as soon as possible during any unscheduled "safety-monitoring" visit triggered by a gastrointestinal adverse event of concern or a serious adverse event.

5.10.2. Specimen Preparation

Blood samples (5mL each) for pharmacokinetic analysis were collected into tubes containing EDTA and immediately placed on ice. Plasma was separated within 30 minutes of collection by centrifugation (1000-1300g for 10 minutes) and transferred into appropriately labeled polypropylene tubes. Plasma was frozen immediately after centrifugation and stored at approximately -20°C until analyzed. Samples were transported via Quest Diagnostics to Pharma Bio-Research, Zuidlaren, the Netherlands.

5.10.3. Assay Methods

Plasma samples were assayed for SB 207499 and the metabolite SB 217493, using protein precipitation followed by negative ion electrospray LC/MS/MS analysis, [16,17] by Pharma Bio-Research, Zuidlaren, the Netherlands. These methods have lower limits of quantitation of 10.0 and 5.00ng/mL, respectively, based on a 0.1mL plasma aliquot. Quality control samples were assayed with each batch of authentic samples, against separately-prepared calibration standards.

5.10.4. Population Pharmacokinetic Analysis

A population pharmacokinetic analysis was conducted for this study. The methodology and results are reported separately [18].

5.11. Medical Care Utilization

Throughout the study, data on the utilization of medical care as a result of COPD exacerbations were collected and recorded in the CRF. Medical care utilization included hospitalization, 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 nebulizer or injection and oxygen).

At entry to the study, patients were asked whether or not they were employed and, if employed, the average number of hours worked per workday. Throughout the study, the number of work days lost as a result of a COPD exacerbation episode were recorded in the CRF. The patients were also asked if they were restricted in performing leisure activities or required paid or unpaid assistance with daily activities due to COPD-related symptoms.

5.12. Data Quality Assurance

To ensure that study procedures were consistent across all Investigator sites, the protocol, case report form and safety reporting were reviewed with the Investigator and his/her personnel responsible for the conduct of the study by the Company representative(s) at the Investigator site. In addition, a multi-Investigator meeting was held on December 5 – 7, 2000 in Orlando, FL. These meetings included spirometry and ECG training sessions.

Adherence to the protocol requirements and verification of data generation accuracy were achieved through monitoring visits to each Investigator site. Subsequent data handling and reporting processes were subject to in-process Quality Control and this final clinical report has, in addition, been subject to an end-stage Quality Control review. All the above procedures were performed according to methodologies detailed in GlaxoSmithKline's Standard Operating Procedures (SOPs).

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

A Contract Research Organization (Biomedical Systems, St. Louis, Missouri, USA) was employed to provide centralized spirometry and ECG services according to an agreed contract. This included supply of spirometry and 12-lead ECG equipment to sites, training sites on use of equipment, and provision for technical support. Biomedical Systems received electronic spirometry and 12-lead ECG data from sites and processed data prior to submission to GlaxoSmithKline. A Board Certified cardiologist at Biomedical Systems performed ECG interpretation and a registered respiratory therapist performed quality assurance review of a sample of pulmonary function tests. The CRO responsibilities were conducted according to SOPs agreed between GSK and Biomedical Systems.

This study was subject to audit by GlaxoSmithKline (Appendix A). A total of 5 Investigators were audited for this study: Dr. [redacted] (04/19/01-04/20/01); Dr. [redacted] (05/08/01 - 05/09/01); Dr. [redacted] (01/28/02); Dr. [redacted] (02/26/02-02/27/02); and Dr. [redacted] (03/06/02 - 03/07/02).

5.13. Statistical Evaluation

5.13.1. Target Sample Size

Originally, a sample size of 740 patients was planned, yet in order to obtain 550 completed patients, the total number of patients planned for randomization was increased to 830. Patients were randomized in a 1:1 ratio of SB 207499 to placebo. Approximately 140 centers in North America (United States and Canada) were expected to participate, with each center aiming to enroll between 4 and 24 patients. Assuming a standard

deviation in FEV_1 change from baseline at any given visit of 210mL, a correlation between visits of 0.68, and a significance level of 0.05, the indicated sample size will have greater than 90% power to detect a clinically meaningful difference of 50mL in FEV_1. A difference of 50mL was chosen based on retrospective analysis of data from Study 039. The sample size will also have more than 90% of power to detect a 4 unit difference (assuming a standard deviation of 12) in SGRQ at significance level of 0.05.

5.13.2. Method of Randomization

Patients were randomized to either SB 207499 15mg twice daily or placebo in a 1:1 ratio. The randomization code (Appendix A, Listing 1) was generated by the Biometrics group of GSK using in-house software. A block size of 4 was used for generating the randomization and patients were stratified within each center.

5.13.3. Planned Efficacy Evaluations

5.13.3.1. Primary Efficacy Variables

- Change from baseline in trough pre-bronchodilator forced expiratory volume in 1 second (FEV_1)
- Change from baseline in total score of the St George's Respiratory Questionnaire (SGRQ)

5.13.3.2. Secondary Efficacy Variables

- Change from baseline in post-exercise breathlessness (modified Borg scale)
- Change from baseline in clinic FVC at trough
- Time to first COPD exacerbation
- Time to first level 2 or 3 COPD exacerbation

5.13.3.3. Tertiary Efficacy Variables

- Use of 'as needed' albuterol
- First and last dose effect on pulmonary function tests (FEV_1, PEFR, FVC, FEF_{25-75})
- Post-bronchodilator effect for FEV_1, PEFR, FVC, FEF_{25-75}
- Clinic PEFR at trough
- Clinic FEF_{25-75} at trough
- Subscales of SGRQ (disease specific quality of life) including symptoms, impacts, and activities
- SF-36 (generic quality of life)
- Health economic endpoints (impact on activities, healthcare utilization)
- Global Investigator and Patient Assessments

- Exercise performance (distance walked) during the exercise tolerance test (6-minute walk with encouragement)
- Overall breathlessness during usual activity (modified Borg scale)
- Post-exercise SaO_2 and breathlessness
- SaO_2 at rest in patients with FEV_1 of <40% predicted for age, height, and sex
- Arterial blood gases, PO_2 and PCO_2 in patients with FEV_1 of <40% living at high altitudes or having a resting SaO_2 <88%
- Cough and sputum assessments

5.13.4. Methods of Analysis

5.13.4.1. Data Analysis Conventions and Data Deviations

DLCO (carbon monoxide diffusing capacity): For analysis of % predicted DLCO values >200% and <20% were assumed implausible and suppressed.

ECGs and Sitting Vital Signs: Baseline was defined as the last evaluation prior to receiving initial dose of randomized study medication. Visit 3 trough assessments occurring >15 minutes after first dose of randomized study medication were not considered for baseline. Only on-therapy ECG evaluations and vital signs were used in the analysis. An on-therapy evaluation was defined as any which occurred after the first dose of randomized study medication and no later than one day after the last dose of randomized study medication.

Laboratory Data: Baseline was defined as the last evaluation prior to receiving initial dose of randomized study medication. Only on-therapy labs and were used in the analysis. An on-therapy evaluation was defined as any which occurred after the first dose of randomized study medication and no later than 1 day after the last dose of randomized study medication.

Pulmonary Function Tests (PFTs): Baseline for pulmonary function was defined as the evaluation performed at Visit 3. PFTs occurring >10 minutes after first dose of randomized study medication were not considered for baseline. When PFTs were repeated for a particular visit, the later of the two assessments was used in the evaluation. The following rules were applied for choosing the effort to use in the analysis:

FEV_1: Best FEV_1 value from technically acceptable loops was used. This corresponds to reading = 1. There were a small number of cases where the maximum value did not correspond to this reading.

FVC: The maximum FVC value from technically acceptable loops was used (not necessarily from the same loop as FEV_1).

PEFR: The maximum PEFR value from technically acceptable loops was used (not necessarily from the same loop as FEV_1 or FVC).

FEF_{25-75}: The values for the analysis were derived from the effort with the maximum summed value of FEV_1 + FVC from a single acceptable loop. If two loops had the same summed value, the maximum FEF_{25-75} from the two loops was used in the analysis. If FEF_{25-75} was not available from the effort with the maximum summed value then the value was treated as missing in the analysis.

SGRQ: Baseline for the SGRQ was defined as the Visit 3 evaluation. Missing values in Part 1 of the questionnaire were assigned a weight of 0 provided at least one of the items in Part 1 was answered. If none of the items were answered in Part 1 then the entire section was set to missing. Missing values in Part 2 of the questionnaire were not considered in the calculation of the denominator. If more than 10 items were missing in Part 2, the entire portion of the questionnaire was invalidated and set to missing. If multiple responses were available for a particular item, the average weight for that item was used in the analysis. Further details of the scoring algorithm are available in Appendix A.

SF-36: Baseline for the SF-36 was defined as the Visit 3 evaluation. For those items that were missing, the average across all completed items in the same scale was imputed. If a respondent left more than 50% of the items blank within a scale, then no imputation was performed. If multiple responses were available for a particular item, the average score for that item was used in the analysis.

COPD Exacerbations and Resource Utilization: Only those exacerbations with an onset after the first dose of randomized study medication and no later than one day after the last dose of randomized study medication were used in the analysis. For patients who were censored, the censoring time was defined as the total number of days on randomized study medication. An identical approach was adopted for events associated with healthcare resource utilization.

Pooling of Centers for Efficacy Analysis: Centers randomizing less than four patients were pooled together with each other on a regional basis according to the following strategy:

Region 1: Centers in [redacted]

Region 2: Centers in [redacted]

Region 3: Centers in [redacted]

Region 4: Centers in [redacted]

Region 5: All centers in Canada.

5.13.4.2. Comparisons of Interest

The primary comparisons were based on two-tailed tests of hypothesis. The first primary comparison was the difference in change from baseline in pre-bronchodilator FEV_1 between the SB 207499 and placebo treatment groups averaged over all double-blind visits (protocol defined Visits 4, 5, 6, 7, 8, 9, 10) in the intent-to-treat population (see

Section 5.13.5 for definition). The second primary comparison was the difference in change from baseline in total score of the SGRQ between the SB 207499 and placebo treatment groups averaged over all double-blind visits in the intent-to-treat population. Each primary comparison was performed at an alpha level of 0.05.

If both primary endpoints were significant, the Hochberg method [20] was used to adjust the significance level of multiple secondary endpoints in the test for treatment difference.

Secondary comparisons of interest were the comparison between groups for FEV_1, SGRQ total score, and all other secondary efficacy variables at Week 24 and the comparison of groups at endpoint. Endpoint of treatment was defined as the last observation for a patient in the double-blind period.

Additional comparisons between treatment groups were made for all efficacy variables at Weeks 4, 8, 12, 16, 20, and for tertiary variables at Week 24 and endpoint of the double-blind period.

For COPD exacerbations the comparison of interest was based on differences in the distribution of time to the first occurrence of the event.

5.13.4.3. Efficacy Analysis

The primary conclusion of the study was based on a repeated-measures model [19] on the change from baseline in the primary endpoints. Effects for treatment, time and center were included in the model. Inference was based on the average treatment effect over all protocol-defined double-blind visits. Follow-up and unscheduled visits for early withdrawal or other reasons were not included in the repeated measures analysis. Time was treated as a nominal variable. An unstructured correlation matrix was used and estimated using restricted maximum likelihood (REML). The difference between treatment groups was evaluated through a t-test on the least-square means. Ninety-five percent (95%) confidence intervals were calculated on the least-square means of the two groups and on their difference. The default (model-based) estimator was used to estimate the standard errors of the fixed effects.

In the pre-NDA meeting with FDA, GSK was requested to change the covariance structure from compound symmetry to unstructured to be consistent with the previous three pivotal studies. For some variables, the pre-defined model (with center and treatment as factors) did not converge in using SAS procedure Proc Mixed. In these cases, center was removed from the model.

For the primary endpoints, the homogeneity of treatment effect with respect to week and center was assessed through addition of treatment-by-week interaction and treatment-by-center interaction terms to the final model described above. Interaction terms were tested at a significance level of 0.10. Consistency of the treatment effect over visits was further examined through graphical methods. As a treatment-by-time interaction in FEV_1 was observed, a repeated measures model as described above was performed using only the data from Weeks 16 to 24 of the double-blind period.

The effects of age, sex, % predicted FEV_1 and baseline smoking status on response were also explored. All four covariates were added to the final model described above.

Although the estimation of treatment effect is usually robust with respect to the choice of covariance structure, and the unstructured covariance model generally provides reasonable assumptions about the relationship in longitudinal data, other structures were also explored. Likelihood ratio tests were performed to evaluate the degree to which information was lost by moving away from the unstructured covariance matrix.

To further examine the normality assumption, normal probability plots of the marginal residuals were examined. The residuals were output from the final model described above.

Sporadically missing data from patients completing the study was assumed to be missing at random (MAR). For patients who discontinued the study, MAR was not assumed. Patients were classified as withdrawals or completers and a nominal variable reflecting this categorization was defined in the mixed model and assessed for significance. No further formal exploration of the MAR assumption was carried out. To further describe the impact of dropouts, descriptive analyses were provided for the subgroup of patients who completed the study. An additional analysis was performed in which the worst (lowest) FEV_1 and worst (highest) SGRQ values were imputed for withdrawn patients at visits subsequent to their withdrawal. In addition, a pattern mixture model was used to assess the impact of missing data.

In addition to the repeated measures analysis described above an analysis of variance (ANOVA) model was performed at each protocol-defined double-blind visit as well as at endpoint. Endpoint was defined as the last on-therapy observation for each patient during the double-blind period. The ANOVA model included effects for treatment and center. Least squares means and associated 95% confidence intervals were calculated for each treatment group. Ninety-five percent (95%) confidence intervals were also calculated on the difference in the least-square means.

Subgroup analyses were performed to describe the response in the populations described below (see Section 5.13.5). Descriptive statistics (mean, median, standard deviation, minimum and maximum) of the baseline, endpoint and change from baseline to endpoint were provided for each of the subgroups. No inferential analyses were performed.

The analysis of continuous secondary and tertiary endpoints was performed using the repeated measures methodology described above. An ANOVA model as described above was also performed at each protocol-defined visit and endpoint.

Differences in the distribution of time-to-first COPD exacerbation were tested using the log-rank test. The exacerbation-free survival rate at 24 weeks along with 95% confidence intervals was estimated for each treatment group using the Kaplan-Meier product limit method. Patients with no exacerbations were censored at the date of their last dose of randomized study medication.

To assess the impact of age, sex, baseline smoking status and %predicted FEV_1 on time-to-first COPD exacerbation, a Cox Proportional Hazards model was used. The relative

risk (for SB 207499 versus placebo) of a COPD exacerbation and associated 95% confidence interval were estimated after adjusting for the effects of these covariates.

To take account of the recurring nature of COPD exacerbations, a marginal proportional hazards model proposed by Wei, Lin and Weissfeld [21] was also performed. The first two exacerbations for each patient were used for the analysis. This analysis proceeds by analyzing the first and second exacerbations separately, estimating the variance-covariance matrix of the parameter estimates, and performing simultaneous inference. A weighted estimate of the relative risk along with 95% confidence intervals is then estimated.

The analysis of healthcare utilization data was performed in a similar way to the analysis of COPD exacerbations. For each type of utilization (hospitalization, physician/ emergency room [ER] visit or intensive care unit [ICU] stay), Kaplan-Meier estimates and log rank test as described above were performed. An analysis which looks at any utilization, regardless of type, was also performed.

Additionally, a Poisson regression model was used to estimate an annualized rate of utilization along with 95% confidence intervals for each treatment group. This analysis was done for each utilization type and across utilization types.

5.13.5. Populations to be Evaluated

The intent-to-treat (ITT) population included all patients who received randomized study medication and had a baseline efficacy evaluation and at least one on-therapy efficacy evaluation during the double-blind period. Data collected more than one day after the last dose of study medication were excluded from the analysis. All efficacy analyses, with the exception of COPD exacerbations, were performed for the ITT population, the primary population in this study. COPD exacerbations were analyzed for randomized patients.

The per-protocol (PP) population included all patients in the ITT population who did not violate the protocol according to predetermined criteria. A complete list of protocol violations and patients excluded from the PP analysis was specified prior to the unblinding of the study (see Section 6.3). Patients who violated the protocol could be excluded from the PP analysis by week or for the entire study.

Response on the primary endpoints was also evaluated in subgroups defined based on sex, COPD severity at study entry as defined by % of predicted FEV_1, race, and smoking history.

5.13.6. Safety Evaluation

All patients who received at least one dose of double-blind study medication were evaluated for clinical safety and tolerability. Clinical interpretation was based upon a review of displays of AEs, laboratory values, vital signs, and ECG parameters. For all safety parameters, baseline was defined as the last measurement recorded prior to the start of double-blind medication.

The incidence of on-therapy AEs was summarized by relationship to study medication, severity, time of initial onset, and action taken. Gastrointestinal adverse events of concern were also summarized separately. On-therapy AEs were defined as those which started after the initial dose of randomized study medication and no later than one day after the last dose of randomized study medication. The WHOART dictionary was used for coding AEs.

Descriptive statistics, including mean change from baseline were calculated by visit for laboratory data, sitting vital signs, and ECG parameters (at trough and C_{max}).

Two-way contingency tables of the baseline laboratory values versus endpoint laboratory values were provided to enumerate the number of patients with values of concern. Similar tables were provided for sitting vital signs, ECGs and orthostatic vital signs. Values of clinical concern are defined for vital signs (Section 8.9), ECG parameters (Section 8.10), and laboratory parameters (Section 8.11).

The incidence of new-onset ECG abnormalities was also summarized. A new-onset ECG finding was defined as one that was present on-therapy but not present at any time pre-therapy. Systematized nomenclature of human (and veterinary) medicine (SNOMED) codes were provided for decoding ECG findings.

6. STUDY POPULATION

6.1. Study Dates

The first dose of single-blind medication was taken on 12 December 2000. The first and last doses of double-blind medication were administered on 11 January 2001 and 16 July 2002, respectively (Appendix B, Listing 12).

6.2. Patient Disposition

6.2.1. Number and Distribution of Patients

Table 5 presents the number of patients who entered the single-blind period, were randomized to receive study medication, completed the study, and were eligible for analyses. The randomization code is supplied in Appendix A, Listing 1.

Table 5 Disposition of Patients

Disposition	Treatment Group: Placebo n (%)		Treatment Group: SB 207499 15mg BID n (%)		Total n (%)	
Entered single-blind phase	---		---		1252	
Randomized	407	(100.0)	418	(100.0)	825	(100.0)
Withdrawn from double-blind	96	(23.6)	143	(34.2)	239	(29.0)
ITT efficacy analysis [a]	377	(92.6)	364	(87.1)	741	(89.8)
PP efficacy analysis [b]	363	(89.2)	353	(84.4)	716	(86.8)
Safety analysis	407	(100.0)	418	(100.0)	825	(100.0)
Completed double-blind phase	311	(76.4)	275	(65.8)	586	(71.0)

a. Includes all patients who received randomized study medication, had a baseline visit, and had at least one on-therapy efficacy assessment during the double-blind period.
b. Patients included in per-protocol population for FEV_1 repeated measures analysis.
Data Source: Section 13, Table 13.1A, Table 13.1B, and Table 13.4.

A total of 1252 patients met eligibility criteria and entered the single-blind phase of the study at 132 centers in the United States and Canada. Of the 1252 patients who were enrolled, 427 patients (34.1%) were withdrawn prior to randomization and 825 patients (65.9%) were randomized. The reasons for non-randomization are discussed in Section 6.2.3, and the reasons for exclusion of patients from the per-protocol efficacy population are discussed in Section 6.3.

A total of 126 centers in the United States and 7 centers in Canada randomized 776 and 49 patients, respectively. The distribution of patients by center is provided in Section 13, Table 13.1B.

6.2.2. Number of Patients Present at Each Week

Table 6 presents the number and percentage of patients remaining in the study at each week. Six hundred twenty two (75.4%) of 825 patients remained in the study at Week 16 and 588 patients (71.3%) remained up to Week 24. During the first 4 weeks of double-blind treatment, the rate of withdrawal for SB 207499-treated patients was disproportionate relative to the placebo treatment group; however, the ratio of withdrawals between the two groups stabilized from Week 8 through the end of the study.

Table 6 Distribution of Randomized Patients by Week

Week	Treatment Group: Placebo (N=407) n (%)	Treatment Group: SB 207499 15mg BID (N=418) n (%)	Total (N=825) n (%)
Baseline	407 (100.0)	418 (100.0)	825 (100.0)
Week 1	397 (97.5)	410 (98.1)	807 (97.8)
Week 2	382 (93.9)	373 (89.2)	755 (91.5)
Week 4	372 (91.4)	350 (83.7)	722 (87.5)
Week 8	357 (87.7)	329 (78.7)	686 (83.2)
Week 12	342 (84.0)	312 (74.6)	654 (79.3)
Week 16	325 (79.9)	297 (71.1)	622 (75.4)
Week 20	317 (77.9)	285 (68.2)	602 (73.0)
Week 24	312 (76.7)	276 (66.0)	588[a] (71.3)
Follow-up	368 (90.4)	355 (84.9)	723 (87.6)

a. Two patients withdrew from double-blind treatment at Visit 10 (Week 24).
Data Source: Section 13, Table 13.2; Appendix B, Listing 1.

6.2.3. Withdrawal Reasons

Prior to randomization into the double-blind period, 427 patients were withdrawn from the study after entering the single-blind run-in period. The most common reasons for withdrawal of nonrandomized patients were failure to meet inclusion/exclusion criteria (196 of 427 patients, 45.9%), baseline signs and symptoms (97 patients, 22.7%) that included exacerbation of COPD (59 patients, 13.8%), and "other reasons" (97 patients, 22.7%). Patients were also withdrawn due to deviation from protocol (13 patients, 3.0%) and loss to follow-up (24 patients, 5.6%) (Section 13, Table 13.3).

Reasons for withdrawal of randomized patients are summarized in Table 7 and presented by patient in Appendix B, Listing 1.

Table 7 Number (%) of Randomized Patients Who Completed the Study or Were Withdrawn by Reason for Withdrawal

	Treatment Group	
Reason for Withdrawal	Placebo (N=407) n (%)	SB 207499 15mg BID (N=418) n (%)
Adverse event[a]	42 (10.3)	80 (19.1)
COPD exacerbation	9 (2.2)	11 (2.6)
Protocol deviation	10 (2.5)	6 (1.4)
Lost to follow-up	5 (1.2)	7 (1.7)
Insufficient therapeutic effect	6 (1.5)	8 (1.9)
Other[b]	33 (8.1)	42 (10.0)
Total withdrawn	96 (23.6)	143 (34.2)
Completed double-blind phase	311 (76.4)	275 (65.8)

a. Adverse event row includes COPD exacerbations.
b. The most common "other" reason for withdrawal was withdrawn consent.
Data Source: Section 13, Table 13.4; Appendix B, Listing 1 and Listing 14

The percentage of randomized patients completing the study was lower in patients who received SB 207499 (65.8% of 418) than in those who received placebo (76.4% of 407). The most common reasons for withdrawal of randomized patients during the double-blind phase were adverse event (10.3% of placebo-treated patients and 19.1% of patients who received SB 207499) and other reasons (8.1% of placebo-treated patients and 10.0% of patients who received SB 207499). The percentage of patients who were withdrawn due to adverse events, including COPD exacerbations, was lower in patients who received placebo (10.3%) than in patients who received SB 207499 (19.1%). The percentage of patients who were withdrawn due to COPD exacerbations was similar between the two treatment groups (2.2% placebo vs. 2.6% SB 207499).

The time course of withdrawal due to AEs was similar between the two treatment groups from Day 56 onward (Table 8).

Table 8 Cumulative Percentage of Patients Withdrawn by Time of Withdrawal and Reason for Withdrawal

	Treatment Group									
	Placebo (N=407)					SB 207499 15mg BID (N=418)				
Time (Days)	AE %	PD %	LTFU %	ITE %	Other %	AE %	PD %	LTFU %	ITE %	Other %
≤7	1.2	0.5	0.2	0.3	1.7	3.9	0.2	0.0	0.3	1.9
≤14	2.3	1.0	0.5	0.3	2.7	8.8	0.2	0.3	0.3	3.7
≤28	3.8	1.0	0.5	0.8	3.5	12.4	0.5	0.5	0.5	5.9
≤56	5.4	1.6	0.8	1.1	5.4	15.3	0.8	1.1	0.5	6.7
≤84	7.3	1.8	1.3	1.4	7.3	17.4	0.8	1.1	1.2	9.1
≤112	9.5	2.1	1.3	1.7	8.1	18.8	0.8	1.5	2.1	10.3
≤140	10.7	2.8	1.3	1.7	8.1	19.3	1.5	1.8	2.5	11.2
≤168	11.0	2.8	1.3	1.7	8.4	20.5	1.9	2.2	2.5	11.6
≤200	11.8	2.8	1.3	1.7	12.1	20.5	1.9	2.2	2.5	11.6

Percentages are cumulative and are estimated based on total number of randomized patients using the Kaplan-Meier product limit.
AE=Adverse Event, PD=Protocol Deviation, LTFU=Lost to Follow-up, ITE=Insufficient Therapeutic Effect, Other=Other Reasons.
Data Source: Section 13, Table 13.5; Appendix B, Listing 1.

6.3. Protocol Violations

Patients who violated the protocol could be excluded from the per-protocol analysis for the entire study, for a specific visit, or from the time of the violation to the end of the study. The following protocol violations were specified prior to the unblinding of the study and led to either complete or partial exclusion of a patient from the study.

Violations of Eligibility Criteria (All data excluded for PP analysis)

- Pre-albuterol FEV_1/FVC ratio >0.71 at Visit 1
- Increase in FEV_1 of >17% and >200mL following albuterol at Visit 1
- Post-albuterol FEV_1 <27% or >72% of predicted value at Visit 1
- Participation in a pulmonary rehabilitation program (PRP) within four weeks prior to Visit 1
- Change of >22% in pre-albuterol clinic FEV_1 between Visits 1 and 3
- Patients previously randomized in a SB 207499 study

Exclusionary Medications (any data collected after initiation excluded from PP analysis)

- Concomitant oral or IV xanthine use during the run-in period (within 2 weeks prior to Visit 3)
- Concomitant oral or inhaled long-acting beta-2 agonist use during the run-in period

- Concomitant inhaled short-acting beta-2 agonist use other than albuterol during the run-in period
- Concomitant leukotriene modifiers during the run-in period
- Concomitant combined beta-2 agonist/ipratropium use during the run-in period
- Concomitant long term oxygen therapy use during the run-in period
- Concomitant oral and/or inhaled corticosteroid (ICS/OCS) during run-in period
- Nebulized or oral albuterol or nebulized anticholinergics during the run-in period
- Concomitant antibiotic use for COPD exacerbation during the run-in period
- Concomitant use of nedocromil during the run-in period
- Anticholinergics at Visit 1 that are not continued post-randomization
- Anticholinergics initiated after Visit 1
- Exclusionary medication use for the indication of COPD exacerbation for durations >6 weeks total exposure during the double-blind period (all data subsequent to 6 weeks exposure will be excluded)

Visit Specific Violations (the following data collected at the visit when the violation occurred were excluded from PP analysis)

- Study medication noncompliance of <80% or >120% during active, on-therapy dosing
- Albuterol and/or anticholinergic medication within 2 hours of pulmonary function testing
- Entered a PRP during the study (all data collected subsequent to entry excluded)
- Use of study medication within 7 hours of first (trough) PFTs

Additional minor protocol deviations from the protocol were defined as Conduct of Study Deviations. The following conduct of study deviations were identified and did not result in exclusion of data from the PP analysis.

Conduct of Study Deviations (no data excluded from PP analysis)

- Age <40 or >80 years
- Cigarette smoking history <10 pack years
- Level 2 or level 3 exacerbation of COPD within 6 weeks prior to Visit 3
- Study medication noncompliance of <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
- Exclusionary medications use >2 weeks for each COPD exacerbation (did not include patients exceeding 6 weeks total exposure as described above)

- Exclusionary medications use for indication other than COPD exacerbation for <2 weeks
- Smoking within 2 hours of pulmonary function testing (at Visit 3 or later)

6.3.1. Protocol Violations That Led to Exclusion From the Per-Protocol Analysis

Protocol violations that resulted in partial or total exclusion of patients from the per-protocol analysis are summarized in Table 9. These data are presented by patient in Appendix B, Listing 2A and Listing 2B.

Table 9 Summary of Protocol Violations Resulting in Exclusion From Per-protocol Analysis by Treatment Group

Violation	Treatment Group: Placebo (N=377) n (%)	Treatment Group: SB 207499 15mg BID (N=364) n (%)
Eligibility criteria	**8 (2.1)**	**3 (0.8)**
Pre-albuterol/salbutamol FEV_1/FVC ratio >0.71 at Visit 1	2 (0.5)	1 (0.3)
Increase FEV_1 of >17% and 200mL following albuterol/salbutamol at Visit 1	3 (0.8)	1 (0.3)
Participation in a pulmonary rehabilitation program (PRP) within 4 weeks prior to Visit 1	1 (0.3)	0
Greater than 22% change in pre-albuterol/salbutamol clinic FEV_1 between Visits 1 and 3	2 (0.5)	1 (0.3)
Exclusionary medications	**18 (4.6)**	**12 (3.3)**
Concomitant oral or inhaled long-acting beta-2 agonist use within 2 weeks prior to Visit 3	1 (0.3)	0
Concomitant leukotriene modifiers use within 2 weeks prior to Visit 3	0	1 (0.3)
Concomitant combined beta-2 agonist/ipratropium use within 2 weeks prior to Visit 3	1 (0.3)	0
Concomitant long-term oxygen therapy use within 2 weeks prior to Visit 3	2 (0.5)	3 (0.8)
Concomitant oral and/or inhaled corticosteroids (ICS/OCS) within 2 weeks prior to Visit 3	8 (2.1)	4 (1.1)
Nebulized or oral salbutamol/albuterol or nebulized anticholinergics within 2 weeks prior to Visit 3	3 (0.8)	0
Concomitant antibiotic use for COPD exacerbation within 2 weeks prior to Visit 3	1 (0.3)	1 (0.3)
Anticholinergics initiated after Visit 1	6 (1.6)	4 (1.1)
Visit Specific Violations	**73 (19.4)**	**93 (25.5)**
Study medication compliance <80% or >120% during active, on-therapy dosing	52 (13.8)	74 (20.3)
Albuterol/salbutamol and/or anti-cholinergic medication within 2 hours of pulmonary function testing	3 (0.8)	3 (0.8)
Entered a pulmonary rehabilitation program during the study	12 (3.2)	11 (3.0)
Use of study medication within 7 hours of first (trough) PFTs	12 (3.2)	12 (3.3)
Total Number of Patients Completely Excluded	**14 (3.7)**	**11 (3.0)**
Total Number of Patients Partially Excluded[a]	**75 (19.9)**	**94 (25.8)**
Total Number of Patients With at Least One PV	**89 (23.6)**	**105 (28.8)**

a. Number of patients with visit specific exclusions from per-protocol analyses.
Data Source: Section 13, Table 13.6A; Appendix B, Listing 2A and Listing 2B

The percentage of patients completely excluded from the per-protocol efficacy analysis was similar among those who received placebo (3.7% of 377 patients) and those who received SB 207499 (3.0% of 364 patients).

The percentages of patients with partial data excluded from the per-protocol efficacy analysis were 19.9% (75 of 377) in the placebo treatment group and 25.8% (94 of 364) in the SB 207499 treatment group. The most common protocol violations in both treatment groups leading to partial data exclusion were study medication noncompliance of <80% or >120%, entry into a pulmonary rehabilitation program (PRP) during the study, and the use of study medication within seven hours of the first (trough) PFTs (Section 13, Table 13.6A; Appendix B, Listing 2A). Non-compliance with study medication was higher in the SB 207499 treatment group (20.3% of patients) than the placebo treatment group (13.8% of patients).

A summary of protocol violations resulting in exclusion from the per-protocol primary efficacy analysis (repeated measures) by visit/week is provided in Section 13, Table 13.6B.

6.3.2. Conduct of Study Deviations

Protocol violations that did not result in the exclusion of patients from the per-protocol analysis were considered to be conduct of study deviations. These deviations were not considered to have an impact on the pharmacologic measurement of treatment effect. Conduct of study deviations is summarized in Section 13, Table 13.6C and provided by patient in Appendix B, Listing 2C.

A total of 56 of 377 patients (14.9%) who received placebo and 57 of 364 patients (15.7%) who received SB 207499 were reported to have conduct of study deviations. Conduct of study deviations included the following:

- Smoking within 2 hours of pulmonary function testing (at visit 3 or later) reported for 47 (12.5%) patients who received placebo and 48 (13.2%) patients who received SB 207499
- Non-compliance with study medication of <80% or >120% during the placebo run-in period reported for 6 (1.6%) patients who received placebo and 6 (1.6%) patients who received SB 207499
- Level 2 or level 3 exacerbation of COPD within 6 weeks prior to visit 3 reported for 4 (1.1%) patients in the placebo treatment group and 3 (0.8%) patients in the active treatment group

6.4. Demographic and Baseline Characteristics

6.4.1. Demographic Characteristics

Demographic characteristics at screening are presented for all randomized patients in Table 10. Information for individual patients is provided in Appendix B, Listing 1.

Table 10 Summary of Demographic Characteristics at Screening (All Randomized Patients)

Characteristic		Treatment Group: Placebo (N=407) n (%)	Treatment Group: SB 207499 15mg BID (N=418) n (%)
Sex	Female	156 (38.1)	183 (43.8)
	Male	251 (61.7)	235 (56.2)
Race	Caucasian	377 (92.6)	392 (93.8)
	Oriental	1 (0.2)	0
	Black	25 (6.1)	25 (6.0)
	Other[a]	4 (1.0)	1 (0.2)
Employed	Yes	153 (37.6)	148 (35.4)
	No	254 (62.4)	270 (64.6)
Prior Steroid Use	Inhalation	119 (29.2)	117 (28.0)
	Systemic	11 (2.7)	10 (2.4)
Age, y	<50	25 (6.1)	17 (4.1)
	50-65	184 (45.2)	201 (48.1)
	>65	198 (48.6)	200 (47.8)
	Mean (SD)	64.4 (8.7)	64.5 (8.2)
	Min, Max	41, 80	41, 80
Weight, kg	Mean (SD)	77.6 (18.6)	76.8 (18.0)
	Min, Max	34, 167	35, 144
Height, cm	Mean (SD)	171.0 (10.1)	169.9 (9.7)
	Min, Max	146, 198	145, 201

a. Not further defined.
Data Source: Section 13, Table 13.7A; Appendix B, Listing 1

There were no marked differences in the demographic characteristics between the two treatment groups. The mean age of the two groups was similar, and nearly all of the patient population for the study was ≥50 years of age. The great majority of patients were Caucasian (92.6% in the placebo treatment group, 93.8% in the SB 207499 treatment group) and more male patients were randomized compared to female patients for both the placebo (61.7% vs. 38.1%, respectively) and SB 207499 (56.2% vs. 43.8%, respectively) treatment groups.

The demographic characteristics of patients who completed the study were comparable to those of patients who withdrew from the study (Appendix I, Listing 10A and Listing 10B).

Demographic characteristics at screening for the per-protocol population are presented in Section 13, Table 13.7B. The per-protocol population was similar to all randomized patients with regard to demographic characteristics.

6.4.2. Baseline Characteristics

A summary of smoking history, alcohol intake, and duration of COPD is presented for all randomized patients by treatment group in Table 11. Information for individual patients is provided in Appendix B, Listing 4, Listing 5, and Listing 6.

Table 11 Descriptive Statistics for Smoking History, Alcohol Intake, and Duration of COPD by Treatment Group (All Randomized Patients)

		Treatment Group	
Characteristic		Placebo (N=407)	SB 207499 15mg BID (N=418)
Smoking history, pack years	Mean (SD)	61.8 (34.4)	58.9 (31.1)
	Min, Max	11.0, 240.0	10.0, 220.0
Current smoker	n (%)	187 (45.9)	195 (46.7)
Previous smoker	n (%)	220 (54.1)	223 (53.3)
Cigarettes per day	n	187	195
	Mean (SD)	22.4 (12.3)	24.1 (12.8)
	Min, Max	1.0, 80.0	0.3, 80.0
Alcohol intake, units/week	n	404	418
	Mean (SD)	3.2 (5.9)	3.5 (7.3)
	Min, Max	0.0, 42.0	0.0, 96.0
COPD duration, y	n	404	414
	Mean (SD)	5.8 (6.6)	6.4 (7.4)
	Min, Max	0.0, 45.0	0.0, 51.0

Data Source: Section 13, Table 13.12A; Appendix B, Listing 4, Listing 5, and Listing 6.

At Screening, there were no marked differences in smoking history, alcohol intake, and duration of COPD between the two treatment groups. By the end of the study, there were only small changes in smoking status, with no marked differences between the two treatment groups. Smoking status at each visit is summarized in Section 13, Table 13.17 and data is provided by patient in Appendix B, Listing 13.

The per-protocol population was similar to all randomized patients with regard to smoking history, alcohol intake, and duration of COPD (Section 13, Table 13.12B).

Pulmonary function parameters and % predicted DLCO at Screening are presented by treatment group for all randomized patients in Table 12. Information for individual patients is provided in Appendix B, Listing 3 and Listing 4.

Table 12 Descriptive Statistics for Pulmonary Function Parameters and % Predicted DLCO at Screening (All Randomized Patients)

Parameter		Treatment Group: Placebo (N=407)	Treatment Group: SB 207499 15mg BID (N=418)
FEV_1,[a] L	Mean (SD)	1.45 (0.53)	1.40 (0.48)
	Min, Max	0.48, 3.18	0.50, 2.98
% Predicted FEV_1[b]	Mean (SD)	50.0 (12.1)	50.3 (11.6)
	Min, Max	21.9, 71.8	28.6, 71.4
Reversibility, %	Mean (SD)	8.6 (6.4)	8.6 (6.4)
	Min, Max	0.0, 34.7	0.0, 31.3
FEV_1/FVC ratio[a]	Mean (SD)	0.53 (0.10)	0.53 (0.10)
	Min, Max	0.25, 0.73	0.24, .073
FVC,[a] L	Mean (SD)	2.83 (0.92)	2.75 (0.86)
	Min, Max	0.84, 5.65	0.91, 5.35
PEFR,[a] L/min	Mean (SD)	212 (86.1)	210 (80.0)
	Min, Max	60, 537	68, 622
FEF_{25-75},[a] L/min	Mean (SD)	0.61 (0.32)	0.57 (0.29)
	Min, Max	0.11, 1.89	0.16, 2.60
% Predicted DLCO	n	392	399
	Mean (SD)	54.6 (21.18)	55.8 (21.76)
	Min, Max	2.5, 138.0	6.2, 165.2

a. FEV_1, FVC, PEFR, FEF_{25-75} are reported pre-albuterol inhalation.
b. % Predicted FEV_1 is reported post-albuterol inhalation.
Data Source: Section 13, Table 13.9A; Appendix B, Listing 3 and Listing 4.

The treatment groups were similar with respect to pulmonary function at screening, except that the placebo group had a mean FEV_1 that was 50mL greater than the SB 207499 treatment group (1.45L placebo vs. 1.40L SB 207499). This difference in FEV_1 is likely due to a gender effect since a higher number of female patients were enrolled in the SB 207499 treatment group (43.8%) compared to the placebo treatment group (38.1%). However, the % predicted FEV_1 for the patients randomized to placebo (50.0%) and SB 207499 (50.3%) were nearly identical. Overall, the patients were representative of a moderate COPD population; however, mild and severe disease states were also represented in this study.

The pulmonary function characteristics of the per-protocol population were similar to those of all randomized patients (Section 13, Table 13.9B).

The distance walked by randomized patients during the 6-minute walk test at Screening and Week -2 is presented in Section 13, Table 13.10 (Appendix C, Listing 3). The mean distance walked at Screening was 364.7m (range: 8 - 903m) in the placebo treatment group and 353.2m (range: 4 - 1141m) in the SB 207499 treatment group. At Week -2 the mean distance walked was 370.0m (range: 8 - 808m) in the placebo treatment group and 362.7m (range: 44 - 869m) in the SB 207499 treatment group.

6.5. Presenting Conditions and Medical History

Medical history included evaluation of pulmonary history, prior medical conditions, and medical conditions present at the Screening Visit.

Vital signs at screening for all randomized patients are presented by treatment group in Section 13, Table 13.8. No marked differences in systolic blood pressure, diastolic blood pressure or heart rate were noted between treatment groups.

A summary of pulmonary history is presented by treatment group for all randomized patients in Section 13, Table 13.11. One patient in each treatment group had exacerbation of COPD within the 2 weeks prior to Screening, and one patient in the placebo treatment group had received pulmonary rehabilitation within 4 weeks prior to Screening. At Screening, the treatment groups were similar with respect to the distribution of number of prior emergency department visits and hospitalizations (Section 18, Table 18.1).

A summary of prior medical conditions for all randomized patients is provided in Section 13, Table 13.13A; individual patient data are provided in Appendix B, Listing 5. In total, 358 of 407 patients (88.0%) randomized to placebo and 376 of 418 patients (90.0%) randomized to SB 207499 had prior medical conditions recorded at Screening. Overall, the most frequently reported prior condition was nose/mouth operation (14.0% and 14.1% of patients randomized to placebo vs. SB 207499, respectively). The next two most common prior conditions other than operations were pneumonia (10.8% randomized to placebo vs. 10.5% randomized to SB 207499) and benign neoplasms (5.9% randomized to placebo vs. 6.5% randomized to SB 207499). Female genital operations were reported by 81 of 156 female patients (51.2%) randomized to placebo and 112 of 183 female patients (61.2%) randomized to SB 207499.

Table 13 shows the most common presenting conditions, by disease classification occurring in ≥10% of randomized patients in either treatment group. Details of presenting conditions by patient are presented in Appendix B, Listing 6.

Table 13 Summary of Most Common (≥10% of Patients in Either Treatment Group) Current/Active Medical Conditions at Screening (All Randomized Patients)

Current/Active Medical Condition Preferred Term	Treatment Group: Placebo (N=407) n (%)	Treatment Group: SB 207499 15mg BID (N=418) n (%)
Total	406 (99.8)	417 (99.8)
Lung Disease, obstructive	406 (99.8)	417 (99.8)
Hypertension	171 (42.0)	164 (39.2)
Bronchitis, chronic	137 (33.7)	135 (32.3)
Rhinitis, allergic	85 (20.9)	106 (25.4)
Arthropathy	77 (18.9)	101 (24.2)
Headache	66 (16.2)	75 (17.9)
Cholest/Triglyceride, elevated	65 (16.0)	72 (17.2)
Esophagitis	52 (12.8)	65 (15.6)
Depression	58 (14.3)	63 (15.1)
Back Pain	45 (11.1)	56 (13.4)
Osteoarthrosis	55 (13.5)	51 (12.2)
Insomnia	35 (8.6)	49 (11.7)
Emphysema	51 (12.5)	49 (11.7)
Hyperlipemia	48 (11.8)	47 (11.2)
Alopecia	52 (12.8)	46 (11.0)
Anxiety	30 (7.4)	45 (10.8)
Genital Female Disorder, other	26 (16.7)[a]	42 (23.0)[a]
Visual Disturbance	51 (12.5)	41 (9.8)
Prostate Disorder	49 (19.5)[b]	40 (17.0)[b]

a. Percentages are based on n=156 females in the placebo treatment group and n=183 females in the SB 207499 treatment group.
b. Percentages are based on n=251 males in the placebo treatment group and n=235 males in the SB 207499 treatment group.

Data Source: Section 13, Table 13.13B; Appendix B, Listing 6.

The most common concurrent medical condition present at Screening was hypertension (42.0% and 39.2% in the placebo and SB 207499 treatment groups, respectively). [redacted]

6.6. Baseline Signs and Symptoms

Table 14 presents adverse events that were reported by ≥2% of randomized patients in either treatment group during the placebo run-in phase of the study. Individual patient information is provided in Appendix B, Listing 10.

Table 14 Summary of Most Common (≥2% of Patients in Either Treatment Group) Baseline Signs and Symptoms (All Randomized Patients)

Baseline Sign/Symptom (Preferred Term)	Treatment Group: Placebo (N=407) n (%)	Treatment Group: SB 207499 15mg BID (N=418) n (%)
Total[a]	195 (47.9)	194 (46.4)
Diarrhea	29 (7.1)	29 (6.9)
Headache	27 (6.6)	26 (6.2)
Chronic Obstructive Airways Disease	21 (5.2)	20 (4.8)
Abdominal Pain	19 (4.7)	19 (4.5)
Dyspnea	13 (3.2)	14 (3.3)
Nausea	7 (1.7)	14 (3.3)
Upper Respiratory Tract Infection	18 (4.4)	12 (2.9)
Dyspepsia	16 (3.9)	11 (2.6)
Coughing	10 (2.5)	11 (2.6)
Sinusitis	10 (2.5)	11 (2.6)
Injury	10 (2.5)	11 (2.6)
Dizziness	11 (2.7)	10 (2.4)
Flatulence	3 (0.7)	10 (2.4)
Rhinitis	9 (2.2)	9 (2.2)
Back Pain	6 (1.5)	9 (2.2)
Fatigue	11 (2.7)	9 (2.2)
Pharyngitis	8 (2.0)	8 (1.9)
Insomnia	10 (2.5)	6 (1.4)
Constipation	13 (3.2)	4 (1.0)

a. Total represents total number of patients reporting at least one sign/symptom.
Data Source: Section 13, Table 13.14; Appendix B, Listing 10.

In general, there were no marked differences between treatment groups in the incidence of signs and symptoms at baseline. Despite the relative high incidence of gastrointestinal signs and symptoms in this patient population, the differences between the two groups at baseline were comparable for the GI system, except that a greater percentage of SB 207499-treated patients reported nausea (3.3% SB 207499 vs. 1.7% placebo) and flatulence (2.4% SB 207499 vs. 0.7% placebo) at baseline compared to placebo. Also, a higher percentage of placebo-treated patients reported dyspepsia (3.9% placebo vs. 2.6% SB 207499) and constipation (3.2% placebo vs. 1.0% SB 207499) at baseline compared to the SB 207499 treatment group. Of note, chronic obstructive airways disease, dyspnea, and coughing were reported by similar percentages of patients in the placebo and SB 207499 treatment groups at baseline.

6.7. Prior and Concomitant Medications

6.7.1. Prior Medications

Prior medications used by ≥5% of randomized patients in either treatment group are presented in Table 15 and detailed by patient in Appendix B, Listing 7.

Table 15 Summary of Most Common (≥5% of Patients in Either Treatment Group) Prior Medications (All Randomized Patients)

	Treatment Group	
	Placebo (N=407)	SB 207499 15mg BID (N=418)
Prior Medication	n (%)	n (%)
Total[a]	406 (99.8)	418 (100.0)
Salbutamol	406 (99.8)	418 (100.0)
Ipratropium Bromide[b]	215 (52.8)	223 (53.3)
Acetylsalicylic Acid	140 (34.4)	126 (30.1)
Salmeterol Hydroxynaphthoate	83 (20.4)	96 (23.0)
Fluticasone Propionate	92 (22.6)	95 (22.7)
Vitamins, NOS	82 (20.1)	90 (21.5)
Paracetamol	83 (20.4)	84 (20.1)
Tocopherol	51 (12.5)	56 (13.4)
Estrogens Conjugated	39 (9.6)	48 (11.5)
Ibuprofen	34 (8.4)	48 (11.5)
Hydrochlorothiazide	49 (12.0)	43 (10.3)
Calcium	38 (9.3)	41 (9.8)
Ascorbic Acid	38 (9.3)	35 (8.4)
Atorvastatin Calcium	31 (7.6)	32 (7.7)
Levothyroxine Sodium	27 (6.6)	32 (7.7)
Amlodipine	16 (3.9)	31 (7.4)
Simvastatin	34 (8.4)	30 (7.2)
Lisinopril	30 (7.4)	29 (6.9)
Guaifenesin	24 (5.9)	27 (6.5)
Loratadine	21 (5.2)	27 (6.5)
Calcium Carbonate	19 (4.7)	24 (5.7)
Minerals, NOS	21 (5.2)	24 (5.7)
Omeprazole	19 (4.7)	23 (5.5)
Theophylline	25 (6.1)	23 (5.5)
Furosemide	24 (5.9)	14 (3.3)
Digoxin	21 (5.2)	11 (2.6)

a. Total represents total number of patients receiving prior medication.
b. Includes prior medications listed as Ipratropium Bromide and Ipratropium Hydroxide.
Data Source: Section 13, Table 13.15A; Appendix B, Listing 7

In general, there were no marked differences between the treatment groups in the receipt of prior medication. The most frequently reported prior medications in both groups were salbutamol (99.8% of patients randomized to placebo vs. 100.0% of patients randomized to SB 207499) and ipratropium bromide (including prior medications listed as ipratropium bromide and ipratropium hydroxide) (52.8% of patients randomized to placebo vs. 53.3% of patients randomized to SB 207499). A similar percentage of patients randomized to placebo and SB 207499 had previously used inhalation (29.2% vs. 28.0%, respectively) as well as systemic steroids (2.7% vs. 2.4%, respectively) (Section 13, Table 13.7C and Table 13.7D). Similar percentages of patients in both treatment groups had previously used the following corticosteroids: fluticasone propionate, triamcinolone acetonide, beclomethasone dipropionate, and budesonide (Section 13, Table 13.15A).

6.7.2. Concomitant Medications

Medications most commonly used by ≥5% of randomized patients in any treatment group following the initial dose of double-blind medication are presented in Table 16 and detailed by patient in Appendix B, Listing 8A. Medications taken for COPD exacerbations are included in this data and are also discussed separately in Section 6.7.3. Concomitant medications include prior medications continued after first dose of double-blind study medication. During the study, albuterol/salbutamol was supplied to all patients for use as rescue medication.

Post-therapy medications are summarized in Section 13, Table 13.15C (Appendix B, Listing 8C).

Table 16 Summary of Most Common (≥5% of Patients in Either Treatment Group) Concomitant Medications (All Randomized Patients)

	Treatment Group	
	Placebo (N=407)	SB 207499 15mg BID (N=418)
Concomitant Medication	n (%)	n (%)
Total[a]	407 (100.0)	418 (100.0)
Salbutamol	407 (100.0)	417 (99.8)
Acetylsalicylic Acid	148 (36.4)	140 (33.5)
Ipratropium Bromide	125 (30.7)	137 (32.8)
Paracetamol	117 (28.7)	113 (27.0)
Vitamins, NOS	83 (20.4)	88 (21.1)
Ibuprofen	52 (12.8)	63 (15.1)
Tocopherol	51 (12.5)	59 (14.1)
Guaifenesin	56 (13.8)	52 (12.4)
Estrogens Conjugated	41 (10.1)	49 (11.7)
Hydrochlorothiazide	55 (13.5)	45 (10.8)
Prednisone	42 (10.3)	44 (10.5)
Calcium	39 (9.6)	42 (10.0)
Ascorbic Acid	38 (9.3)	38 (9.1)
Atorvastatin Calcium	32 (7.9)	35 (8.4)
Loratadine	26 (6.4)	34 (8.1)
Amlodipine	18 (4.4)	33 (7.9)
Simvastatin	33 (8.1)	33 (7.9)
Levothyroxine Sodium	27 (6.6)	32 (7.7)
Calcium Carbonate	23 (5.7)	31 (7.4)
Lisinopril	38 (9.3)	31 (7.4)
Azithromycin	35 (8.6)	30 (7.2)
Pseudoephedrine Hydrochloride	38 (9.3)	29 (6.9)
Lansoprazole	15 (3.7)	28 (6.7)
Fluticasone Propionate	28 (6.9)	27 (6.5)
Levofloxacin	24 (5.9)	26 (6.2)
Celecoxib	18 (4.4)	25 (6.0)
Diphenhydramine Hydrochloride	29 (7.1)	25 (6.0)
Minerals, NOS	22 (5.4)	25 (6.0)
Omeprazole	19 (4.7)	22 (5.3)
Influenza Virus Vaccine Polyvalent	20 (4.9)	21 (5.0)
Ranitidine	7 (1.7)	21 (5.0)
Fexofenadine Hydrochloride	21 (5.2)	19 (4.5)
Hydrocodone Bitartrate	24 (5.9)	19 (4.5)
Amfebutamone Hydrochloride	22 (5.4)	17 (4.1)
Dextromethorphan Hydrobromide	30 (7.4)	17 (4.1)
Atenolol	21 (5.2)	16 (3.8)
Furosemide	26 (6.4)	16 (3.8)

a. Total represents total number of patients receiving concomitant medication.
Data Source: Section 13, Table 13.15B; Appendix B, Listing 8A.

Overall, there were no marked differences between the treatment groups in the use of concomitant medications except that SB 207499-treated patients generally used medications for the gastrointestinal system more frequently compared to patients who

received placebo. The most frequently received concomitant medications in both groups were salbutamol (100.0% placebo vs. 99.8% SB 207499) and acetylsalicylic acid (36.4% placebo vs. 33.5% SB 207499).

6.7.3. Medications for COPD Exacerbations

Medications most commonly used by ≥2% of randomized patients for COPD exacerbations during the double-blind treatment period are presented in Table 17 and detailed by patient in Appendix B, Listing 8B.

Table 17 Summary of Most Common (≥2% of Patients in Either Treatment Group) Medications for Treatment of COPD Exacerbations During Double-blind Treatment (All Randomized Patients)

	Treatment Group	
COPD Medication	Placebo (N=407) n (%)	SB 207499 15mg BID (N=418) n (%)
Total[a]	92 (22.6)	93 (22.2)
Prednisone	34 (8.4)	37 (8.9)
Salbutamol[b]	35 (8.6)	34 (8.1)
Azithromycin	22 (5.4)	22 (5.3)
Levofloxacin	14 (3.4)	15 (3.6)
Amoxicillin Trihydrate	3 (0.7)	9 (2.2)
Guaifenesin	11 (2.7)	8 (1.9)
Ipratropium Bromide	8 (2.0)	7 (1.7)
Clarithromycin	8 (2.0)	4 (1.0)

a. Total represents total number of patients receiving medication for COPD exacerbations.
b. Increased Salbutamol use for COPD exacerbations only.
Data Source: Section 13, Table 13.15D; Appendix B, Listing 8B.

The percentage of patients receiving medication for COPD exacerbation was similar in both groups (22.6% placebo vs. 22.2% SB 207499). The most frequently administered medications were prednisone, salbutamol, and azithromycin (Appendix B, Listing 8B).

6.8. Treatment Compliance

As stipulated in the protocol, patients were to be withdrawn from the study if study medication compliance at 2 consecutive visits during the double-blind period was <80% or >120%. Table 18 presents overall compliance for all randomized patients, and Appendix B, Listing 11 details study medication compliance by individual patient.

Table 18 Overall Compliance With Double-blind Medication (All Randomized Patients)

Compliance %[a]	Treatment Group: Placebo (N=407) n (%)	Treatment Group: SB 207499 15mg BID (N=418) n (%)
<80	19 (4.7)	41 (10.0)
80 – 120	382 (95.3)	369 (89.6)
>120	0	2 (0.5)
N	401	412
Mean (SD)	95.34 (9.38)	93.60 (24.50)
Min, Max	30.00, 114.29	3.85, 500.00

a. Percentages are calculated using the number evaluated for each group.
Data Source: Section 13, Table 13.16A and Table 13.16B; Appendix B, Listing 11.

Overall, a higher proportion of patients with 80-120% compliance was observed in the placebo treatment group compared to the SB 207499 treatment group (95.3% vs. 89.6%). This difference is due to a greater percentage of patients in the SB 207499 treatment group demonstrating lower (<80%) compliance vs. the placebo treatment group. However, at each week during double-blind treatment the mean compliance was at least 96.6% in the placebo treatment group and 95.4% in the SB 207499 treatment group (Section 13, Table 13.16B).

7. EFFICACY RESULTS

7.1. Efficacy Evaluation

7.1.1. Data Sets Analyzed

All efficacy measures were analyzed for the intent-to-treat (ITT) population, defined as all patients who received randomized study medication, had a baseline evaluation, and had at least one on-therapy efficacy assessment during the double-blind period. For time-to-event endpoints (e.g., COPD exacerbations) the ITT population was defined as all patients who received a dose of randomized study medication. The per-protocol (PP) population was defined as all patients in the intent-to-treat population who did not significantly violate the protocol, see Section 5.13.5.

Week by week analysis included all ITT patients (regardless of whether patient withdrawals coincided with a scheduled visit or not); whereas, the 24 week average analysis only included patients who had at least one dose of randomized study medication and who had both a baseline and at least one scheduled on-therapy assessment.

The results of all analyses in the ITT population are discussed in the following sections. Results of analyses in the per-protocol population were generally similar to the ITT population.

7.2. Primary Efficacy Parameters

The primary measures of efficacy were the change from baseline in trough pre-bronchodilator FEV_1 and the change from baseline in total score of the SGRQ, each averaged over 24 weeks.

7.2.1. Trough FEV_1 (L)

A summary of the mean change from baseline in trough FEV_1 averaged over 24 weeks of treatment is presented in Table 19 and graphically in Section 19, Figure 19.1B.

Table 19 Change From Baseline in Trough FEV_1 (L) Averaged Over 24 Weeks (Repeated Measures Analysis) - ITT

		Change from Baseline				Comparison with Placebo			
Treatment Group	n	Mean[a]	SEM	Lower 95% CI	Upper 95% CI	Mean Difference	Lower 95% CI	Upper 95% CI	P-value
Placebo	377	-0.02	0.01	-0.03	-0.00	-	-	-	-
SB 207499[b]	364	0.01	0.01	-0.01	0.02	0.02	0.00	0.04	0.024[c]

a. Mean values are adjusted for center and week.
b. The dosage of SB 207499 is 15mg BID.
c. Significantly different from placebo.
Data Source: Section 14, Table 14.1A; Appendix C, Listing 1.

When averaged over 24 weeks, there was a 10mL mean increase over baseline in trough FEV_1 in the SB 207499 treatment group and a 20mL mean decrease from baseline in the placebo treatment group. There was a statistically significant ($p = 0.024$) difference of 20mL in mean change from baseline in trough FEV_1 between the two treatment groups.

When the data for change from baseline in FEV_1 averaged over 24 weeks was carried to three decimal places, the difference for the SB 207499 treatment group over placebo was 24mL (7mL mean increase and 17mL mean decrease over baseline in trough FEV_1 in the SB 207499 and placebo treatment group, respectively), Section 14, Table 14.1P.

Table 20 presents the mean change from baseline in trough FEV_1 at Weeks 2, 4, 8, 12, 16, 20, 24, and at endpoint. Descriptive statistics for change from baseline in trough FEV_1 are presented in Section 14, Table 14.1C, while summary statistics for the percent change from baseline are presented in Section 14, Table 14.1H. Data are provided by individual patient in Appendix C, Listing 1.

Table 20 Mean Change From Baseline in Trough FEV_1 (L) – ITT

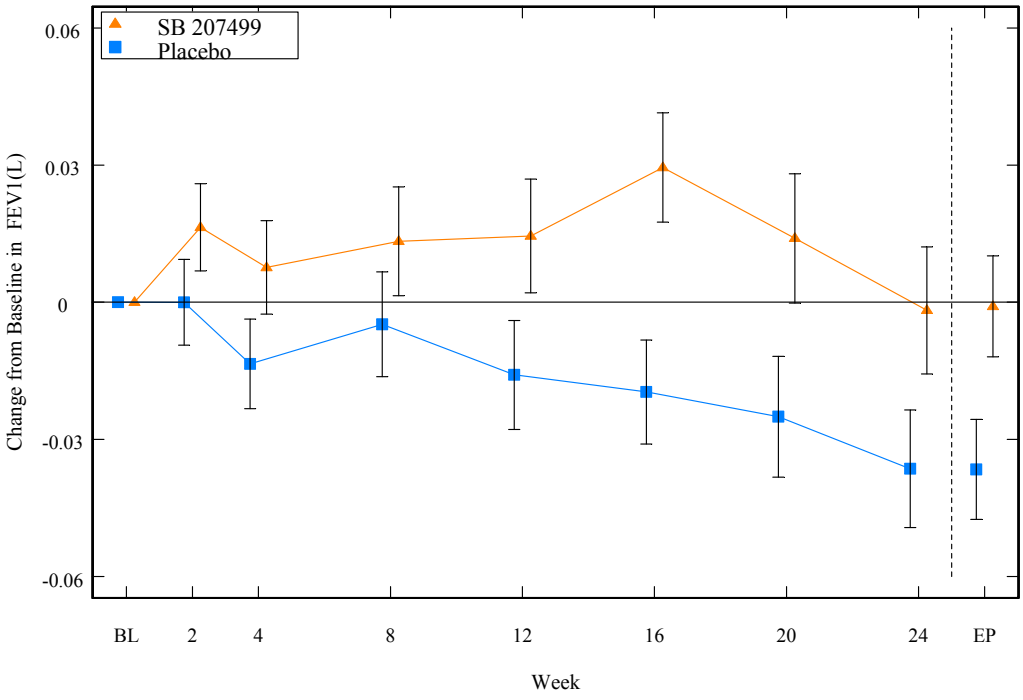
Week of Double-Blind Treatment.	Treatment Group	n	Assessment		Change from Baseline				Comparison with Placebo			
			Mean[a]	SEM	Mean[a]	SEM	Lower 95% CI	Upper 95% CI	Mean Difference	Lower 95% CI	Upper 95% CI	P-value
Baseline	Placebo	383	1.39	0.03	-	-	-	-	-	-	-	-
	SB 207499[b]	377	1.35	0.03	-	-	-	-	-	-	-	-
Week 2	Placebo	373	1.38	0.03	-0.00	0.01	-0.02	0.02	-	-	-	-
	SB 207499	361	1.37	0.03	0.02	0.01	-0.00	0.04	0.02	-0.01	0.04	0.174
Week 4	Placebo	365	1.37	0.03	-0.01	0.01	-0.03	0.01	-	-	-	-
	SB 207499	338	1.37	0.03	0.01	0.01	-0.01	0.03	0.02	-0.00	0.05	0.103
Week 8	Placebo	351	1.37	0.03	-0.00	0.01	-0.03	0.02	-	-	-	-
	SB 207499	319	1.37	0.03	0.01	0.01	-0.01	0.04	0.02	-0.01	0.05	0.219
Week 12	Placebo	332	1.37	0.03	-0.02	0.01	-0.04	0.01	-	-	-	-
	SB 207499	302	1.37	0.03	0.01	0.01	-0.01	0.04	0.03	-0.00	0.06	0.052
Week 16	Placebo	317	1.37	0.03	-0.02	0.01	-0.04	0.00	-	-	-	-
	SB 207499	292	1.39	0.03	0.03	0.01	0.01	0.05	0.05	0.02	0.08	0.001[c]
Week 20	Placebo	315	1.36	0.03	-0.03	0.01	-0.05	0.00	-	-	-	-
	SB 207499	278	1.38	0.04	0.01	0.01	-0.01	0.04	0.04	0.00	0.07	0.028[c]
Week 24	Placebo	311	1.35	0.03	-0.04	0.01	-0.06	-0.01	-	-	-	-
	SB 207499	273	1.37	0.04	-0.00	0.01	-0.03	0.03	0.03	0.00	0.07	0.047[c]
Endpoint	Placebo	383	1.35	0.03	-0.04	0.01	-0.06	-0.02	-	-	-	-
	SB 207499	377	1.35	0.03	-0.00	0.01	-0.02	0.02	0.04	0.01	0.06	0.013[c]

a. Mean values are adjusted for center.
b. The dosage of SB 207499 is 15mg BID.
c. Significantly different from placebo.
Data Source: Section 14, Table 14.1B; Appendix C, Listing 1.

The SB 207499 treatment group showed an increase over baseline in trough FEV_1 from Week 2 through Week 20, ranging from 10mL to 30mL, while the placebo treatment group showed a decrease or no change from baseline in trough FEV_1 at these time points. At Week 16 through Week 24, there were statistically significant mean differences of 30mL to 50mL in the change from baseline in trough FEV_1 between the SB 207499 and placebo treatment groups ($p = 0.047$ to 0.001). At endpoint, there was a statistically significant difference in the change from baseline in trough FEV_1 of 40mL between the SB 207499 and placebo treatment groups, with the placebo treatment group decreasing by 40mL and the SB 207499 treatment group showing no change from baseline ($p = 0.013$). When averaged over Week 16 through Week 24, there was a statistically significant mean difference from placebo in trough FEV_1 of 40mL ($p = 0.002$), thereby confirming the larger treatment differences observed at the later time points (Appendix I, Listing 11B).

The mean change from baseline in FEV_1 over time is presented graphically in Figure 2, and the distribution of change from baseline at endpoint for the placebo and SB 207499 treatment groups is presented in Section 19, Figure 19.1D and Figure 19.1E, respectively. The change from baseline in trough FEV_1 versus the change from baseline in total score of the SGRQ is presented in Section 19, Figure 19.1C. A summary of mean change from baseline in FEV_1 over time is presented by center, time and treatment-by-time interaction in Appendix I, Listing 11A.

Figure 2 Mean (SEM) Change from Baseline in Trough FEV_1 - ITT



EP = Endpoint
Data Source: Section 19, Figure 19.1A.

Descriptive statistics for trough FEV_1 at endpoint by center (Table 14.1I), sex (Table 14.1J), COPD severity (using ATS criteria) (Table 14.1K), race (Table 14.1L), and

smoking status (Table 14.1M) are presented in Section 14. A significant treatment-by-center interaction was observed (p = 0.0719; significance level of 0.1) (Section 14, Table 14.1N). A large number of sites were used (127) to randomize the 825 patients, and enrollment was well balanced between the treatment groups. There were no individual sites with a large enrollment, and many sites only had a few patients. Centers with small numbers of patients had a large variability, which might explain the interaction observed in this study (Section 14, Table 14.1I). Many of the sites that participated in this study also contributed to the Phase III pivotal study 039. Analysis of FEV_1 by study sites showed that there was no difference in the mean FEV_1 change from baseline (averaged over 24 weeks) between SB 207499- and placebo-treated patients who were assessed at study sites that also participated in Study 039 (20mL, p = 0.063) and those assessed at sites that did not (20mL, p = 0.281) (Appendix I, Listing 16).

Smoking status was a significant covariate for FEV_1 (p = 0.0034). Both current smokers and previous smokers treated with SB 207499 had better mean change from baseline FEV_1 values compared to patients treated with placebo, but current smokers improved more than previous smokers (Section 14, Table 14.1M). The mean FEV_1 change from baseline for current smokers improved to 10mL compared to a reduction in placebo patients (-50mL), and previous smokers had small reduction in FEV_1 of -20mL compared to a larger reduction in placebo patients (-50mL). Age, sex, and percent-predicted FEV_1 were not significant covariates for FEV_1 (Section 14, Table 14.1O). Enrollment was reopened after assessment that the number of completed patients specified in the protocol would not be achieved. Descriptive statistics for change from baseline in FEV_1 are provided for patients who enrolled before and after Amendment #3 in Section 14, Table 14.1T. The majority of patients enrolled before the amendment and the difference in FEV_1 between the two treatment groups was consistent with the overall result. However, the mean change from baseline for FEV_1 was higher for SB 207499-treated (-10mL) compared to placebo-treated (-90mL) patients who enrolled after the amendment.

Results in the PP analysis were similar to those of the ITT analysis. When averaged over 24 weeks, the difference in trough FEV_1 between the SB 207499 and placebo treatment groups was 20mL with the placebo treatment group showing a mean decrease of 20mL and the SB 207499 treatment group showing no change in FEV_1 (p = 0.083) (Section 14, Table 14A.1A, Table 14A.1B and Table 14A.1C; Section 19, Figure 19A.1A and Figure 19A.1B).

Analyses of the FEV_1 of patients who completed the study and patients who withdrew from the study are presented in Appendix I, Listing 4, Listing 12A, Listing 12B and Listing 15A. Effects on FEV_1 of missing values due to withdrawal were assessed by analyzing only the completed patients and by imputing the missing values with the worst value. The results were comparable to the ITT analysis. Treatment by drop effect was also assessed and it was not significant. These two sensitivity analyses confirm the robustness of the results.

Additional analyses conducted for FEV_1 are presented in Appendix I, Listing 1A, Listing 1B, Listing 1C, Listing 6A, Listing 7A, Listing 7C, Listing 8A, Listing 9A, and Listing 18.

7.2.2. SGRQ

The average change from baseline in total score of the SGRQ over 24 weeks of treatment is presented in Table 21 and graphically in Section 19, Figure 19.2B.

Table 21 Change From Baseline in SGRQ (Total Score) Averaged Over 24 Weeks (Repeated Measures Analysis) - ITT

		Change from Baseline				Comparison with Placebo			
Treatment Group	n	Mean[a]	SEM	Lower 95% CI	Upper 95% CI	Mean Difference	Lower 95% CI	Upper 95% CI	P-value
Placebo	337	-1.3	0.6	-2.5	-0.1	-	-	-	-
SB 207499[b]	304	-3.2	0.6	-4.5	-2.0	-1.9	-3.5	-0.3	0.017[c]

a. Mean values are adjusted for center and week.
b. The dosage of SB 207499 is 15mg BID.
c. Significantly different from placebo.
Data Source: Section 14, Table 14.2A; Appendix C, Listing 2.

When averaged over 24 weeks, there was an improvement of 3.2 points in the mean total score of the SGRQ in the SB 207499 treatment group (relative to a mean baseline SGRQ score of 43.8) and only 1.3 points in the placebo treatment group (relative to a mean baseline SGRQ score of 43.5). There was a significantly greater improvement (1.9 points; $p = 0.017$) in the mean change from baseline in total score of the SGRQ in patients who received SB 207499 compared to patients who received placebo.

Table 22 shows the mean change from baseline in total score of the SGRQ at Weeks 12 and 24, and at endpoint. Descriptive statistics for change from baseline in total score of the SGRQ are presented in Section 14, Table 14.2C. Data are provided by individual patient in Appendix C, Listing 2.

Table 22 Mean Change from Baseline in SGRQ (Total Score) - ITT

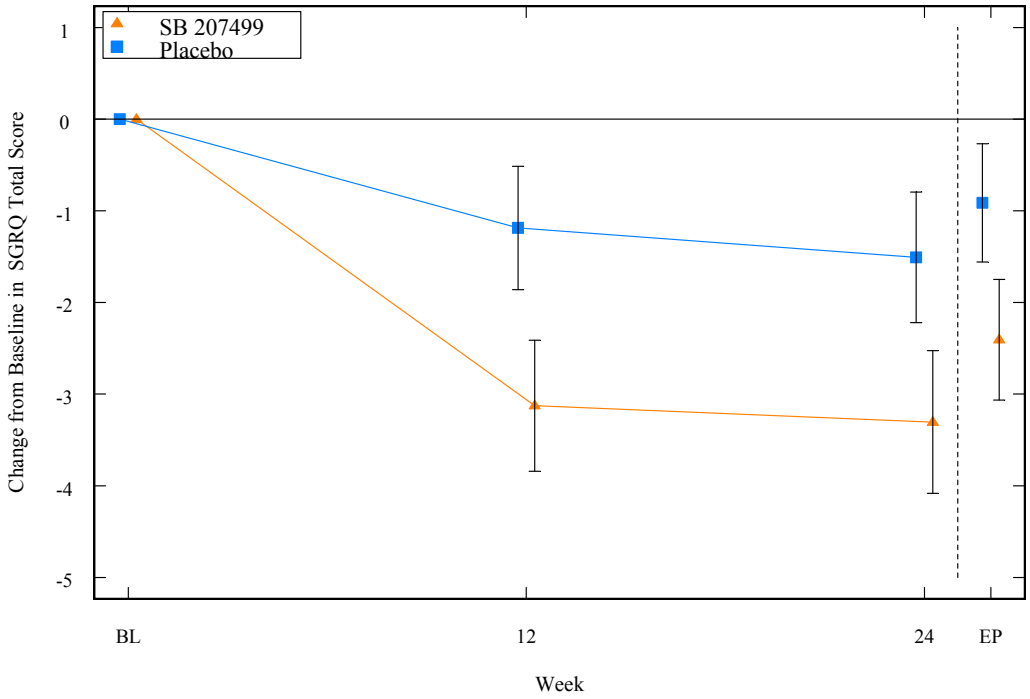
Week of Double-Blind Treatment.	Treatment Group	N	Assessment		Change from Baseline				Comparison with Placebo			
			Mean[a]	SEM	Mean[a]	SEM	Lower 95% CI	Upper 95% CI	Mean Difference	Lower 95% CI	Upper 95% CI	P-value
Baseline	Placebo	369	43.5	0.9	-	-	-	-	-	-	-	-
	SB 207499[b]	359	43.8	0.9	-	-	-	-	-	-	-	-
Week 12	Placebo	335	42.0	1.0	-1.2	0.7	-2.5	0.1	-	-	-	-
	SB 207499	294	41.5	1.1	-3.1	0.7	-4.5	-1.7	-1.9	-3.7	-0.2	0.029[c]
Week 24	Placebo	304	40.7	1.1	-1.5	0.7	-2.9	-0.1	-	-	-	-
	SB 207499	264	40.6	1.2	-3.3	0.8	-4.8	-1.8	-1.8	-3.7	0.1	0.064
Endpoint	Placebo	369	42.6	1.0	-0.9	0.6	-2.2	0.4	-	-	-	-
	SB 207499	359	41.4	1.0	-2.4	0.7	-3.7	-1.1	-1.5	-3.2	0.2	0.077

a. Mean values are adjusted for center.
b. The dosage of SB 207499 is 15mg BID.
c. Significantly different from placebo.
Data Source: Section 14, Table 14.2B; Appendix C, Listing 2

In the SB 207499 treatment group, there was an improvement in the mean SGRQ from baseline at Weeks 12, 24, and endpoint by 3.1, 3.3, and 2.4 points, respectively. In the placebo treatment group, the mean SGRQ showed a smaller decrease from baseline of 1.2, 1.5, and 0.9 points at Weeks 12, 24, and at endpoint, respectively. At Week 12, there was a statistically significant mean difference of 1.9 points in the change from baseline in total score of the SGRQ in the SB 207499 treatment group compared to the placebo treatment group ($p = 0.029$).

The mean change from baseline over time is presented graphically in Figure 3, and the distribution of change from baseline at endpoint for the placebo and SB 207499 treatment groups are presented in Section 19, Figure 19.2D and Figure 19.2E, respectively.

Figure 3 Mean (SEM) Change From Baseline in Total Score of the SGRQ – ITT



EP = Endpoint
Data Source: Section 19, Figure 19.2A.

Descriptive statistics for the total score of the SGRQ at endpoint by center (Table 14.2I), sex (Table 14.2J), COPD severity (ATS criteria) (Table 14.2K), race (Table 14.2L), and smoking status (Table 14.2M) are presented in Section 14. The results of the subgroup analyses were similar to the analyses for all patients, except for COPD severity. An improvement in the mean change from baseline for total score of the SGRQ (2.9 points) was observed in SB 207499-treated patients with severe COPD. A deterioration of 3.2 points was observed for placebo-treated patients with severe COPD. This difference of 6.1 points between the treatment groups represents a clinically important change. Among moderate COPD patients, there was also an improvement in the mean change from baseline in the total score of the SGRQ for SB 207499-treated (2.5 points) versus a slight improvement in placebo-treated patients (0.9 points).

There were no significant treatment-by-time or center interactions for the total score of the SGRQ (Section 14, Table 14.2N and Appendix I, Listing 17). Sex, age, % predicted FEV_1, and smoking status were not significant covariates for the total score of the SGRQ (Section 14, Table 14.2O).

Results of the PP analysis were similar to the ITT analysis. When averaged over 24 weeks, there was a mean difference of 1.6 points ($p = 0.048$) in the change from baseline in the total score of the SGRQ for per-protocol SB 207499-treated patients compared to patients who received placebo (Section 14, Table 14A.2A, Table 14A.2B, and Table 14A.2C; Section 19, Figure 19A.2A and Figure 19A.2B).

Analyses of the total score of the SGRQ of patients who completed the study and patients who withdrew from the study are presented in Appendix I, Listing 4, Listing 13A, Listing 13B, and Listing 15B. The analyses performed to assess the impact of withdrawals on SGRQ suggest that patients in both treatment groups who were withdrawn had a comparable response relative to those who completed. The total score of the SGRQ for the whole population was comparable to the completers-only sub-group for both SB 207499 and placebo treatment groups. The results of the analysis of the data when the worst SGRQ was imputed for the withdrawn patients were comparable to those for the ITT population as a whole.

Additional analyses conducted for the total score of the SGRQ are presented in Appendix I, Listing 2A, Listing 2B, Listing 2C, Listing 6B, Listing 7B, Listing 7D, Listing 8B, Listing 9B, and Listing 19.

7.3. Secondary Efficacy Parameters

7.3.1. Pulmonary Function Tests – Clinic Trough FVC

The mean change from baseline in clinic trough FVC averaged over 24 weeks of treatment is presented in Table 23 and graphically in Section 19, Figure 19.5B

Table 23 Change From Baseline in Clinic Trough FVC (L) Averaged Over 24 Weeks (Repeated Measures Analysis) - ITT

		Change from Baseline				Comparison with Placebo			
Treatment Group	n	Mean[a]	SEM	Lower 95% CI	Upper 95% CI	Mean Difference	Lower 95% CI	Upper 95% CI	P-value
Placebo	377	-0.02	0.01	-0.05	0.01	-	-	-	-
SB 207499[b]	364	0.00	0.01	-0.03	0.03	0.02	-0.02	0.06	0.254

a. Mean values are adjusted for center and week.
b. The dosage of SB 207499 is 15mg BID.
Data Source: Section 14, Table 14.5A; Appendix C, Listing 1.

When averaged over 24 weeks, there was no change in mean clinic trough FVC in the SB 207499 treatment group and a 20mL decrease in the placebo treatment group,

resulting in a mean difference in the trough FVC of 20mL between the two treatment groups (p = 0.254).

Table 24 presents the mean change from baseline in trough FVC at Weeks 2, 4, 8, 12, 16, 20, 24 and at endpoint. Descriptive statistics for change from baseline in FVC are presented in Section 14, Table 14.5C. Summary statistics for the percent change from baseline are presented in Section 14, Table 14.5H. Data are provided by individual patient in Appendix C, Listing 1.

Table 24 Mean Change From Baseline in Clinic Trough FVC (L) - ITT

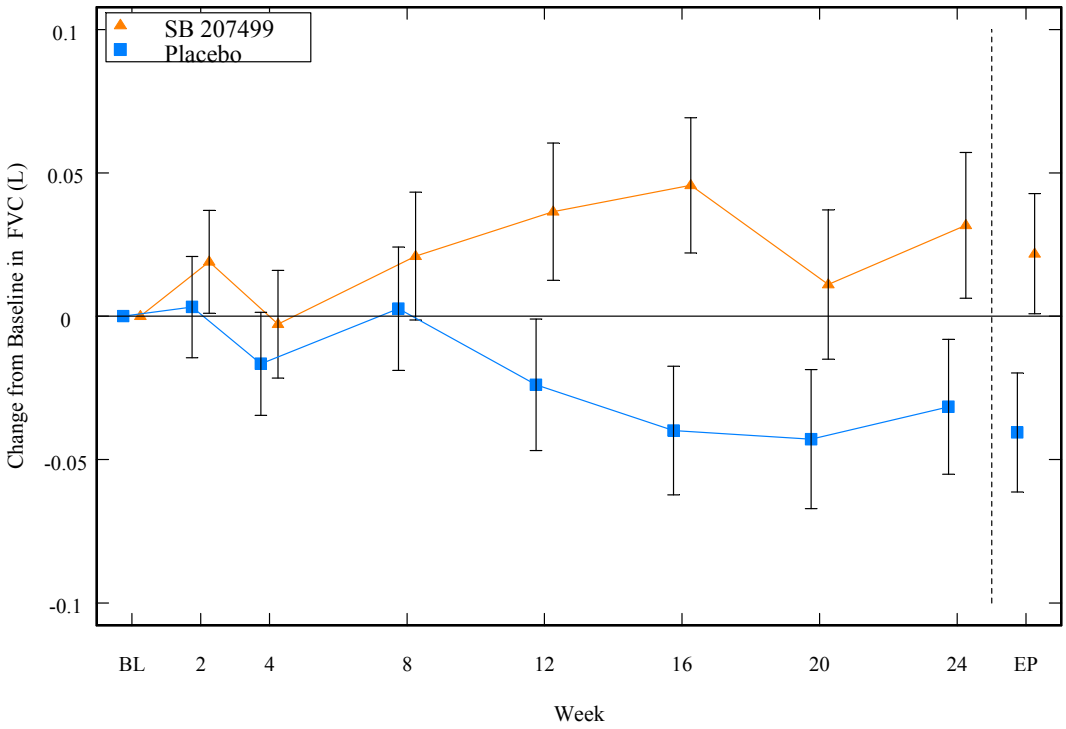
Week of Double-Blind Treatment.	Treatment Group	n	Assessment		Change from Baseline				Comparison with Placebo			
			Mean[a]	SEM	Mean[a]	SEM	Lower 95% CI	Upper 95% CI	Mean Difference	Lower 95% CI	Upper 95% CI	P-value
Baseline	Placebo	383	2.75	0.05								
	SB 207499[b]	377	2.69	0.05								
Week 2	Placebo	373	2.74	0.05	0.00	0.02	-0.03	0.04	-	-	-	-
	SB 207499	361	2.72	0.05	0.02	0.02	-0.02	0.05	0.02	-0.03	0.06	0.487
Week 4	Placebo	365	2.74	0.05	-0.02	0.02	-0.05	0.02	-	-	-	-
	SB 207499	338	2.71	0.05	-0.00	0.02	-0.04	0.03	0.01	-0.03	0.06	0.559
Week 8	Placebo	351	2.74	0.05	0.00	0.02	-0.04	0.04	-	-	-	-
	SB 207499	319	2.72	0.05	0.02	0.02	-0.02	0.06	0.02	-0.04	0.07	0.508
Week 12	Placebo	332	2.72	0.05	-0.02	0.02	-0.07	0.02	-	-	-	-
	SB 207499	302	2.76	0.05	0.04	0.02	-0.01	0.08	0.06	0.00	0.12	0.045[c]
Week 16	Placebo	317	2.72	0.05	-0.04	0.02	-0.08	0.00	-	-	-	-
	SB 207499	292	2.76	0.05	0.05	0.02	-0.00	0.09	0.09	0.03	0.14	0.004[c]
Week 20	Placebo	315	2.71	0.05	-0.04	0.02	-0.09	0.00	-	-	-	-
	SB 207499	278	2.74	0.06	0.01	0.03	-0.04	0.06	0.05	-0.01	0.12	0.099
Week 24	Placebo	311	2.72	0.05	-0.03	0.02	-0.08	0.01	-	-	-	-
	SB 207499	273	2.76	0.06	0.03	0.03	-0.02	0.08	0.06	0.00	0.13	0.047[c]
Endpoint	Placebo	383	2.71	0.05	-0.04	0.02	-0.08	0.00	-	-	-	-
	SB 207499	377	2.71	0.05	0.02	0.02	-0.02	0.06	0.06	0.01	0.12	0.022[c]

a. Mean values are adjusted for center.
b. The dosage of SB 207499 is 15mg BID.
c. Significantly different from placebo.
Data source: Section 14, Table 14.5B; Appendix C, Listing 1.

The SB 207499 treatment group showed an increase over baseline in trough FVC from Week 8 through Week 24 and at endpoint, ranging from 10mL to 50mL, while the placebo treatment group showed a decrease or no change from baseline in trough FVC at these time points. At Weeks 12, 16, and 24, there were mean differences of 60mL to 90mL in the change from baseline in trough FVC between the SB 207499 and placebo treatment groups (p = 0.045, 0.004, and 0.047, respectively). At endpoint, there was a difference in the change from baseline in trough FVC of 60mL between the SB 207499 and placebo treatment groups, with the placebo treatment group decreasing by 40mL and the SB 207499 treatment group increasing by 20mL (p = 0.022).

The change from baseline in trough FVC over time is presented schematically in Figure 4.

Figure 4 Mean (SEM) Change From Baseline in Trough FVC – ITT



EP = Endpoint
Data Source: Section 19, Figure 19.5A

Results of the PP analysis were similar to those of the ITT analysis (Section 14, Table 14A.5A, Table 14A.5B, Table 14A.5C, Table 14A.5D, Table 14A.5E, Table 14A.5F, and Table 14A.5G; Section 19, Figure 19A.5A and Figure 19A.5B).

7.3.2. Post-Exercise Breathlessness

The change from baseline in post-exercise breathlessness (post-exercise dyspnea) averaged over 24 weeks of double-blind treatment is presented in Table 25 and graphically in Section 19, Figure 19.3B. Post-exercise breathlessness was determined

using the modified Borg scale (see Section 5.8.4.3). Summary and descriptive statistics for post-exercise heart rate are listed in Section 14, Table 14.37B and Table 14.37C.

Table 25 Change From Baseline in Post-exercise Dyspnea Averaged Over 24 Weeks (Repeated Measures Analysis) - ITT

Treatment Group	n	Change from Baseline				Comparison with Placebo			
		Mean[a]	SEM	Lower 95% CI	Upper 95% CI	Mean Difference	Lower 95% CI	Upper 95% CI	P-value
Placebo	362	0.05	0.06	-0.07	0.17	-	-	-	-
SB 207499[b]	334	-0.10	0.06	-0.22	0.02	-0.15	-0.31	0.01	0.070

a. Mean values are adjusted for center and week.
b. The dosage of SB 207499 is 15mg BID.
Data Source: Section 14, Table 14.3A; Appendix C, Listing 3.

When averaged over 24 weeks, there was a decrease in the mean post-exercise breathlessness in the SB 207499 treatment group (0.10 points) and an increase in the placebo treatment group (0.05 points). There was a mean difference of 0.15 points in the change from baseline in post-exercise breathlessness in patients who received SB 207499 compared to patients who received placebo ($p = 0.070$).

Table 26 shows the mean change from baseline in post-exercise breathlessness by week of double-blind treatment and at endpoint. Descriptive statistics for change from baseline in post-exercise breathlessness are presented in Section 14, Table 14.3C. Data are provided by individual patient in Appendix C, Listing 3.

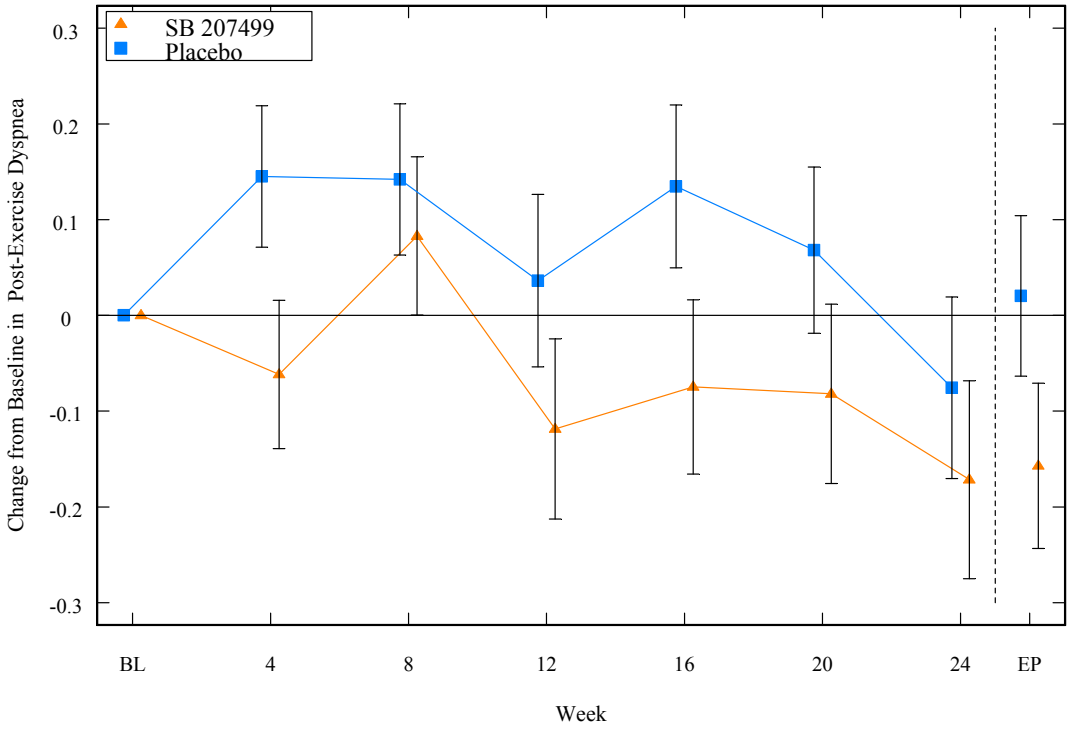
Table 26 Mean Change From Baseline in Post-Exercise Dyspnea - ITT

Week of Double-Blind Treatment.	Treatment Group	n	Assessment		Change from Baseline				Comparison with Placebo			
			Mean[a]	SEM	Mean[a]	SEM	Lower 95% CI	Upper 95% CI	Mean Difference	Lower 95% CI	Upper 95% CI	P-value
Baseline	Placebo	369	3.22	0.08	-	-	-	-	-	-	-	-
	SB 207499[b]	347	3.37	0.08	-	-	-	-	-	-	-	-
Week 4	Placebo	359	3.36	0.09	0.15	0.07	-0.00	0.29	-	-	-	-
	SB 207499	329	3.26	0.09	-0.06	0.08	-0.21	0.09	-0.21	-0.40	-0.02	0.033[c]
Week 8	Placebo	338	3.34	0.09	0.14	0.08	-0.01	0.30	-	-	-	-
	SB 207499	309	3.43	0.10	0.08	0.08	-0.08	0.25	-0.06	-0.26	0.14	0.564
Week 12	Placebo	321	3.26	0.10	0.04	0.09	-0.14	0.21	-	-	-	-
	SB 207499	290	3.21	0.10	-0.12	0.09	-0.30	0.07	-0.15	-0.38	0.07	0.185
Week 16	Placebo	307	3.33	0.10	0.13	0.09	-0.03	0.30	-	-	-	-
	SB 207499	279	3.28	0.10	-0.07	0.09	-0.25	0.10	-0.21	-0.43	0.01	0.066
Week 20	Placebo	306	3.24	0.10	0.07	0.09	-0.10	0.24	-	-	-	-
	SB 207499	271	3.26	0.11	-0.08	0.09	-0.27	0.10	-0.15	-0.38	0.08	0.195
Week 24	Placebo	302	3.08	0.10	-0.08	0.10	-0.26	0.11	-	-	-	-
	SB 207499	264	3.19	0.10	-0.17	0.10	-0.37	0.03	-0.10	-0.35	0.16	0.454
Endpoint	Placebo	369	3.24	0.09	0.02	0.08	-0.14	0.18	-	-	-	-
	SB 207499	347	3.21	0.09	-0.16	0.09	-0.33	0.01	-0.18	-0.39	0.04	0.106

a. Mean values are adjusted for center.
b. The dosage of SB 207499 is 15mg BID.
c. Significantly different from placebo.
Data Source: Section 14, Table 14.3B; Appendix C, Listing 3.

Overall, there were small differences in the mean change from baseline in post-exercise breathlessness for the SB 207499 treatment group compared to placebo. These data are presented graphically in Figure 5.

Figure 5 Mean (SEM) Change From Baseline in Post-Exercise Dyspnea – ITT



EP = Endpoint
Data Source: Section 19, Figure 19.3A.

Results of the PP analysis were similar to the ITT analysis (Section 14, Table 14A.3A, Table 14A.3B, and Table 14A.3C; Section 19, Figure 19A.3A and Figure 19A.3B).

7.3.3. Time to First COPD Exacerbation

A summary of exacerbation-free survival at 24 weeks is presented in Table 27 and graphically in Section 19, Figure 19.7A. The percentage of patients who were exacerbation-free at 24 weeks was comparable for the placebo treatment group (67.4%) and the SB 207499 treatment group (66.7%). Summary of marginal regression analysis by time to exacerbation is listed in Section 14, Table 14.7F.

Table 27 Exacerbation-Free Survival at 24 Weeks– ITT

	Exacerbation-Free Survival[a] at 24 Weeks			
Treatment Group	Number of Patients Exacerbation Free	Percent Exacerbation Free	95% CI	p-value[b]
Placebo	286	67.4	(62.6, 72.3)	
SB 207499[c]	305	66.7	(61.6, 71.8)	0.999

a. Exacerbation-free survival is estimated using a Kaplan-Meier estimate of time-to-first exacerbation.
b. P-value is based on a Log-Rank Test.
c. The dose of SB 207499 is 15mg BID.
Data Source: Section 14, Table 14.7A.

A summary of the number of patients and number of COPD exacerbations by level is presented in Section 14, Table 14.7C, while COPD exacerbations by patient number are presented in Appendix C, Listing 4. In the placebo treatment group, 121 patients experienced a total of 207 exacerbations. There were fewer patients experiencing fewer total exacerbations in the SB 207499 treatment group, with 113 patients experiencing a total of 180 exacerbations.

Baseline smoking status, age, and percent predicted FEV_1 did not prove to be significant risk factors for a COPD exacerbation. Sex was, however, a significant risk factor for a COPD exacerbation ($p = 0.003$), with a relative risk of 1.47 in females versus males (Section 14, Table 14.7D). Summaries of exacerbation-free survival and proportional hazards regression of time to first exacerbation for completers only are presented in Appendix I, Listing 14A and Listing 14B, respectively. Summaries of exacerbation-free survival by study sites that participated and did not participate in Study 039 are presented in Appendix I, Listing 20 and Listing 21, respectively. Summaries of exacerbation free survival by diagnosis of patients with and without emphysema are presented in Appendix I, Listing 22 and Listing 23, respectively.

7.3.4. Time to First Level 2 and 3 COPD Exacerbations

A summary of level 2 and 3 exacerbation-free survival at 24 weeks is presented in Table 28 and graphically in Section 19, Figure 19.7B. There were small differences in the percentage of patients who were level 2 and 3 exacerbation-free at 24 weeks in the placebo treatment group (79.5%) compared to the SB 207499 treatment group (75.6%).

Table 28 Level 2/Level 3 Exacerbation-Free Survival at 24 Weeks– ITT

	Exacerbation-Free Survival[a] at 24 Weeks			
Treatment Group	Number of Patients Exacerbation Free	Percent Exacerbation Free	95% CI	p-value[b]
Placebo	333	79.5	(75.3, 83.7)	-
SB 207499[c]	337	75.6	(70.9, 80.3)	0.212

a. Exacerbation-free survival is estimated using a Kaplan-Meier estimate of time-to-first exacerbation.
b. P-value is based on a Log-Rank Test.
c. The dose of SB 207499 is 15mg BID.
Data Source: Section 14, Table 14.7B.

Baseline smoking status, age, and percent predicted FEV_1 did not prove to be significant risk factors for a level 2 or 3 COPD exacerbation. Sex was, however, a significant risk factor for a level 2 or 3 COPD exacerbation ($p = 0.002$), with a relative risk of 1.65 in females versus males (Section 14, Table 14.7E). Summaries of Level 2/Level 3 exacerbation-free survival and proportional hazards regression of time to first Level 2/Level 3 exacerbation for completers only are presented in Appendix I, Listing 14C and Listing 14D, respectively.

7.4. Tertiary Efficacy Parameters

In addition to the tertiary efficacy parameters discussed below, health economics were also assessed and considered a tertiary endpoint of efficacy, and are presented in Section 7.4.8.

7.4.1. Pulmonary Function

7.4.1.1. Clinic Trough PEFR

When averaged over 24 weeks, there was a decrease of 1.5L/min in the mean clinic trough PEFR in the placebo treatment group and an increase of 2.3L/min in the SB 207499 treatment group. There was a small difference of 3.8L/min in change from baseline clinic trough PEFR between the treatment groups ($p = 0.066$) (Section 14, Table 14.9A; Appendix C, Listing 1).

Summary statistics for change from baseline in PEFR are provided in Section 14, Table 14.9B and descriptive statistics in Section 14, Table 14.9C. The results are presented graphically in Section 19, Figure 19.9A. Summary statistics for the percentage change from baseline in PEFR are presented in Section 14, Table 14.9H. Data are provided by individual patient in Appendix C, Listing 1.

7.4.1.2. Clinic Trough FEF_{25-75}

The change from baseline in clinic trough FEF_{25-75} averaged over 24 weeks of treatment is presented in Table 29.

Table 29 Change From Baseline in Clinic Trough FEF_{25-75} (L/sec) Averaged Over 24 Weeks (Repeated Measures Analysis) - ITT

		Change from Baseline				Comparison with Placebo			
Treatment Group	n	Mean[a]	SEM	Lower 95% CI	Upper 95% CI	Mean Difference	Lower 95% CI	Upper 95% CI	P-value
Placebo	377	-0.01	0.01	-0.02	0.00	-	-	-	-
SB 207499[b]	364	0.02	0.01	0.00	0.03	0.02	0.01	0.04	0.013[c]

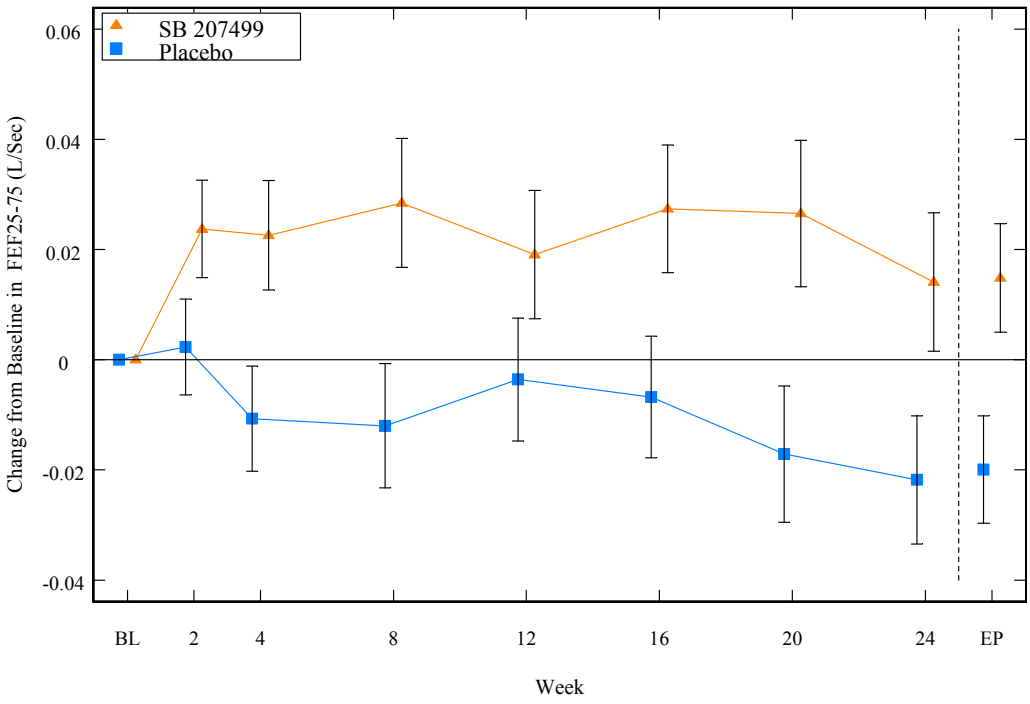
a. Mean values are adjusted for center.
b. The dosage of SB 207499 is 15mg BID.
c. Significantly different from placebo.
Data Source: Section 14, Table 14.24A; Appendix C, Listing 1.

When averaged over 24 weeks, there was a decrease of 0.01L/sec in mean clinic trough FEF_{25-75} in the placebo treatment group and an increase of 0.02L/sec in the SB 207499 treatment group. There was a difference in the mean change from baseline in trough FEF_{25-75} between the two treatment groups of 0.02L/sec (p = 0.013).

Summary statistics for change from baseline in FEF_{25-75} are provided in Section 14, Table 14.24B and descriptive statistics in Section 14, Table 14.24C. The results are presented graphically in Section 19, Figure 19.24A. Summary statistics for the percentage change from baseline in FEF_{25-75} are presented in Section 14, Table 14.24H. Data are provided by individual patient in Appendix C, Listing 1.

The mean change from baseline in trough FEF_{25-75} is presented graphically in Figure 6.

Figure 6 Mean (SEM) Change From Baseline in Trough FEF_{25-75} – ITT



EP = Endpoint
Data Source: Section 19, Figure 19.24A.

7.4.1.3. First-Dose Effect on Pulmonary Function

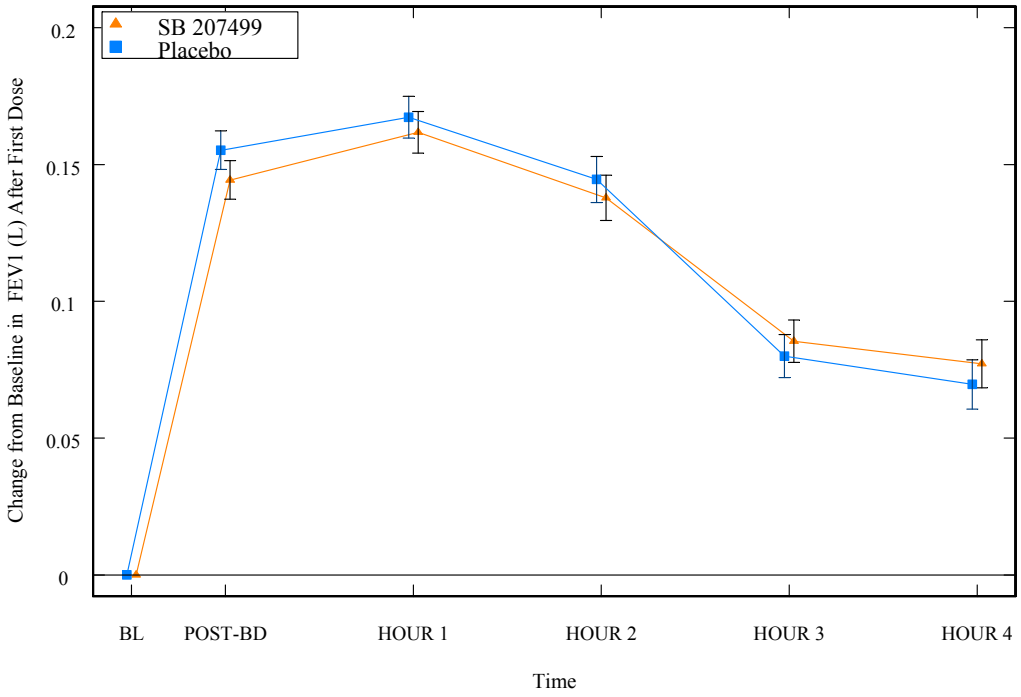
The mean change from baseline in FEV_1 measured after administration of 180mcg of albuterol and 1, 2, 3, and 4 hours after the first dose of double-blind medication is presented Section 14, Table 14.1D and graphically in Figure 7. Descriptive statistics for FEV_1 after the first dose are presented in Section 14, Table 14.1E. Data are provided by individual patient in Appendix C, Listing 1.

At Baseline (Week 3), differences between the treatment groups in FEV_1 were small at each time point. At C_{max} (3 to 4 hours after administration of study medication), the

mean difference in change from baseline in FEV_1 in the SB 207499 treatment group compared to placebo was 10mL. Overall, the two treatment groups were similar in FEV_1 after the first dose of double-blind medication.

Results in the PP population were similar to those observed in the ITT population. (Section 14, Table 14A.1D and Table 14A.1E; Section 19, Figure 19A.1F).

Figure 7 Mean (SEM) Change From Baseline in FEV_1 (L) After First Dose of Double-Blind Study Medication - ITT



Data Source: Section 19, Figure 19.1F.

First-dose effects on FVC, PEFR, and FEF_{25-75} were also measured over 4 hours.

Changes in FVC, PEFR, and FEF_{25-75} at 1 through 4 hours after the first dose did not show a treatment effect (Section 14, Table 14.5D, Table 14.9D, and Table 14.24D; Appendix C, Listing 1). The change from baseline over time is presented graphically in Section 19, Figure 19.5F, Figure 19.9F, and Figure 19.24F. Descriptive statistics for FVC, PEFR, and FEF_{25-75} after the first dose of study medication are presented in Section 14, Table 14.5E, Table 14.9E, and Table 14.24E, respectively.

Results for FVC after the first dose in the PP population were similar to those in the ITT population (Section 14, Table 14A.5D and Table 14A.5E; Section 19, Figure 19A.5F).

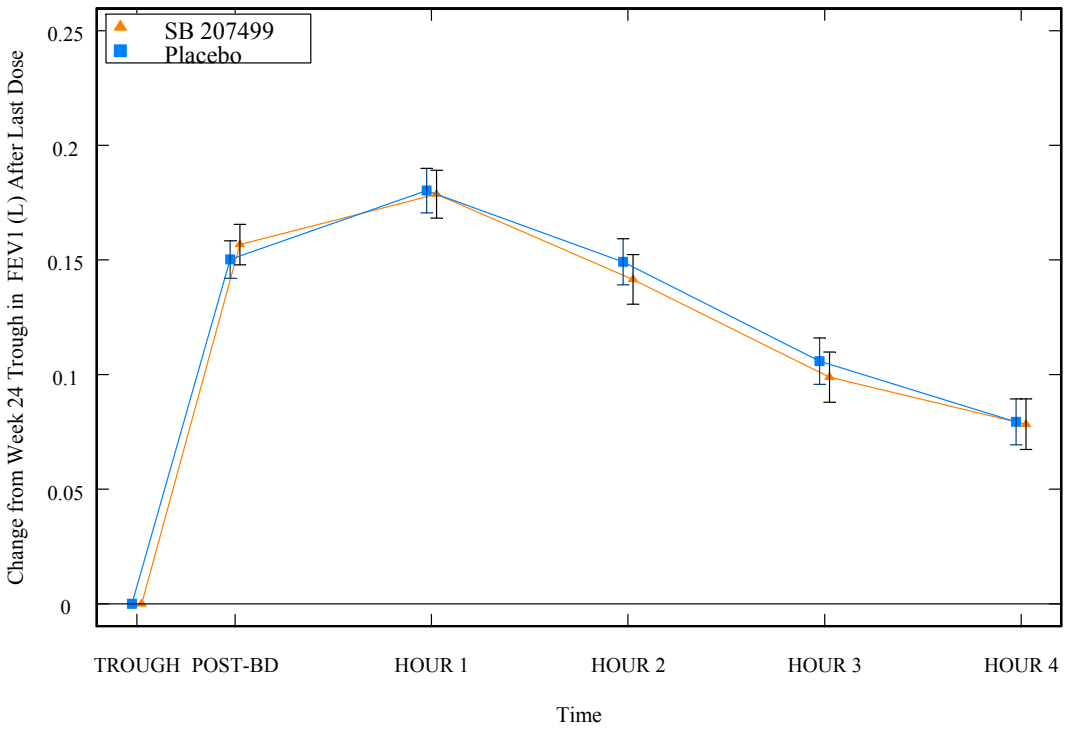
Summary and descriptive statistics for the per-protocol population pulmonary function tests are listed in Section 14, Table 14A.9D, Table 14A.9E (pre-albuterol PEFR), Table 14A.24D, Table 14A.24E (pre-albuterol FEF_{25-75}) and graphically in Section 19, Figure 19A.9F (PEFR) and Figure 19A.24F (FEF_{25-75}).

7.4.1.4. Last-Dose Effects on Pulmonary Function

At Week 24, FEV_1, PEFR, FVC, and FEF_{25-75} were measured after administration of 180mcg of albuterol and 1, 2, 3, and 4 hours after the last dose of double-blind medication. The mean change from Week 24 trough FEV_1 after the last dose of double-blind medication is presented in Section 14, Table 14.1F, Table 14.1G, and graphically in Figure 8.

At Week 24, differences between the treatment groups in FEV_1 were small at each hourly time point. Overall, the two treatment groups were similar in FEV_1 after the last dose of double-blind medication.

Figure 8 Mean (SEM) Change From Week 24 Trough in FEV_1 After the Last Dose of Double-blind Study Medication - ITT



Data Source: Section 19, Figure 19.1G.

Results in the PP population were similar to those observed in the ITT population (Section 14, Table 14A.1F and Table 14A.1G; Section 19, Figure 19A.1G).

Changes in FVC, PEFR, and FEF_{25-75} at 1 through 4 hours after the last dose did not show a treatment effect (Section 14, Table 14.5F, Table 14.9F, Table 14.24F; Appendix C, Listing 1). The change from baseline over time is presented graphically in Section 19, Figure 19.5G, Figure 19.9G, and Figure 19.24G. Descriptive statistics for FVC, PEFR, and FEF_{25-75} after the last dose of study medication are presented in Section 14, Table 14.5G, Table 14.9G, and Table 14.24G, respectively.

Results for the FVC after the last dose in the PP population were similar to those in the ITT population (Section 14, Table 14A.5F and Table 14A.5G; Section 19, Figure 19A.5G). Data for the PP population for PEFR and FEF_{25-75} are presented in Section 14, Table 14A.9F, Table 14A.9G (trough PEFR after the last dose) Table 14A.24F, Table 14A.24G (trough FEF_{25-75} after the last dose) and graphically in Section 19, Figure 19A.9G (trough PEFR after the last dose) and Figure 19A.24G (trough FEF_{25-75} after the last dose).

7.4.1.5. Post-Albuterol Pulmonary Function

Summary and descriptive statistics for post-albuterol trough FEV_1 are listed in Section 14, Table 14.40B and Table 14.40C. Summary and descriptive statistics for per-protocol post-albuterol trough FEV_1 are listed in Section 14, Table 14A.40B and Table 14A.40C. The mean change from baseline in post-albuterol trough FEV_1 at Week 24 is presented in Section 19, Figure 19.40B, and for the per protocol population in Section 19, Figure 19A.40B.

At Week 24, there was an improvement of 40mL for the SB 207499 treatment group versus placebo ($p = 0.020$) in the change from Baseline (Visit 3) post-albuterol FEV_1 (Section 14, Table 14.40B and Section 19, Figure 19.40B). Similar trends were observed in the per protocol population.

Summary and descriptive statistics for post-albuterol pulmonary function data are listed in Section 14, Table 14.41B, Table 14.41C (FVC), Table 14.42B, Table 14.42C (PEFR), and Table 14.43B, Table 14.43C (FEF_{25-75}), and graphically in Section 19, Figure 19.41B, Figure 19A.41B (FVC), Figure 19.42B, Figure 19A.42B (PEFR), Figure 19.43B, and Figure 19A.43B (FEF_{25-75}).

At Week 24, an improvement of 80mL was observed for the SB 207499 treatment group versus placebo ($p = 0.022$) in the change from Baseline (Visit 3) post-albuterol FVC (Section 14, Table 14.41B and Section 19, Figure 19.41B). No meaningful differences were observed in the change from baseline in post-albuterol PEFR and FEF_{25-75}. Similar trends were observed in the per protocol population.

Summary and descriptive statistics for the per-protocol post-albuterol population pulmonary function tests are listed in Section 14, Table 14A.41B, Table 14A.41C (FVC), Table 14A.42B, Table 14A.42C (PEFR), and Table 14A.43B, Table 14A.43C (FEF_{25-75}).

7.4.2. Symptoms of COPD

7.4.2.1. Overall Breathlessness

Summary statistics for mean change from baseline in overall breathlessness are presented in Section 14, Table 14.10A and Table 14.10B. Descriptive statistics are presented in Section 14, Table 14.10C and data are presented graphically in Section 19, Figure 19.10A. Data are presented by patient in Appendix C, Listing 3. Overall breathlessness during usual daily activities was measured using the modified Borg scale. When averaged over 24 weeks, the mean overall breathlessness increased slightly in the

placebo treatment group (0.02 points) and decreased slightly in the SB 207499 treatment group (0.15 points). There was a mean difference from placebo in the change from baseline in overall breathlessness in the SB 207499 treatment group (-0.17 points; $p = 0.029$).

7.4.2.2. Cough and Sputum Assessments

Summary statistics for cough and sputum are presented in Section 14, Table 14.26 and Table 14.25, respectively. Data are provided by individual patient in Appendix C, Listing 6. There were differences in the percentage of patients reporting improvement from baseline in sputum production and cough assessment in the SB 207499 treatment group compared to placebo at Week 12 ($p = 0.0403$ and $p = 0.0059$, respectively) but not at Week 24 or endpoint.

Summary and descriptive statistics for the per-protocol population sputum production and cough assessments are listed in Section 14, Table 14A.25 and Table 14A.26, respectively.

7.4.2.3. Use of Rescue Medication

The use of albuterol on an "as-needed" basis was analyzed as a tertiary efficacy parameter. Summary statistics for on-demand albuterol use are presented in Section 14, Table 14.36. Data are provided by individual patient in Appendix C, Listing 6. The percentage of patients reporting improvement from baseline in the use of as-needed albuterol was comparable for the SB 207499 treatment group versus placebo. However, at most time points (except Week 20) and at endpoint, the percentage of patients whose albuterol use had improved over baseline was higher in the SB 207499 treatment group (ranging from 25.1% to 29.6%) than in the placebo treatment group (ranging from 19.9% to 26.5%).

7.4.3. Quality of Life Assessments

The subscales of the SGRQ and SF-36 were analyzed as tertiary efficacy parameters.

7.4.3.1. Subscales of the SGRQ

Summary and descriptive statistics for symptoms, impacts, and activities scores (subscales of the SGRQ) are presented in Section 14, Table 14.21A, Table 14.21B, and Table 14.21C, Table 14.22A, Table 14.22B, and Table 14.22C and Table 14.23A, Table 14.23B, and Table 14.23C, respectively. Data are provided by individual patient in Appendix C, Listing 2. The average change from baseline in score for the subscales of the SGRQ over 24 weeks of treatment is presented in Table 30.

Table 30 Change From Baseline in Symptoms, Impacts, and Activities Scores of the SGRQ Averaged Over 24 Weeks (Repeated Measures Analysis) - ITT

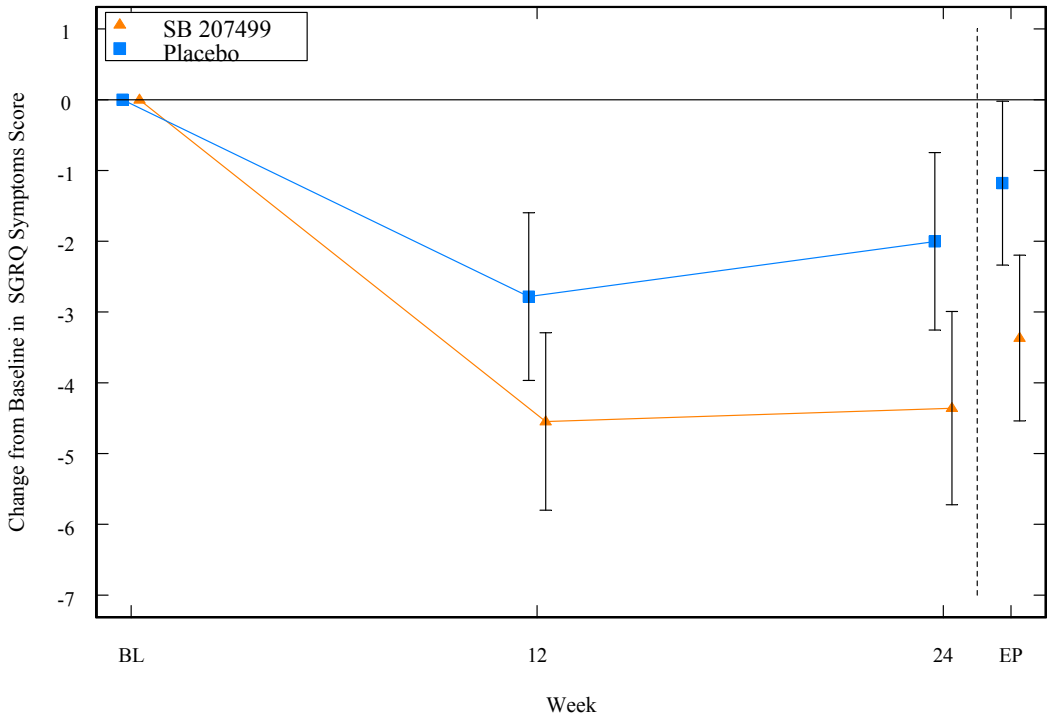
Parameter		Change from Baseline				Comparison with Placebo			
Treatment Group	n	Mean[a]	SEM	Lower 95% CI	Upper 95% CI	Mean Difference	Lower 95% CI	Upper 95% CI	P-value
Symptoms Score									
Placebo	339	-2.3	1.1	-4.4	-0.2				
SB 207499[b]	308	-4.4	1.1	-6.6	-2.1	-2.0	-4.8	0.7	0.149
Impacts Score									
Placebo	337	-1.4	0.6	-2.7	-0.2				
SB 207499[b]	304	-2.7	0.7	-4.0	-1.4	-1.3	-3.1	0.5	0.170
Activities Score									
Placebo	337	-1.2	0.7	-2.5	0.1				
SB 207499[b]	304	-3.7	0.7	-5.1	-2.4	-2.6	-4.5	-0.7	0.008[c]

a. Mean values are adjusted for center and week.
b. The dosage of SB 207499 is 15mg BID.
c. Significantly different from placebo.
Data Source: Section 14, Table 14.21A, Table 14.22A, and Table 14.23A

When averaged over 24 weeks, there was an improvement in the mean symptoms, impacts, and activities scores of the SGRQ in the SB 207499 treatment group (4.4, 2.7, and 3.7 points, respectively). In the placebo treatment group, there were smaller improvements in the mean symptoms, impacts, and activities scores of the SGRQ from baseline when averaged over 24 weeks (2.3, 1.4, and 1.2 points, respectively). There was a difference in the mean activities score (2.6 points; $p = 0.008$) of the SGRQ in patients who received SB 207499 compared to patients who received placebo. Also, there were differences of 2.0 points ($p = 0.149$) and 1.3 points ($p = 0.170$) in the symptoms and impacts scores, respectively, in the SB 207499 treatment group compared to the placebo treatment group.

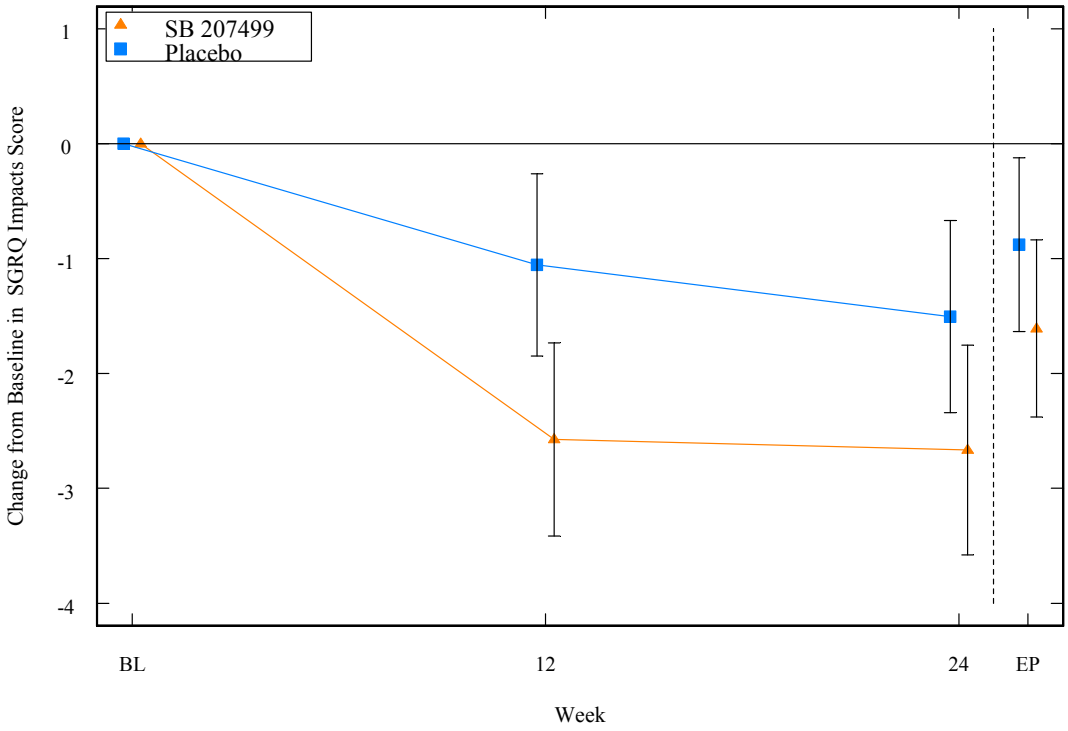
The changes from baseline over time in the symptoms, impacts, and activities scores of the SGRQ are presented graphically in Figure 9, Figure 10, and Figure 11, respectively.

Figure 9 Mean (SEM) Change From Baseline in Symptoms Score of the SGRQ – ITT



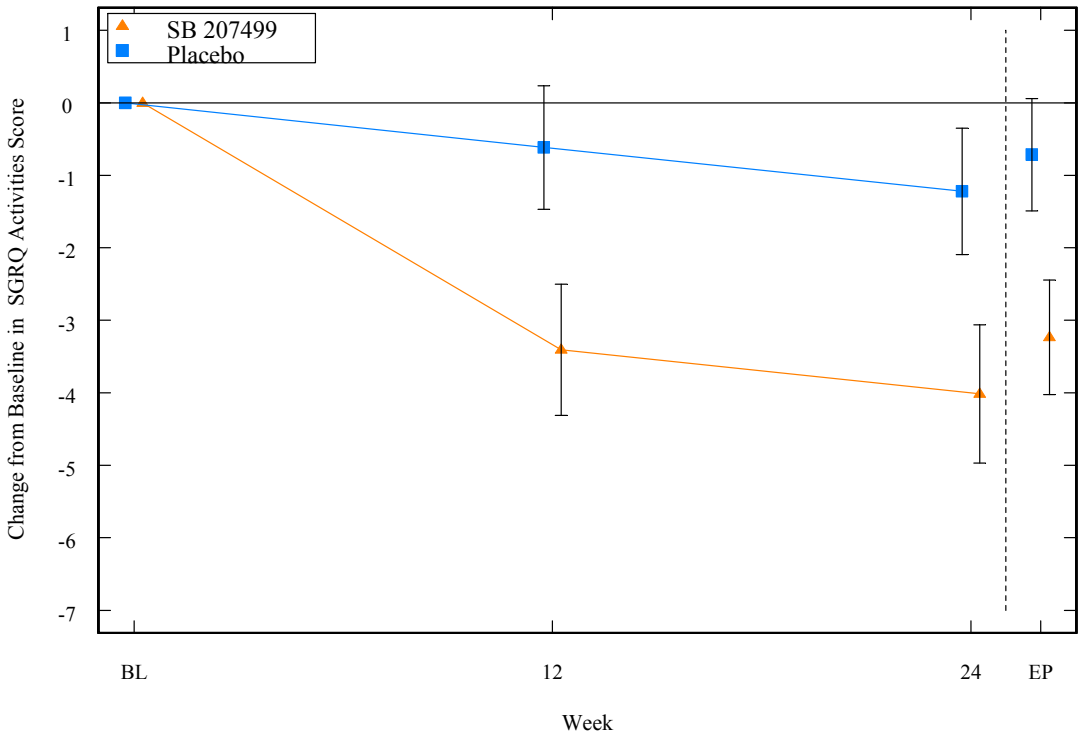
EP = Endpoint
Data Source: Section 19, Figure 19.21A.

Figure 10 Mean (SEM) Change From Baseline in Impacts Score of the SGRQ - ITT



EP = Endpoint
Data Source: Section 19, Figure 19.22A.

Figure 11 Mean (SEM) Change From Baseline in Activities Score of the SGRQ - ITT



EP = Endpoint
Data Source: Section 19, Figure 19.23A.

7.4.3.2. Subscales of the SF-36

Summary and descriptive statistics for the subscales of the SF-36 are presented in Section 14, Table 14.11B, Table 14.11C (Physical Composite Score), Table 14.12B, Table 14.12C (Mental Composite Score), Table 14.13B, Table 14.13C (Physical Functioning Score), Table 14.14B, Table 14.14C (Physical Role Functioning), Table 14.15B, Table 14.15C (Emotional Role Functioning), Table 14.16B, Table 14.16C (Social Functioning Score), Table 14.17B, Table 14.17C (Bodily Pain Score), Table 14.18B, Table 14.18C (Mental Health Score), Table 14.19B, Table 14.19C (Vitality Score), Table 14.20B, and Table 14.20C (General Health). Data are presented by individual patient in Appendix C, Listing 8. There were small improvements in the physical composite, physical functioning, and bodily pain scores in the SB 207499 treatment group, that were greater than those observed in the placebo treatment group. However, there were no meaningful differences in the mean scores for any of the domains or for the physical role or mental composite scores in patients who received SB 207499 compared to patients who received placebo.

7.4.4. Oxygen Saturation at Rest and Arterial Blood Gases

The SaO_2 at rest was measured in patients with an FEV_1 at the Screening Visit that was less than 40% of predicted. Arterial blood gases were measured in patients with FEV_1 of <40% living at high altitudes or having a resting SaO_2 <88%.

Summary and descriptive statistics for oxygen saturation and arterial blood gases are presented in Section 14, Table 14.29B, Table 14.29C (SaO_2), Table 14.30B, Table 14.30C (PO_2), Table 14.31B, Table 14.31C (PCO_2), Table 14.32B, Table 14.32C (pH), Table 14.33B, Table 14.33C (HCO_3), and Table 14.34B, Table 14.34C (Optional SaO_2). Data are presented by patient in Appendix C, Listing 5.

At baseline, the mean resting SaO_2 was 94.6% in the placebo treatment group and 94.5% in the SB 207499 treatment group. At Week 24 and endpoint, there were small increases in mean SaO_2 from baseline for SB 207499-treated patients and no change for placebo patients.

Due to the small numbers of patients for whom arterial blood gas measurements were obtained (4 patients in the placebo treatment group and 4 patients in the SB 207499 treatment group), no conclusions could be drawn regarding arterial blood gases.

7.4.5. Post-exercise Oxygen Saturation

Summary and descriptive statistics for post-exercise oxygen saturation are presented in Section 14, Table 14.28B and Table 14.28C, respectively. Data are presented graphically in Section 19, Figure 19.28A. Data are presented by patient in Appendix C, Listing 3. Unlike oxygen saturation at rest and arterial blood gases, post-exercise oxygen saturation was performed in all patients. At baseline, post-exercise oxygen saturation was 93.2% in the placebo treatment group and 93.0% in the SB 207499 treatment group. There were small changes in post-exercise oxygen saturation at Week 24, with a decrease of 1.1% from baseline in the placebo treatment group and an increase of 3.5% from baseline in the SB 207499 treatment group. There were differences in the mean post-exercise oxygen saturation in patients who received SB 207499 compared to patients who received placebo at Week 4 (0.8%; $p = 0.003$), Week 12 (0.7%; $p = 0.039$), Week 24 (0.7%; $p = 0.042$), and at endpoint (0.9%; $p = 0.003$).

7.4.6. Global Investigator and Patient Assessments

The global investigator and patient assessments of disease status are presented in Section 14, Table 14.38 and Table 14.39, respectively. The PP analyses of investigator and patient assessments of disease status are presented in Section 14, Table 14A.38 and Table 14A.39, respectively.

The global investigator and patient assessments were comparable between the placebo and SB 207499 treatment groups.

7.4.7. Exercise Performance

The change from baseline in exercise performance averaged over 24 weeks of double-blind treatment is presented in Table 31 and graphically in Section 19, Figure 19.6B.

Table 31 Change From Baseline in Distance Walked (Meters) Averaged Over 24 Weeks (Repeated Measures Analysis) - ITT

		Change from Baseline				Comparison with Placebo			
Treatment Group	n	Mean[a]	SEM	Lower 95% CI	Upper 95% CI	Mean Difference	Lower 95% CI	Upper 95% CI	P-value
Placebo	356	2.8	3.6	-4.2	9.8	-	-	-	-
SB 207499[b]	330	7.9	3.7	0.6	15.1	5.0	-5.0	15.0	0.325

a. Mean values are adjusted for week.
b. The dosage of SB 207499 is 15mg BID.
Data Source: Section 14, Table 14.6A

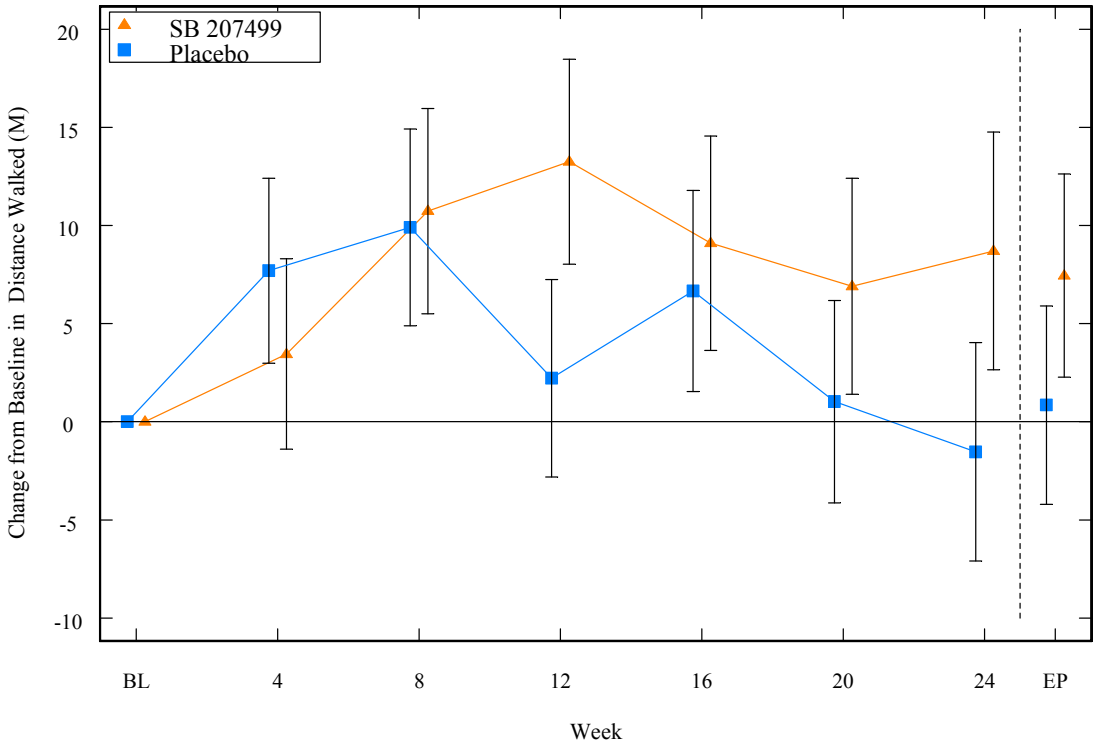
When averaged over 24 weeks, there was an increase in the mean distance walked in both treatment groups, with a greater increase in the SB 207499 treatment group (7.9m) than the placebo treatment group (2.8m). When compared to placebo, there was a difference of 5.0m in the mean distance walked in the SB 207499 treatment group ($p = 0.325$).

Summary and descriptive statistics for change from baseline in exercise performance (distance walked) by week of double-blind treatment and at endpoint are presented in Section 14, Table 14.6B and Table 14.6C, respectively. Data are provided by individual patient in Appendix C, Listing 3. The mean change from baseline in distance walked is presented graphically in Figure 12.

In both the placebo and SB 207499 treatment groups, the mean distance walked increased from baseline to Week 20, but decreased for placebo at Week 24. When compared to placebo, there was an increase (ranging from 0.83m to 11.04m) in the mean distance walked in the SB 207499 treatment group at Weeks 8, 12, 16, 20, 24, and endpoint. An improvement over baseline was observed at endpoint in the SB 207499 treatment group (7.45m) compared to placebo (0.85m) ($p = 0.316$).

Results of the PP analysis were similar to the ITT analysis (Section 14, Table 14A.6A, Table 14A.6B, and Table 14A.6C; Section 19, Figure 19A.6A and Figure 19A.6B).

Figure 12 Mean (SEM) Change From Baseline in Distance Walked – ITT



EP = Endpoint
Data Source: Section 19, Figure 19.6A.

7.4.8. Health Economic Endpoints

7.4.8.1. Summary of COPD-related Healthcare Utilization Prior to Study Entry by Treatment Group

A summary of COPD-related healthcare resource utilization in the year prior to study entry is presented in Table 32.

Table 32 Summary of COPD-related Healthcare Utilization Prior to Study Entry

Utilization in Last Year	Number of Visits	Placebo (N=407) n (%)	SB 207499 15mg BID (N=418) n (%)
ER/Urgent Care Visits	None	373 (91.6)	372 (89.0)
	1	28 (6.9)	27 (6.5)
	2	1 (0.2)	8 (1.9)
	3-4	2 (0.5)	10 (2.4)
Hospitalizations	None	386 (94.8)	403 (96.4)
	1	15 (3.7)	11 (2.6)
	2	2 (0.5)	3 (0.7)
	3-4	1 (0.2)	0

Data Source: Section 18, Table 18.1

Both treatment groups had a similar pattern of emergency room visits and hospitalizations in the year prior to the study enrollment. The majority of the patients in both groups had either none or one ER visit or hospitalization in the year prior to the study.

7.4.8.2. COPD-related Healthcare Utilization-free Survival

Utilization-free survival and the total number of utilizations by type and treatment are presented in

Table 33.

Table 33 Summary of Utilization-Free Survival and Total Number of Utilizations – ITT

		Utilization-Free Survival at 24 Weeks[a]				Total Number of Utilizations	
Utilization	Treatment Group	Number of Patients Utilization-Free	Percent Utilization-Free	95% CI	P-Value	Number of Patients at Risk on Day 1	Total Number of Utilizations Over 24 Weeks
All Utilizations	Placebo	345	(82.8)	(78.8, 86.7)		407	99
	SB 207499[b]	349	(79.3)	(74.9, 83.8)	0.209	418	114
ER/Urgent Care	Placebo	397	(97.2)	(95.6, 98.9)		407	11
	SB 207499	405	(96.0)	(93.9, 98.2)	0.419	418	15
Hospitalization	Placebo	400	(98.0)	(96.6, 99.5)		407	7
	SB 207499	412	(98.2)	(96.8, 99.6)	0.900	418	6
Physician Visits	Placebo	351	(84.2)	(80.4, 88.1)		407	80
	SB 207499	355	(81.1)	(76.8, 85.4)	0.201	418	93
ICU	Placebo	406	(99.7)	(99.2, 100.0)		407	1
	SB 207499	418	(100.0)	(100.0, 100.0)	0.337	418	0

a. Utilization-free survival is estimated using Kaplan-Meier estimates of time-to-first utilization.
b. The dosage of SB 207499 is 15mg BID.
Data Source: Section 18, Table 18.2

Both treatment groups had similar percentages of utilization-free patients in ER/urgent care visits, hospitalizations, physician visits, and ICU visits over the entire 24 weeks. In both groups, physician visits were the type of healthcare resource utilized most frequently.

7.4.8.3. Summary of Poisson Regression of Utilization Rates by Types of Utilization

A summary of poisson regression of utilization rates by type of utilization is presented in Section 18, Table 18.4. Rates of resource utilization by treatment exposure days is listed in Section 18, Table 18.3.

Poisson regression analysis, that adjusted for subject's age, gender, smoking status, and % predicted FEV_1, was used to estimate the relative rates (per patient month of follow up) for 'all utilization', 'ER/urgent care visits', 'hospitalization', and 'physician office visits' between the SB 207499 and placebo treatment groups. Gender was found to be a significant predictor of 'all utilization', 'ER/urgent care visit', and 'physician office visit', while % predicted FEV_1 was found to be a significant predictor of 'all utilization', 'ER/urgent care visit', and 'hospitalization'. Being female resulted in higher 'all utilization' rates (RR: 1.87, 95% CI: 1.43 – 2.46), higher 'ER/urgent care visit' rates (RR: 2.83, 95% CI: 1.27 – 6.31), and higher 'physician office visit' rates (RR: 1.77, 95% CI: 1.31 – 2.39). Percent predicted FEV_1 was found to be inversely related to 'all utilization' (RR: 0.98, 95% CI: 0.97 – 0.99), 'ER/urgent care visit' (RR: 0.95, 95% CI: 0.91 – 0.98), and 'hospitalization' (RR: 0.93, 95% CI: 0.88 – 0.99). The relative utilization rates per patient-month of follow up were not found to significantly differ between the SB 207499 and placebo treatment groups for any of the four outcomes. Also, smoking status and subject's age were not found to be a significant predictors of any of the above mentioned utilization-related outcomes.

7.4.8.4. Summary of the Time In Hospital and ICU, Restricted Leisure Activity, Percent of Days Lost From Work, and Paid and Unpaid Assistance

Analyses of the time spent in the hospital and ICU, percent of time with restricted leisure activity, percent of days lost from work, and average weekly paid and unpaid assistance showed utilization occurring for only a small number of patients and no meaningful differences observed between the two treatment groups.

Summary statistics for the percent of time that patients spent in the hospital and ICU are presented in Section 18, Table 18.5 and Table 18.6, respectively. A summary of the number of patients who spent time in the hospital and ICU is presented in Section 18, Table 18.10 and Table 18.11, respectively. A summary of healthcare resource utilization is presented by patient in Appendix C, Listing 7A.

Summary statistics for the percent of time that patients had restricted leisure activities are listed in Section 18, Table 18.8. A summary of days of restricted leisure activities is presented by patient in Appendix C, Listing 7B.

Summary statistics for the percent of lost days from work are listed in Section 18, Table 18.7. A summary of lost work days is presented by patient in Appendix C, Listing 7A.

A summary of the number of patients that required weekly unpaid and paid assistance is presented in Section 18, Table 18.9A and Table 18.9B. A summary of paid and unpaid assistance is presented by patient in Appendix C, Listing 7B.

8. SAFETY RESULTS

All 825 patients who received at least one dose of double-blind study medication are included in the safety analyses.

8.1. Extent of Exposure

The mean duration of exposure to study medication was 143.6 days (median 169 days) for patients who received placebo and 128.2 days (median 168 days) for patients who received SB 207499. More than 48% of patients in each treatment group received double-blind medication for at least 169 days. Table 34 summarizes the duration of exposure by treatment group, and these data are presented for each patient in Appendix B, Listing 1.

Table 34 Duration of Exposure

	Treatment Group	
	Placebo (N=407)	SB 207499 15mg BID (N=418)
Exposure[a] (days)	n (%)	n (%)
≤14	27 (6.6)	54 (12.9)
15 – 28	11 (2.7)	25 (6.0)
29 – 56	17 (4.2)	17 (4.1)
57 – 84	18 (4.4)	18 (4.3)
85 – 112	13 (3.2)	13 (3.1)
113 – 140	7 (1.7)	10 (2.4)
141 – 168	83 (20.4)	77 (18.4)
169 – 196	228 (56.0)	203 (48.6)
> 196	3 (0.7)	1 (0.2)
Mean (SD)	143.6 (55.5)	128.2 (65.9)
Median	169	168
Min, Max	1, 211	1, 197

a. Calculation of exposure: (Date of last dose of double-blind medication – Date of first dose of double-blind medication) + 1.

Data Source: Section 15, Table 15.1A and Table 15.1B; Appendix B, Listing 1.

8.2. Adverse Events

Adverse events were reported by study phase for the placebo run-in, double-blind, and post-therapy periods. Section 13, Table 13.14 and Appendix B, Listing 10 present adverse events experienced during the placebo run-in period (see Section 6.6, Baseline

Signs and Symptoms), and Section 15, Table 15.10 and Appendix D, Listing 7 present adverse events reported post-therapy. Section 15, Table 15.2A summarizes the on-therapy adverse events by preferred term in descending frequency of occurrence, Section 15, Table 15.2B summarizes on-therapy adverse events by body system and preferred term, and Appendix D, Listing 1 presents these data by individual patient. Medical procedures conducted during the placebo run-in, double-blind, and post-therapy periods are presented in Appendix B, Listing 9.

8.2.1. Incidence of On-therapy Adverse Events

SB 207499 was generally well-tolerated. The percentages of patients who reported at least one adverse event were comparable between the two treatment groups, with overall incidences of 83.3% of 407 patients in the placebo treatment group and 87.1% of 418 patients in the SB 207499 treatment group. Adverse events associated with the gastrointestinal body system were reported more frequently in the SB 207499 treatment group (51.9%) as compared with the placebo treatment group (33.4%). In addition, a higher incidence of adverse events associated with the respiratory body system was observed in the placebo treatment group (47.2%) compared with the SB 207499 treatment group (39.7%). Review of the adverse event profile provided no evidence for an adverse effect of SB 207499 on other body systems including the cardiovascular system (including heart rate and rhythm), liver and biliary system, psychiatric, central and peripheral nervous system, resistance mechanism (i.e., infection) and reproductive system (Section 15, Table 15.2B).

Adverse events occurring in ≥2% of patients in either treatment group are presented in descending order of frequency for SB 207499 in Table 35.

Table 35 Summary of Most Frequently Reported (≥2% of Patients in Either Treatment Group) On-therapy Adverse Events

	Treatment Group			
	Placebo (N=407)		SB 207499 15mg BID (N=418)	
Adverse Event (Preferred Term)	n	(%)	n	(%)
Total[a]	339	(83.3)	364	(87.1)
Chronic Obstructive Airways Disease	125	(30.7)	114	(27.3)
Nausea	27	(6.6)	109	(26.1)
Diarrhea	44	(10.8)	82	(19.6)
Abdominal Pain	38	(9.3)	52	(12.4)
Headache	33	(8.1)	46	(11.0)
Upper Respiratory Tract Infection	61	(15.0)	46	(11.0)
Dyspepsia	10	(2.5)	38	(9.1)
Vomiting	11	(2.7)	33	(7.9)
Injury	28	(6.9)	31	(7.4)
Sinusitis	34	(8.4)	30	(7.2)
Dizziness	22	(5.4)	24	(5.7)
Arthralgia	18	(4.4)	22	(5.3)
Coughing	34	(8.4)	21	(5.0)
Fatigue	15	(3.7)	20	(4.8)
Flatulence	11	(2.7)	20	(4.8)

	Treatment Group	
	Placebo (N=407)	SB 207499 15mg BID (N=418)
Adverse Event (Preferred Term)	n (%)	n (%)
Insomnia	8 (2.0)	19 (4.5)
Back Pain	24 (5.9)	16 (3.8)
Infection Viral	9 (2.2)	16 (3.8)
Urinary Tract Infection	18 (4.4)	16 (3.8)
Dyspnea	29 (7.1)	15 (3.6)
Myalgia	15 (3.7)	15 (3.6)
Pharyngitis	16 (3.9)	15 (3.6)
Pain	6 (1.5)	14 (3.3)
Anxiety	6 (1.5)	13 (3.1)
Rhinitis	14 (3.4)	13 (3.1)
Anorexia	3 (0.7)	12 (2.9)
Melena	6 (1.5)	12 (2.9)
Constipation	10 (2.5)	11 (2.6)
Hyperglycemia	12 (2.9)	11 (2.6)
Asthenia	5 (1.2)	10 (2.4)
Bronchitis	6 (1.5)	10 (2.4)
Chest Pain	16 (3.9)	10 (2.4)
Gastroesophageal Reflux	4 (1.0)	10 (2.4)
Hematuria	12 (2.9)	10 (2.4)
Hyperkalemia	9 (2.2)	10 (2.4)
Hypertension	15 (3.7)	9 (2.2)
Tremor	1 (0.2)	9 (2.2)
Respiratory Disorder	15 (3.7)	8 (1.9)
Depression	8 (2.0)	5 (1.2)
Somnolence	9 (2.2)	4 (1.0)
Pneumonia	8 (2.0)	3 (0.7)
Periodontitis	9 (2.2)	2 (0.5)
Cramps Legs	9 (2.2)	0

a. Total represents total number of patients reporting at least one adverse event.
Data Source: Section 15, Table 15.2A.

In general, the number of patients who reported individual adverse events was comparable between the SB 207499 and placebo treatment groups with the exception of AEs associated with the gastrointestinal system, which were generally reported more frequently in SB 207499-treated patients. Also, placebo-treated patients generally reported more AEs associated with the respiratory system. Of note, AEs of upper respiratory tract infection, coughing, and dyspnea were reported in 15.0%, 8.4%, and 7.1% of placebo-treated patients compared with 11.0%, 5.0%, and 3.6% of SB 207499-treated patients, respectively.

8.2.2. Adverse Events by Relationship to Study Medication

The most frequently reported adverse events (i.e., occurring in ≥2% of patients in either treatment group) considered to be related to study medication by the Investigator are presented in descending order of frequency for the SB 207499 treatment group in

Table 36. Adverse events considered unlikely or not related to study medication are presented by individual patient in Appendix D, Listing 2B.

Table 36 Summary of Most Frequently Reported (≥2% of Patients in Either Treatment Group) Adverse Events Considered Related to Study Medication

Related[a] Adverse Event (Preferred Term)	Treatment Group: Placebo (N=407) n (%)		Treatment Group: SB 207499 15mg BID (N=418) n (%)	
Total[b]	59	(14.5)	137	(32.8)
Nausea	14	(3.4)	74	(17.7)
Diarrhea	18	(4.4)	51	(12.2)
Abdominal Pain	14	(3.4)	27	(6.5)
Dyspepsia	3	(0.7)	17	(4.1)
Vomiting	6	(1.5)	14	(3.3)
Headache	4	(1.0)	13	(3.1)
Flatulence	6	(1.5)	12	(2.9)

a. Relationships considered "suspected" or "probable" are included in the "Related" category.
b. Total represents total number of patients reporting at least one related adverse event.
NOTE: Frequently occurring adverse events that were not considered related in either treatment group are not included in this table.
Data Source: Section 15, Table 15.3; Appendix D, Listing 2A.

Overall, the percentage of patients with adverse events considered related to study medication was lower for the placebo treatment group than for the SB 207499 treatment group (14.5% vs. 32.8%, respectively), which was likely attributable to the greater number of related GI adverse events reported among SB 207499-treated patients. However, the number of patients who reported adverse events associated with gastrointestinal bleeding (i.e., melena, feces discolored, hemorrhoids, or hemorrhage rectum) that were considered related to study medication were comparable between the placebo (1.0%) and SB 207499 (0.7%) treatment groups.

8.2.3. Adverse Events by Intensity

The total number of patients with adverse events during double-blind treatment is summarized by Investigator-determined intensity and treatment group in Table 37.

Table 37 Number (%) of Patients with On-therapy Adverse Events by Intensity

	Treatment Group	
	Placebo (N=407)	SB 207499 15mg BID (N=418)
Intensity[a]	n (%)	n (%)
Total[b]	339 (83.3)	364 (87.1)
Mild	106 (26.0)	108 (25.8)
Moderate	181 (44.5)	188 (45.0)
Severe	52 (12.8)	68 (16.3)

a. Maximum intensity is used for each adverse event for each patient.
b. Total represents total number of patients reporting at least one adverse event.
Data Source: Section 15, Table 15.4; Appendix D, Listing 1.

The majority of patients reported adverse events that were mild or moderate in intensity. The overall percentage of patients with severe adverse events was slightly higher in the SB 207499 treatment group (16.3%) compared to the placebo treatment group (12.8%). These trends were also observed among patients who reported adverse events in the GI body system in the placebo (mild: 17.4%, moderate: 12.8%, and severe: 3.2%) and SB 207499 treatment groups (mild: 22.2%, moderate: 24.6%, severe: 5.0%).

Table 38 summarizes severe adverse events reported in ≥1% of patients in either treatment group.

Table 38 Summary of Most Frequently Reported (≥1% of Patients in Either Treatment Group) Severe Adverse Events

	Treatment Group	
	Placebo (N=407)	SB 207499 15mg BID (N=418)
Severe Adverse Event (Preferred Term)	n (%)	n (%)
Total[a]	52 (12.8)	68 (16.3)
Chronic Obstructive Airways Disease	10 (2.5)	9 (2.2)
Nausea	2 (0.5)	9 (2.2)
Vomiting	1 (0.2)	6 (1.4)
Injury	2 (0.5)	5 (1.2)
Diarrhea	3 (0.7)	5 (1.2)
Abdominal Pain	5 (1.2)	4 (1.0)
Coughing	4 (1.0)	2 (0.5)
Dyspnea	4 (1.0)	0

a. Total represents the total number of patients reporting at least one severe adverse event.
Data Source: Section 15, Table 15.4; Appendix D, Listing 1.

The percentage of patients with severe nausea, vomiting, and injury was at least twice as high in the SB 207499 treatment group compared with the placebo treatment group, while incidences of coughing and dyspnea were at least twice as high among placebo-treated versus SB 207499-treated patients. The percentages of patients reporting severe chronic obstructive airways disease and severe abdominal pain were similar in the two treatment groups. Of note, no SB 207499-treated and 2 placebo-treated patients reported severe

adverse events associated with gastrointestinal bleeding (i.e., melena, feces discolored, hemorrhoids, or hemorrhage rectum).

8.2.4. Adverse Events by Time of First Occurrence

Table 39 and Table 40 presents the incidence of commonly occurring adverse events (≥2% of patients in the SB 207499 treatment group) by time of first occurrence.

Table 39 Summary of Most Frequently Reported (≥2% of Patients in Either Treatment Group) On-therapy Adverse Events by Initial Time of Onset: Placebo Treatment Group

Adverse Event (Preferred Term)	N[a]	Time of Initial Onset (Days)										
		1 (N=407)[b] n (%)	2–7 (N=402)[b] n (%)	8–14 (N=391)[b] n (%)	15-21 (N=380)[b] n (%)	22–28 (N=377)[b] n (%)	29–56 (N=369)[b] n (%)	57–84 (N=352)[b] n (%)	85–112 (N=334)[b] n (%)	113-140 (N=321)[b] n (%)	141-168 (N=314)[b] n (%)	>168 (N=231)[b] n (%)
Total Placebo		41 (10.1)	64 (15.9)	94 (24.0)	71 (18.7)	59 (15.6)	127 (34.4)	113 (32.1)	98 (29.3)	92 (28.7)	65 (20.7)	33 (14.3)
Chronic Obstructive Airways Disease	125	2 (0.5)	14 (3.5)	13 (3.3)	12 (3.2)	16 (4.2)	18 (4.9)	13 (3.7)	16 (4.8)	17 (5.3)	2 (0.6)	2 (0.9)
Nausea	27	2 (0.5)	3 (0.7)	7 (1.8)	2 (0.5)	2 (0.5)	1 (0.3)	6 (1.7)	1 (0.3)	3 (0.9)	0	0
Diarrhea	44	0	9 (2.2)	7 (1.8)	4 (1.1)	4 (1.1)	4 (1.1)	3 (0.9)	5 (1.5)	3 (0.9)	2 (0.6)	3 (1.3)
Abdominal Pain	38	1 (0.2)	4 (1.0)	4 (1.0)	8 (2.1)	1 (0.3)	4 (1.1)	3 (0.9)	4 (1.2)	5 (1.6)	3 (1.0)	0
Headache	33	2 (0.5)	4 (1.0)	5 (1.3)	4 (1.1)	3 (0.8)	6 (1.6)	5 (1.4)	2 (0.6)	1 (0.3)	1 (0.3)	0
Upper Respiratory Tract Infection	61	0	5 (1.2)	3 (0.8)	4 (1.1)	1 (0.3)	5 (1.4)	11 (3.1)	13 (3.9)	10 (3.1)	6 (1.9)	3 (1.3)
Dyspepsia	10	1 (0.2)	1 (0.2)	2 (0.5)	1 (0.3)	0	1 (0.3)	1 (0.3)	1 (0.3)	0	1 (0.3)	1 (0.4)
Vomiting	11	0	0	4 (1.0)	1 (0.3)	0	1 (0.3)	2 (0.6)	0	1 (0.3)	2 (0.6)	0
Injury	28	1 (0.2)	1 (0.2)	1 (0.3)	0	3 (0.8)	7 (1.9)	5 (1.4)	3 (0.9)	3 (0.9)	4 (1.3)	0
Sinusitis	34	0	1 (0.2)	3 (0.8)	2 (0.5)	3 (0.8)	5 (1.4)	3 (0.9)	8 (2.4)	6 (1.9)	3 (1.0)	0
Dizziness	22	1 (0.2)	0	6 (1.5)	2 (0.5)	1 (0.3)	5 (1.4)	3 (0.9)	2 (0.6)	1 (0.3)	0	1 (0.4)
Arthralgia	18	0	2 (0.5)	0	0	2 (0.5)	3 (0.8)	1 (0.3)	4 (1.2)	3 (0.9)	2 (0.6)	1 (0.4)
Coughing	34	2 (0.5)	1 (0.2)	2 (0.5)	3 (0.8)	1 (0.3)	6 (1.6)	10 (2.8)	2 (0.6)	3 (0.9)	4 (1.3)	0
Fatigue	15	1 (0.2)	3 (0.7)	2 (0.5)	0	1 (0.3)	2 (0.5)	0	1 (0.3)	2 (0.6)	2 (0.6)	1 (0.4)
Flatulence	11	1 (0.2)	1 (0.2)	2 (0.5)	1 (0.3)	2 (0.5)	3 (0.8)	0	0	1 (0.3)	0	0
Insomnia	8	0	1 (0.2)	1 (0.3)	0	0	1 (0.3)	2 (0.6)	0	2 (0.6)	0	0
Urinary Tract Infection	18	0	2 (0.5)	3 (0.8)	1 (0.3)	1 (0.3)	3 (0.8)	4 (1.1)	2 (0.6)	0	0	2 (0.9)
Infection Viral	9	0	0	2 (0.5)	1 (0.3)	2 (0.5)	0	0	2 (0.6)	1 (0.3)	1 (0.3)	0
Back Pain	24	0	2 (0.5)	1 (0.3)	1 (0.3)	3 (0.8)	5 (1.4)	2 (0.6)	2 (0.6)	3 (0.9)	4 (1.3)	1 (0.4)
Pharyngitis	16	0	2 (0.5)	1 (0.3)	2 (0.5)	1 (0.3)	2 (0.5)	1 (0.3)	2 (0.6)	2 (0.6)	2 (0.6)	1 (0.4)

Adverse Event (Preferred Term)	N[a]	Time of Initial Onset (Days)										
		1 (N=407)[b] n (%)	2–7 (N=402)[b] n (%)	8–14 (N=391)[b] n (%)	15-21 (N=380)[b] n (%)	22–28 (N=377)[b] n (%)	29–56 (N=369)[b] n (%)	57–84 (N=352)[b] n (%)	85–112 (N=334)[b] n (%)	113-140 (N=321)[b] n (%)	141-168 (N=314)[b] n (%)	>168 (N=231)[b] n (%)
Dyspnea	29	1 (0.2)	3 (0.7)	5 (1.3)	3 (0.8)	1 (0.3)	7 (1.9)	2 (0.6)	3 (0.9)	2 (0.6)	1 (0.3)	1 (0.4)
Myalgia	15	2 (0.5)	1 (0.2)	1 (0.3)	1 (0.3)	1 (0.3)	4 (1.1)	2 (0.6)	0	1 (0.3)	2 (0.6)	0
Pain	6	0	0	1 (0.3)	0	0	3 (0.8)	0	0	0	1 (0.3)	1 (0.4)
Rhinitis	14	1 (0.2)	1 (0.2)	1 (0.3)	0	1 (0.3)	2 (0.5)	3 (0.9)	2 (0.6)	1 (0.3)	2 (0.6)	0
Anxiety	6	0	1 (0.2)	0	1 (0.3)	1 (0.3)	0	1 (0.3)	1 (0.3)	1 (0.3)	0	0
Anorexia	3	0	0	0	1 (0.3)	0	0	2 (0.6)	0	0	0	0
Melena	6	0	1 (0.2)	0	0	0	1 (0.3)	0	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.4)
Constipation	10	0	0	3 (0.8)	1 (0.3)	3 (0.8)	0	0	0	1 (0.3)	2 (0.6)	0
Hyperglycemia	12	4 (1.0)	0	3 (0.8)	4 (1.1)	0	0	0	0	0	0	1 (0.4)
Asthenia	5	0	1 (0.2)	0	1 (0.3)	0	0	1 (0.3)	0	2 (0.6)	0	0
Chest Pain	16	1 (0.2)	1 (0.2)	2 (0.5)	3 (0.8)	0	3 (0.8)	2 (0.6)	3 (0.9)	1 (0.3)	0	0
Gastroesophageal Reflux	4	0	1 (0.2)	0	0	1 (0.3)	0	0	0	1 (0.3)	1 (0.3)	0
Hyperkalemia	9	0	0	1 (0.3)	1 (0.3)	1 (0.3)	0	3 (0.9)	0	0	1 (0.3)	2 (0.9)
Bronchitis	6	1 (0.2)	0	0	0	0	0	0	0	3 (0.9)	2 (0.6)	0
Hematuria	12	4 (1.0)	0	1 (0.3)	2 (0.5)	0	1 (0.3)	3 (0.9)	0	0	0	1 (0.4)
Hypertension	15	0	0	0	2 (0.5)	1 (0.3)	2 (0.5)	2 (0.6)	1 (0.3)	4 (1.2)	0	3 (1.3)
Tremor	1	0	0	0	0	0	0	0	0	0	0	0

a. N is the total number of patients reporting the particular AE at least once on-therapy. Each patient was counted once per preferred term.
b. Percentages for each interval are based on these "N" values.
Data Source: Section 15, Table 15.5; Appendix D, Listing 1.

Table 40 Summary of Most Frequently Reported (≥2% of Patients in Either Treatment Group) On-therapy Adverse Events by Initial Time of Onset: SB 207499 Treatment Group

Adverse Event (Preferred Term)	N[a]	Time of Initial Onset (Days) 1 (N=418)[b] n (%)	2–7 (N=413)[b] n (%)	8–14 (N=392)[b] n (%)	15-21 (N=364)[b] n (%)	22–28 (N=353)[b] n (%)	29–56 (N=339)[b] n (%)	57–84 (N=322)[b] n (%)	85–112 (N=304)[b] n (%)	113-140 (N=291)[b] n (%)	141-168 (N=281)[b] n (%)	>168 (N=204)[b] n (%)
Total SB 207499 15mg BID		84 (20.1)	132 (32.0)	86 (21.9)	67 (18.4)	59 (16.7)	112 (33.0)	103 (32.0)	79 (26.0)	73 (25.1)	68 (24.2)	19 (9.3)
Chronic Obstructive Airways Disease	114	2 (0.5)	17 (4.1)	12 (3.1)	5 (1.4)	7 (2.0)	24 (7.1)	15 (4.7)	14 (4.6)	6 (2.1)	11 (3.9)	1 (0.5)
Nausea	109	25 (6.0)	41 (9.9)	14 (3.6)	3 (0.8)	7 (2.0)	10 (2.9)	5 (1.6)	2 (0.7)	1 (0.3)	1 (0.4)	0
Diarrhea	82	7 (1.7)	29 (7.0)	11 (2.8)	6 (1.6)	12 (3.4)	9 (2.7)	2 (0.6)	4 (1.3)	2 (0.7)	0	0
Abdominal Pain	52	9 (2.2)	11 (2.7)	3 (0.8)	9 (2.5)	2 (0.6)	7 (2.1)	4 (1.2)	3 (1.0)	3 (1.0)	1 (0.4)	0
Headache	46	3 (0.7)	15 (3.6)	11 (2.8)	0	2 (0.6)	5 (1.5)	4 (1.2)	1 (0.3)	1 (0.3)	3 (1.1)	1 (0.5)
Upper Respiratory Tract Infection	46	1 (0.2)	1 (0.2)	4 (1.0)	4 (1.1)	5 (1.4)	4 (1.2)	8 (2.5)	2 (0.7)	12 (4.1)	5 (1.8)	0
Dyspepsia	38	6 (1.4)	10 (2.4)	2 (0.5)	5 (1.4)	0	4 (1.2)	6 (1.9)	0	2 (0.7)	3 (1.1)	0
Vomiting	33	2 (0.5)	10 (2.4)	2 (0.5)	2 (0.5)	5 (1.4)	6 (1.8)	3 (0.9)	2 (0.7)	0	1 (0.4)	0
Injury	31	0	1 (0.2)	1 (0.3)	5 (1.4)	1 (0.3)	8 (2.4)	1 (0.3)	6 (2.0)	4 (1.4)	3 (1.1)	1 (0.5)
Sinusitis	30	0	1 (0.2)	3 (0.8)	1 (0.3)	2 (0.6)	6 (1.8)	3 (0.9)	7 (2.3)	5 (1.7)	0	2 (1.0)
Dizziness	24	4 (1.0)	4 (1.0)	1 (0.3)	1 (0.3)	2 (0.6)	6 (1.8)	1 (0.3)	5 (1.6)	0	0	0
Arthralgia	22	1 (0.2)	0	1 (0.3)	3 (0.8)	2 (0.6)	2 (0.6)	1 (0.3)	4 (1.3)	5 (1.7)	2 (0.7)	1 (0.5)
Coughing	21	0	4 (1.0)	1 (0.3)	2 (0.5)	0	1 (0.3)	6 (1.9)	3 (1.0)	4 (1.4)	0	0
Fatigue	20	2 (0.5)	9 (9.2)	2 (0.5)	1 (0.3)	0	2 (0.6)	0	2 (0.7)	0	2 (0.7)	0
Flatulence	20	1 (0.2)	10 (2.4)	1 (0.3)	0	2 (0.6)	3 (0.9)	1 (0.3)	1 (0.3)	0	1 (0.4)	0
Insomnia	19	1 (0.2)	6 (1.5)	1 (0.3)	3 (0.8)	1 (0.3)	5 (1.5)	0	1 (0.3)	1 (0.3)	0	0
Urinary Tract Infection	16	2 (0.5)	1 (0.2)	1 (0.3)	1 (0.3)	0	2 (0.6)	6 (1.9)	1 (0.3)	0	1 (0.4)	1 (0.5)
Infection Viral	16	0	5 (1.2)	1 (0.3)	2 (0.5)	1 (0.3)	0	0	2 (0.7)	3 (1.0)	1 (0.4)	1 (0.5)
Back Pain	16	0	2 (0.5)	1 (0.3)	2 (0.5)	2 (0.6)	4 (1.2)	1 (0.3)	2 (0.7)	0	2 (0.7)	0
Pharyngitis	15	0	2 (0.5)	0	0	2 (0.6)	3 (0.9)	2 (0.6)	2 (0.7)	2 (0.7)	2 (0.7)	0
Dyspnea	15	2 (0.5)	1 (0.2)	1 (0.3)	1 (0.3)	3 (0.8)	0	1 (0.3)	3 (1.0)	2 (0.7)	1 (0.4)	0
Myalgia	15	0	2 (0.5)	3 (0.8)	2 (0.5)	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	3 (1.1)	0
Pain	14	0	1 (0.2)	3 (0.8)	0	2 (0.6)	1 (0.3)	1 (0.3)	0	4 (1.4)	2 (0.7)	0
Rhinitis	13	0	0	2 (0.5)	0	1 (0.3)	2 (0.6)	1 (0.3)	4 (1.3)	1 (0.3)	2 (0.7)	0

Adverse Event (Preferred Term)	N[a]	Time of Initial Onset (Days)										
		1 (N=418)[b] n (%)	2–7 (N=413)[b] n (%)	8–14 (N=392)[b] n (%)	15-21 (N=364)[b] n (%)	22–28 (N=353)[b] n (%)	29–56 (N=339)[b] n (%)	57–84 (N=322)[b] n (%)	85–112 (N=304)[b] n (%)	113-140 (N=291)[b] n (%)	141-168 (N=281)[b] n (%)	>168 (N=204)[b] n (%)
Anxiety	13	1 (0.2)	3 (0.7)	0	0	1 (0.3)	2 (0.6)	4 (1.2)	1 (0.3)	1 (0.3)	0	0
Anorexia	12	1 (0.2)	1 (0.2)	2 (0.5)	1 (0.3)	0	1 (0.3)	4 (1.2)	2 (0.7)	0	0	0
Melena	12	1 (0.2)	2 (0.5)	2 (0.5)	0	2 (0.6)	0	0	1 (0.3)	2 (0.7)	2 (0.7)	0
Constipation	11	1 (0.2)	5 (1.2)	0	1 (0.3)	0	2 (0.6)	1 (0.3)	0	0	1 (0.4)	0
Hyperglycemia	11	2 (0.5)	0	3 (0.8)	1 (0.3)	0	1 (0.3)	1 (0.3)	2 (0.7)	0	0	1 (0.5)
Asthenia	10	0	3 (0.7)	3 (0.8)	0	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	0	0	0
Chest Pain	10	0	3 (0.7)	0	0	2 (0.6)	1 (0.3)	1 (0.3)	0	1 (0.3)	1 (0.4)	1 (0.5)
Gastroesophageal Reflux	10	2 (0.5)	2 (0.5)	3 (0.8)	0	1 (0.3)	0	2 (0.6)	0	0	0	0
Hyperkalemia	10	3 (0.7)	0	2 (0.5)	0	0	0	3 (0.9)	1 (0.3)	0	1 (0.4)	0
Bronchitis	10	0	0	0	0	2 (0.6)	3 (0.9)	2 (0.6)	3 (1.0)	0	0	0
Hematuria	10	1 (0.2)	1 (0.2)	2 (0.5)	0	0	2 (0.6)	3 (0.9)	1 (0.3)	0	0	0
Hypertension	9	1 (0.2)	0	1 (0.3)	1 (0.3)	0	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	2 (0.7)	0
Tremor	9	0	4 (1.0)	0	0	0	2 (0.6)	1 (0.3)	1 (0.3)	1 (0.3)	0	0

a. N is the total number of patients reporting the particular AE at least once on-therapy. Each patient was counted once per preferred term.
b. Percentages for each interval are based on these "N" values.
Data Source: Section 15, Table 15.5; Appendix D, Listing 1.

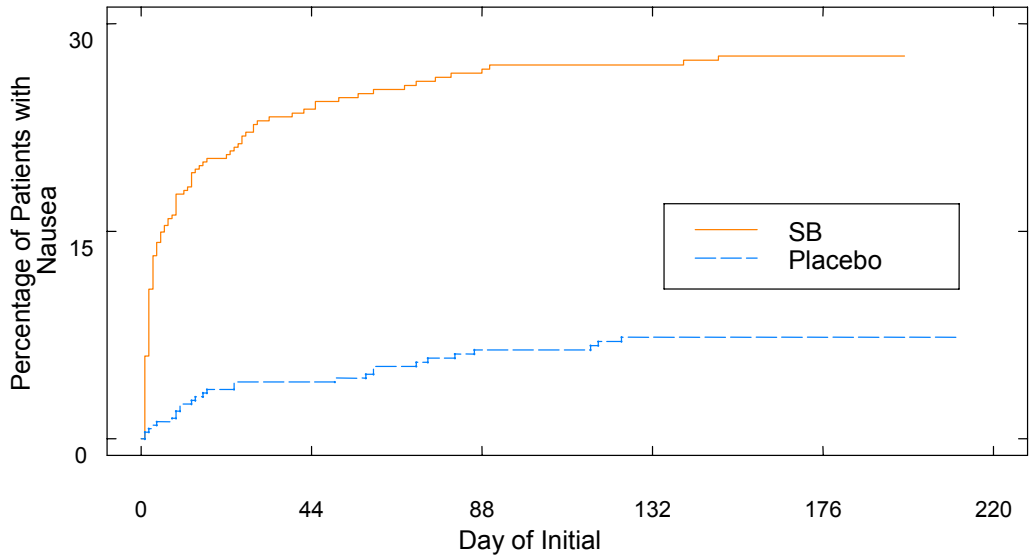
During the first 4 weeks of double-blind study treatment, a majority (>50%) of SB 207499-treated patients reported the initial onset of nausea, diarrhea, abdominal pain, headache, dyspepsia, vomiting, fatigue, flatulence, insomnia, infection viral, dyspnea, myalgia, melena, constipation, hyperglycemia, asthenia, and gastroesophageal reflux compared with the remaining 20 weeks.

For placebo-treated patients who reported diarrhea, the incidence was higher during the first 14 days compared with the remaining intervals. Upper respiratory tract infection was reported at a higher incidence for the first time during the intervals that spanned from Day 57 through 140 for both treatment groups compared with other intervals during the double-blind treatment period. Incidence of melena for the SB 207499 treatment group (8 patients) was more prevalent during the first 4 weeks of double-blind treatment compared to the placebo treatment group (1 patient), but were similar between the two treatment groups during the remainder of the study (5 patients in each group). Therefore, the relative likelihood of developing symptoms of gastrointestinal bleeding are higher for short term (≤4 weeks) versus long term (>4 weeks) exposure to SB 207499. For the remaining adverse events reported with the highest frequency during the first week of double-blind study medication in the SB 207499 treatment group, the distribution was more even over time in the placebo treatment group. There were no other notable trends over time for common on-therapy adverse events.

Graphical representation of the cumulative incidence of nausea, abdominal pain, diarrhea, and vomiting are presented in Figure 13, Figure 14,

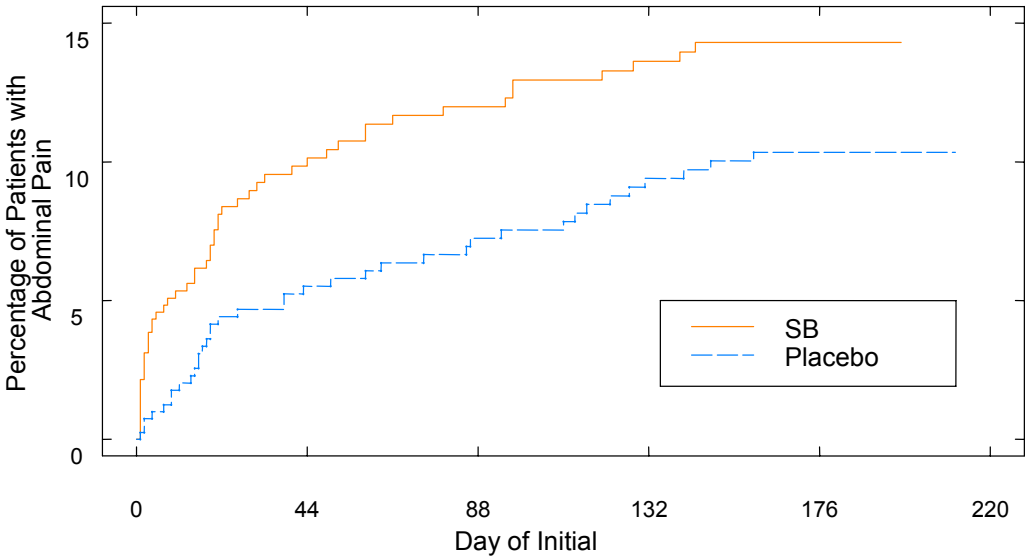
Figure 15, and Figure 16, respectively (Section 19, Figure 19.15, Figure 19.16, Figure 19.17, Figure 19.18, respectively). The incidence of nausea, abdominal pain, diarrhea, and vomiting show the initial time of onset for the majority of patients in the SB 207499 treatment group was during the first 4 weeks of double-blind treatment. In general, there was a gradual increase in incidence over the course of the double-blind treatment period in the placebo treatment group. Differences between the groups were clearly apparent within the first week of double-blind treatment.

Figure 13 Cumulative incidence of Nausea



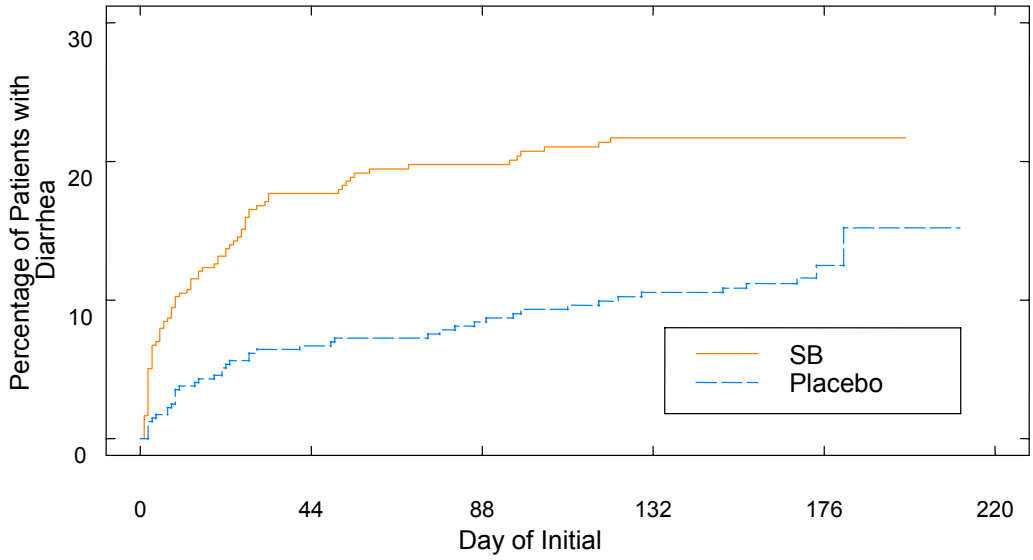
Data Source: Section 19, Figure 19.15

Figure 14 Cumulative incidence of Abdominal Pain



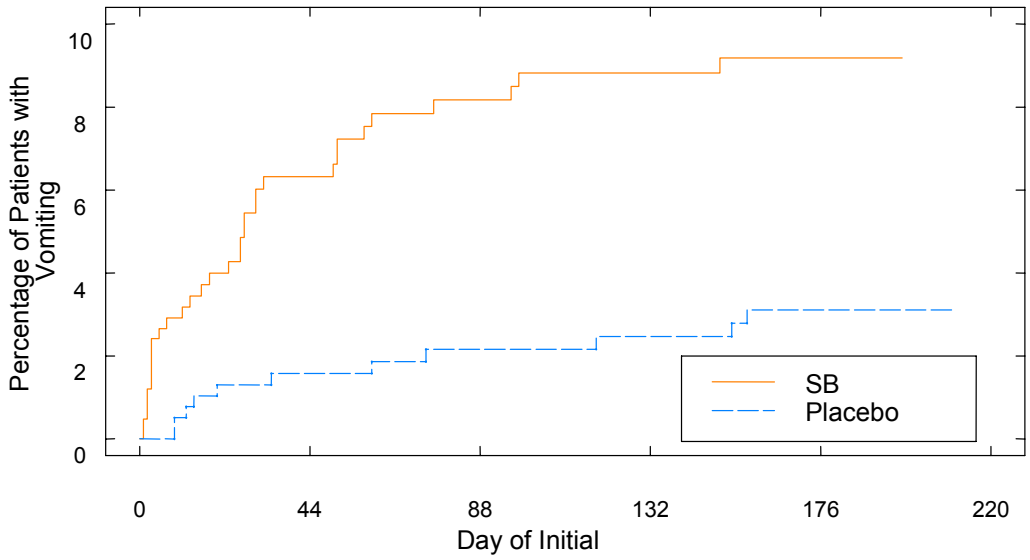
Data Source: Section 19, Figure 19.16

Figure 15 Cumulative incidence of Diarrhea



Data Source: Section 19, Figure 19.17

Figure 16 Cumulative incidence of Vomiting



Data Source: Section 19, Figure 19.18

8.3. Adverse Events Requiring Corrective Treatment

As shown in Table 41, 269 patients (66.1% of 407) who received placebo had an adverse event that required corrective therapy as compared with 269 patients (64.4% of 418) who received SB 207499. The most common adverse events that required corrective therapy were chronic obstructive airways disease, sinusitis, and upper respiratory tract infection.

Chronic obstructive airways disease that required corrective therapy comparable in patients receiving placebo (26.0%) and SB 207499 (24.9%). Among the most commonly occurring adverse events (i.e., ≥2% of patients in the SB 207499 treatment group) that required corrective therapy, dyspepsia, injury, nausea, diarrhea, headache, abdominal pain, arthralgia, bronchitis, gastroesophageal reflux, infection viral, and pharyngitis required therapy more frequently in patients receiving SB 207499 than in patients receiving placebo. Conversely, coughing, urinary tract infection, back pain, rhinitis, hypertension, respiratory disorder, sinusitis, upper respiratory tract infection, dyspnea, and periodontitis required corrective therapy more frequently among placebo-treated versus SB 207499-treated patients.

Table 41 Summary of Most Frequently Reported (≥2% of Patients in Either Treatment Group) On-therapy Adverse Events That Required Corrective Therapy

Adverse Event (Preferred Term)	Treatment Group: Placebo (N=407) n (%)		Treatment Group: SB 207499 15mg BID (N=418) n (%)	
Total[a]	269	(66.1)	269	(64.4)
Chronic Obstructive Airways Disease	106	(26.0)	104	(24.9)
Sinusitis	27	(6.6)	27	(6.5)
Upper Respiratory Tract Infection	35	(8.6)	25	(6.0)
Dyspepsia	5	(1.2)	24	(5.7)
Injury	18	(4.4)	23	(5.5)
Nausea	3	(0.7)	22	(5.3)
Diarrhea	7	(1.7)	21	(5.0)
Headache	15	(3.7)	20	(4.8)
Abdominal Pain	10	(2.5)	19	(4.5)
Arthralgia	7	(1.7)	16	(3.8)
Coughing	13	(3.2)	13	(3.1)
Urinary Tract Infection	16	(3.9)	13	(3.1)
Back Pain	16	(3.9)	11	(2.6)
Bronchitis	6	(1.5)	10	(2.4)
Rhinitis	10	(2.5)	10	(2.4)
Gastroesophageal Reflux	2	(0.5)	9	(2.2)
Infection Viral	5	(1.2)	9	(2.2)
Pharyngitis	4	(1.0)	9	(2.2)
Hypertension	10	(2.5)	7	(1.7)
Respiratory Disorder	8	(2.0)	6	(1.4)
Dyspnea	8	(2.0)	4	(1.0)
Periodontitis	9	(2.2)	2	(0.5)

a. Total represents the total number of patients reporting at least one adverse event that required corrective therapy.
Data Source: Section 15, Table 15.7; Appendix D, Listing 4.

8.4. Deaths

No patients died during the double-blind treatment period or within 30 days post-therapy. A total of 3 patients died during the placebo run-in period. A listing of the patients who died is presented in Table 42.

Table 42 Deaths



a. All patients died during the placebo run-in period.
Data Source: Appendix D, Listing 5D; Appendix B, Listing 1.

Complete narratives for the patients who died are provided in Section 15, Table 15.8D. CRFs for patients with fatal adverse events are provided in Appendix G.

8.5. Serious Adverse Events

Serious adverse events during treatment with double-blind medication were reported for 38 (9.3%) of 407 patients who received placebo compared with 25 (6.0%) of 418 patients who received SB 207499 (Section 15, Table 15.8B). In addition, serious adverse events were reported within 30 days of stopping double-blind treatment for 4 patients (1.0%) who received placebo and for 2 patients (0.5%) who received SB 207499 (Section 15, Table 15.8C). The incidence of serious adverse events experienced during the placebo run-in phase are presented in Section 15, Table 15.8A and Appendix D, Listing 5A. All 3 fatal adverse events occurred only during the placebo run-in phase and are presented in Section 8.4. The most frequently reported on-therapy serious adverse events (i.e., occurring in >1 patient in either treatment group) are presented by preferred term in descending order of frequency for the SB 207499 treatment group in Table 43.

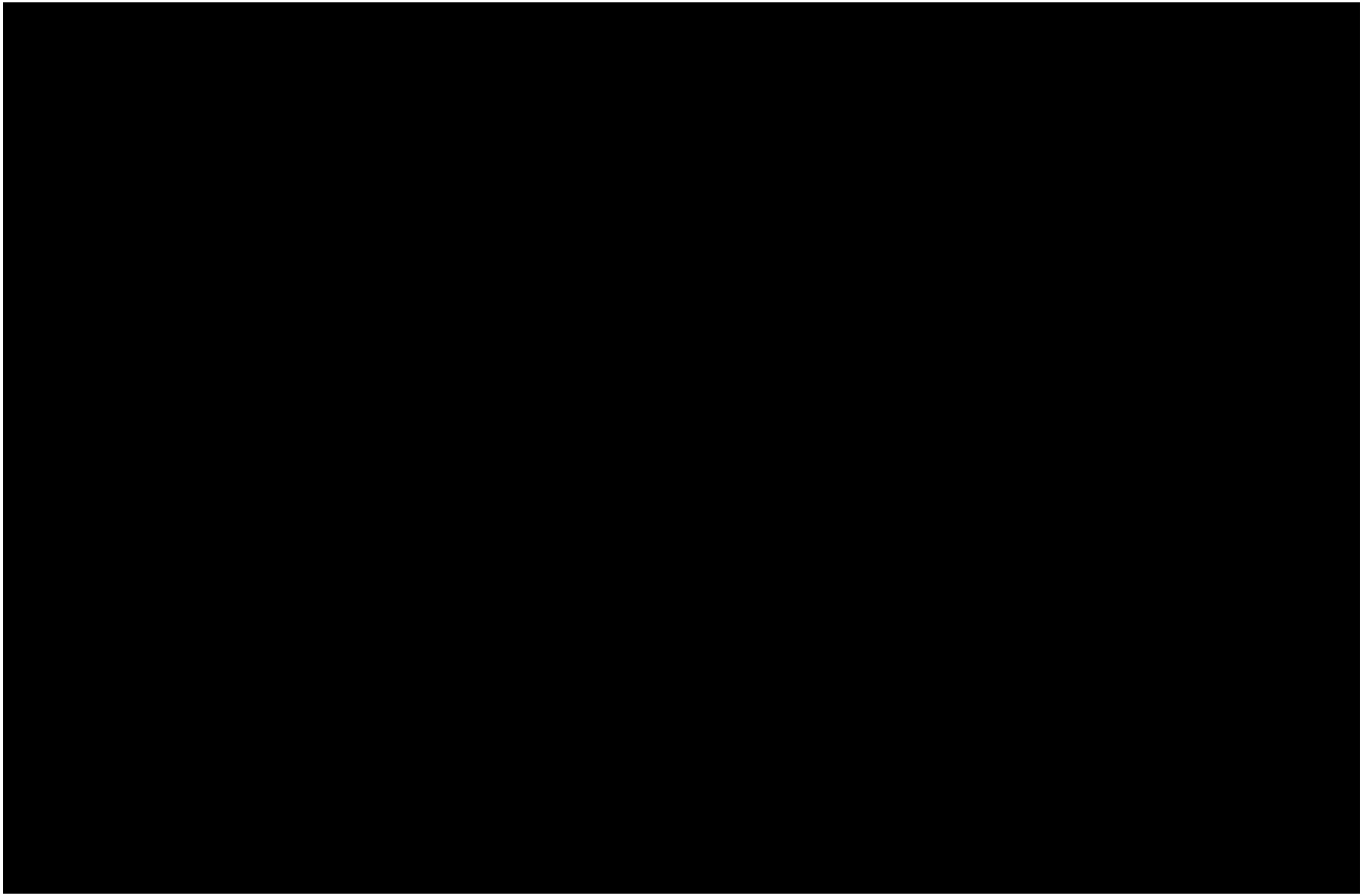
Table 43 Summary of Most Frequently Reported (>1 Patient in Either Treatment Group) On-therapy Serious Adverse Events

Serious Adverse Event (Preferred Term)	Treatment Group: Placebo (N=407) n (%)	Treatment Group: SB 207499 15mg BID (N=418) n (%)
Total[a]	38 (9.3)	25 (6.0)
Chronic Obstructive Airways Disease	7 (1.7)	6 (1.4)
Cerebrovascular Disorder	1 (0.2)	2 (0.5)
Basal Cell Carcinoma	4 (1.0)	1 (0.2)
Chest Pain	3 (0.7)	1 (0.2)
Pneumonia	3 (0.7)	1 (0.2)
Cardiac Failure	3 (0.7)	0
Myocardial Infarction	3 (0.7)	0
Fibrillation Atrial	2 (0.5)	0
Pulmonary Carcinoma	2 (0.5)	0

a. Total represents the total number of patients reporting at least one serious adverse event.
Data Source: Section 15, Table 15.8B; Appendix D, Listing 5B.

All serious, non-fatal adverse events that occurred during the placebo run-in, double-blind, and post-therapy periods are listed in Table 44.

Table 44 Non-fatal Serious Adverse Events



The most common on-therapy non-fatal serious adverse event was chronic obstructive airways disease, which occurred at a lower incidence in the SB 207499 treatment group (1.4%) compared with the placebo treatment group (1.7%) (Section 15, Table 15.8B). Almost all of the serious non-fatal adverse events were considered not related or of unlikely relationship to study medication. [redacted] No patients had SAEs considered to have a probable relationship to study medication by the Investigator. Patients withdrawn due to the non-fatal serious adverse events are presented in Section 8.6.

Narratives for all patients with non-fatal serious adverse events are provided in Section 15, Table 15.8E. CRFs for patients with non-fatal serious adverse events are provided in Appendix G.

8.6. Withdrawals Due to Adverse Events

A total of 40 (9.8%) of 407 placebo-treated patients and 75 (17.9%) of 418 patients in the SB 207499 treatment group were withdrawn from double-blind treatment due to an adverse event. On-therapy adverse events leading to withdrawal in either treatment group are presented by body system, preferred term, and treatment group in decreasing frequency of occurrence in Section 15, Table 15.9A and by body system, preferred term, and treatment group in Section 15, Table 15.9B. Run-in adverse events that led to withdrawal are presented in Appendix D, Listing 6B. On-therapy adverse events leading to withdrawal in more than one patient in either treatment group are summarized in Table 45. CRFs for patients withdrawn due to adverse events are provided in Appendix G.

Table 45 Incidence of On-therapy Adverse Events Leading to Withdrawal in More Than One Patient in Either Treatment Group

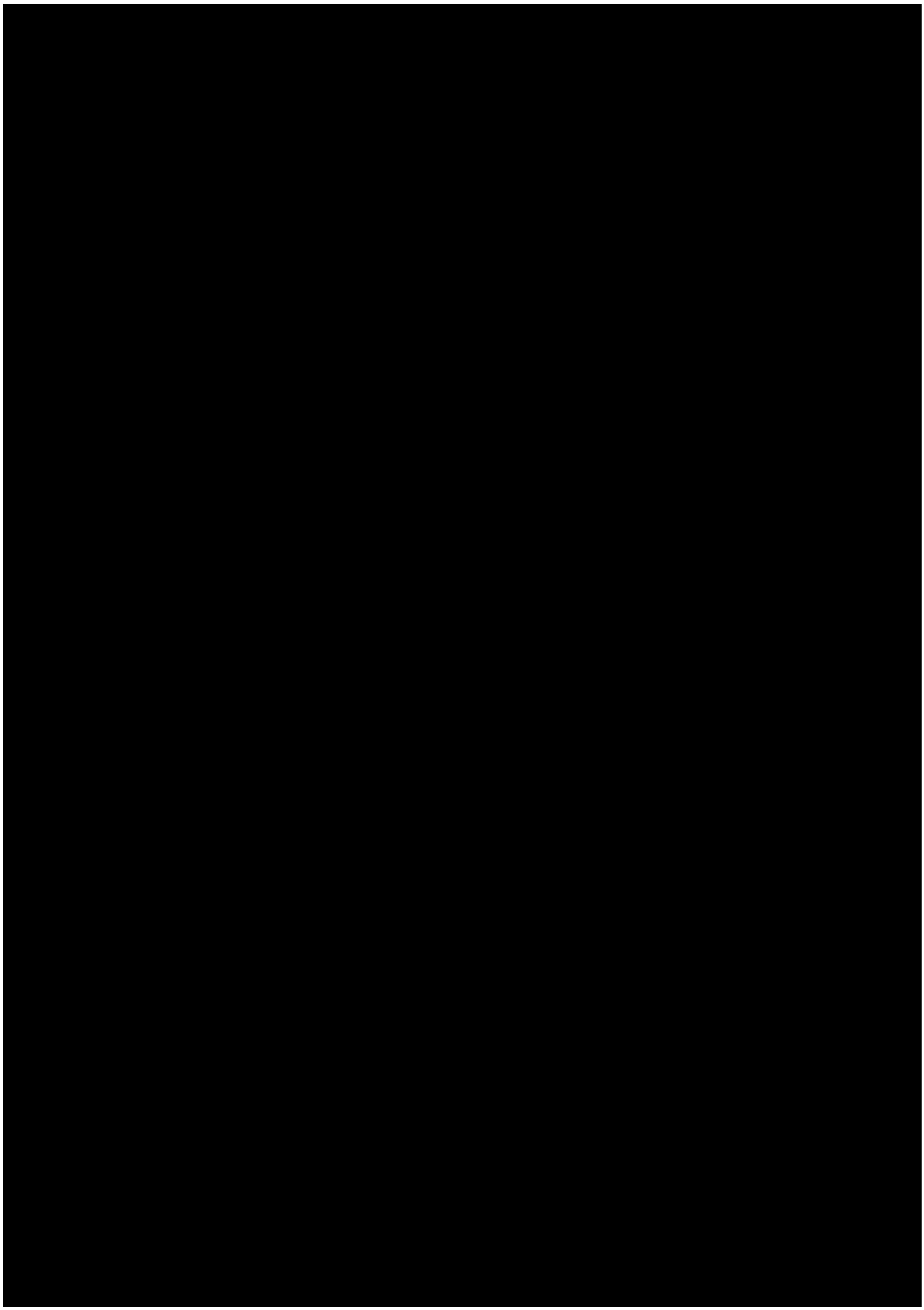
Adverse Event (Preferred Term)	Treatment Group: Placebo (N=407) n (%)	Treatment Group: SB 207499 15mg BID (N=418) n (%)
Total[a]	40 (9.8)	75 (17.9)
Nausea	3 (0.7)	35 (8.4)
Diarrhea	2 (0.5)	16 (3.8)
Abdominal Pain	3 (0.7)	11 (2.6)
Chronic Obstructive Airways Disease	9 (2.2)	11 (2.6)
Dizziness	2 (0.5)	4 (1.0)
Vomiting	1 (0.2)	4 (1.0)
Headache	0	3 (0.7)
Dyspepsia	1 (0.2)	3 (0.7)
Flatulence	0	3 (0.7)
Melena	0	3 (0.7)
Pneumonia	3 (0.7)	2 (0.5)
Rash	1 (0.2)	2 (0.5)
Cardiac Failure	2 (0.5)	0
Hypotension	2 (0.5)	0
Fibrillation Atrial	2 (0.5)	0
Myocardial Infarction	2 (0.5)	0
Pulmonary Carcinoma	2 (0.5)	0
Dyspnea	2 (0.5)	0

a. Total represents total number of patients withdrawn due to adverse event.
Data Source: Section 15, Table 15.9A; Appendix D, Listing 6A.

There was a higher incidence of nausea (0.7% placebo vs. 8.4% SB 207499), diarrhea (0.5% placebo vs. 3.8% SB 207499), and abdominal pain (0.7% placebo vs. 2.6% SB 207499) leading to withdrawal among SB 207499-treated versus placebo-treated patients. Other AEs leading to withdrawal reported at a higher incidence in the SB 207499 treatment group compared to the placebo treatment group included vomiting, headache, flatulence, and melena. Several AEs leading to withdrawal were each reported by 2 placebo-treated and by no SB 207499-treated patients including cardiac failure, hypotension, atrial fibrillation, myocardial infarction, pulmonary carcinoma, and dyspnea.

All patients who were withdrawn from double-blind treatment due to adverse events are listed in Table 46. Narratives for patients withdrawn for on-therapy non-serious adverse events are provided in Section 15, Table 15.9C. Patients who were withdrawn from placebo run-in due to adverse events are listed in Appendix D, Listing 6B.

Table 46 Withdrawals Due to Adverse Events





Data Source: Appendix B, Listing 1; Appendix D, Listing 6A and Listing 6B.

On-therapy adverse events that led to dose interruption are provided by preferred term in Section 15, Table 15.6 and by individual patient in Appendix D, Listing 3.

8.7. Gastrointestinal Adverse Events of Concern

Gastrointestinal adverse events of bloody or black stools, abdominal discomfort such as pain or cramps, diarrhea, or vomiting that concerned the patient or interfered with their daily activities were closely monitored during the study. On-therapy GI adverse events of concern and specific assessments of GI symptoms, abdominal pain, stools, and physical examinations for individual patients with GI symptoms of concern are presented in Appendix D, Listing 8, Listing 9, Listing 10, Listing 11, and Listing 12. GI adverse events of concern that occurred during the placebo run-in or post-therapy periods are presented in Appendix D, Listing 8A and Listing 8B, respectively.

Narratives are provided in Section 15, Table 15.8E for patients with serious GI adverse events of concern and in Section 15, Table 15.9C for patients who withdrew from the study due to GI adverse events of concern. Additionally, narratives for patients receiving SB 207499 who had non-serious GI adverse events of concern that did not lead to withdrawal are provided in Section 15, Table 15.11D.

8.7.1. Incidence of On-therapy Gastrointestinal Adverse Events of Concern

The incidence of on-therapy GI adverse events of concern is presented by body system, preferred term, and treatment group in decreasing frequency of occurrence in Section 15, Table 15.11A and by preferred term in order of decreasing frequency for the SB 207499 treatment group in Table 47. A listing of all on-therapy GI adverse events of concern is presented by individual patient in Appendix D, Listing 8. Patients may have had more than one GI adverse event of concern.

Table 47 Incidence of On-therapy Gastrointestinal Adverse Events of Concern

Adverse Event (Preferred Term)	Treatment Group: Placebo (N=407) n (%)	Treatment Group: SB 207499 15mg BID (N=418) n (%)
Total[a]	18 (4.4)	51 (12.2)
Nausea	4 (1.0)	23 (5.5)
Diarrhea	10 (2.5)	21 (5.0)
Abdominal Pain	12 (2.9)	20 (4.8)
Vomiting	4 (1.0)	12 (2.9)
Dyspepsia	2 (0.5)	6 (1.4)
Gastroesophageal Reflux	0	6 (1.4)
Melena	4 (1.0)	6 (1.4)
Constipation	0	3 (0.7)
Flatulence	1 (0.2)	3 (0.7)
Gastroenteritis	0	3 (0.7)
Anorexia	0	1 (0.2)
Anxiety	0	1 (0.2)
Dizziness	0	1 (0.2)
Eructation	0	1 (0.2)
Feces Discolored	1 (0.2)	1 (0.2)
Hemorrhage Rectum	2 (0.5)	1 (0.2)
Hemorrhoids	1 (0.2)	1 (0.2)
Infection Viral	0	1 (0.2)
Irritable Bowel Syndrome	0	1 (0.2)
Vascular Disorder	0	1 (0.2)
Diverticulitis	1 (0.2)	0

a. Total represents total number of patients who experienced at least one GIAE of concern.
Data Source: Section 15, Table 15.11A; Appendix D, Listing 8.

During treatment with double-blind medication, 18 of 407 (4.4%) patients who received placebo and 51 of 418 (12.2%) patients who received SB 207499 had GI adverse events of concern. The most common of these (occurring in ≥2% of SB 207499 patients) were nausea, diarrhea, abdominal pain, and vomiting. All of GI adverse events, with the exception of feces discolored, hemorrhage rectum, hemorrhoids, and diverticulitis, were reported with greater frequency in the SB 207499 treatment group compared with the placebo treatment group. A total of 2 patients had GI adverse events of concern that were considered serious. [redacted] A listing of all on-therapy GI adverse events of concern is presented by individual patient in Table 48 and in Appendix D, Listing 8.

Table 48 Listing of Patients Who Experienced GIAEs of Concern



8.7.2. Gastrointestinal Adverse Events of Concern by Intensity

The majority of GI adverse events of concern in each treatment group were of mild or moderate intensity (Section 15, Table 15.11C). Severe GI adverse events of concern were reported for 4 of 407 patients (1.0%) in the placebo treatment group and 7 of 418 patients (1.7%) in the SB 207499 treatment group.

8.7.2.1. Patients With Severe GI Adverse Events of Concern Who Received Placebo

A total of 4 (1.0%) of 407 patients who received placebo experienced on-therapy severe GI adverse events of concern. Brief narratives for these four patients are provided below. For one of these patients, the GI adverse events were reported as serious.

[redacted] All events had resolved within 15 days of onset. [redacted] There were no orthostatic changes of clinical concern in vital signs at the GIAE or early withdrawal visits. Fecal occult blood tests were not done at the time of the adverse event or at the early withdrawal visit.

[redacted] The patient received corrective therapy and the event resolved after 3 days. There were no orthostatic changes in vital signs of clinical concern and all fecal occult blood tests were negative during the study.

[redacted] The patient received corrective therapy and both events resolved on Day 43. There were no orthostatic changes in vital signs of clinical concern and all fecal occult blood tests were negative during the study.

[redacted] Both GIAEs of concern were considered serious but had resolved after 6 days. The patient received corrective therapy and had a colonoscopy performed. Colonoscopy results are discussed in Section 8.7.8. Fecal occult blood tests were not assessed at the GIAE or early withdrawal visits. Although orthostatic vital signs were not assessed at the time of these GIAEs, there were no changes of concern noted at the early withdrawal visit.

8.7.2.2. Patients with Severe GI Adverse Events of Concern Who Received SB 207499

A total of 7 (1.7%) of 418 patients who received SB 207499 experienced severe GI adverse events of concern during the double-blind period. Brief narratives for these seven patients are provided below, while full narratives are provided in Section 15, Table

15.9C and Table 15.11D. For these patients, no GI adverse events were reported as serious.

[redacted] The events resolved within 13 days and there were no orthostatic changes in vital signs of clinical concern at the last (GIAE) study visit; all fecal occult blood tests were negative.

[redacted] There were no orthostatic changes in vital signs of clinical concern at the GIAE assessment and all fecal occult blood tests were negative during the study. [redacted]

[redacted] Both events resolved after 7 days. There were no orthostatic changes in vital signs of clinical concern at the last (GIAE) study visit and all fecal occult blood tests were negative.

[redacted] There were no orthostatic changes in vital signs of clinical concern at the GIAE or Week 24 study visits and all fecal occult blood tests were negative. The event resolved after 10 days.

[redacted] There were no orthostatic changes in vital signs of clinical concern at the last (GIAE) study visit and all fecal occult blood tests were negative.

[redacted] There were no orthostatic changes in vital signs of clinical concern at the GIAE or early withdrawal study visits and all fecal occult blood tests were negative. [redacted]

[redacted] All

three GIAEs resolved after 23 days. There were no orthostatic changes in vital signs of clinical concern at the last (GIAE) study visit and all fecal occult blood tests were negative.

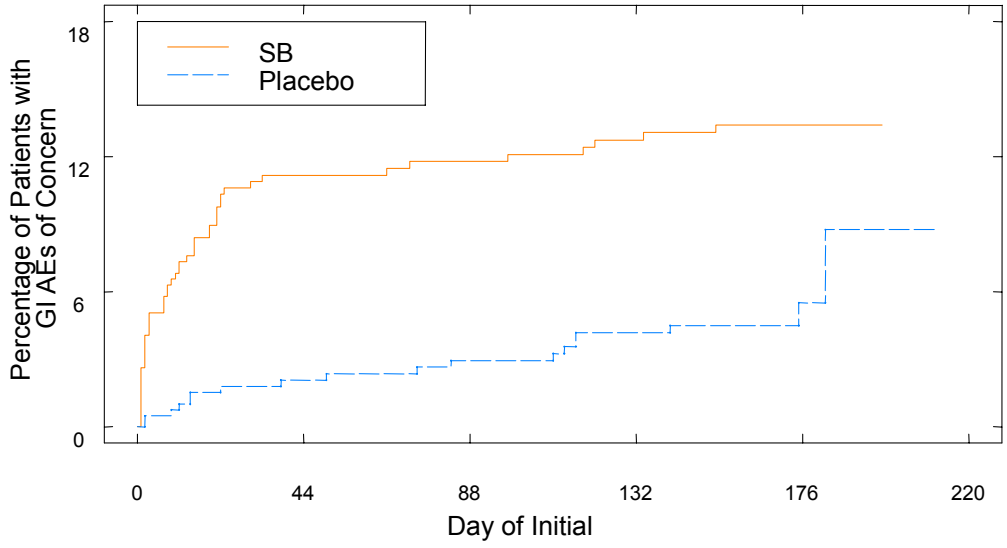
8.7.3. Gastrointestinal Adverse Events of Concern by Relationship

The percentage of patients reporting GI adverse events of concern that were considered by the Investigator to be related (suspected or probable relationship) to study medication was higher in the SB 207499 treatment group (8.1%, 34 of 418 patients) than in the placebo treatment group (2.7%, 11 of 407 patients). The GI adverse events of concern most commonly reported by the Investigators as related to study medication were nausea (placebo, 4 patients; SB 207499, 26 patients), diarrhea (placebo, 8 patients; SB 207499, 19 patients), and abdominal pain (placebo, 9 patients; SB 207499, 13 patients).

8.7.4. Gastrointestinal Adverse Events of Concern by Time of Initial Onset

Time of initial onset for the majority of GI adverse events of concern in patients who received SB 207499 was in the first three weeks of therapy, as shown in Figure 17. There was a gradual increase in incidence over the course of the double-blind treatment period in patients who received placebo. Differences between the groups were apparent within the first week of double-blind treatment, and the difference between the groups in the percentage of patients with GIAEs of concern did not considerably change beginning approximately at Day 21 through the remainder of the study.

Figure 17 Cumulative Incidence of Gastrointestinal Adverse Events of Concern by Time of Initial Onset



Data Source: Section 19, Figure 19.19

8.7.5. Gastrointestinal Adverse Events of Concern That Led to Withdrawal

Overall, GI adverse events of concern led to the withdrawal of 4 (1.0%) of 407 patients who received placebo and 20 (4.8%) of 418 patients who received SB 207499 (Section 15, Table 15.11B). The most common GI adverse events of concern leading to withdrawal from the SB 207499 treatment group were nausea (3.1% of 418 patients), abdominal pain (1.9%), and diarrhea (1.9%).

8.7.6. Fecal Occult Blood Tests in Patients With On-therapy Gastrointestinal Adverse Events of Concern

Of the 18 patients receiving placebo who had on-therapy GI adverse events of concern, 13 patients (72.2%) had fecal occult blood tests recorded by the Investigator specifically as a result of the event(s). [redacted]

Of the 51 patients receiving SB 207499 who had on-therapy GI adverse events of concern, 44 patients (86.3%) had fecal occult blood tests recorded specifically by the Investigator as a result of the event(s). [redacted]

A summary of FOB tests for patients with GIAEs of concern is presented in Table 49.

Table 49 Summary of Fecal Occult Blood Tests

	Patient with GIAEs of Concern			
Treatment Group	N[a]	FOB Test Performed[b] n (%)	FOB Positive n (%)	Colonoscopy Performed n (%)
Placebo	18	13 (72.2)	1 (7.7)[c]	3 (16.7)
SB 207499[d]	51	44 (86.3)	7 (15.9)[c]	4 (7.8)

a. Total represents the total number of patients with GIAEs of concern.
b. Total represents the total number of patients who had a FOB test performed as a result of one or more GIAEs of concern.
c. Percentages are calculated based on the number of patients who had a FOB test.
d. SB 207499 15mg BID.
Data Source: Appendix D, Listing 8, Listing 13, and Listing 14.

[redacted] These patients also did not have a colonoscopy performed. None of these 10 patients had low hemoglobin and hematocrit values that reached a level of clinical concern during the study. All FOB results for these 10 patients were negative. [redacted]

For patients with GI adverse events of concern during the 24-week double-blind treatment phase, transitions from baseline to on-therapy FOB results are provided in Section 15, Table 15.12A.

8.7.7. Adverse Events of Gastrointestinal Bleeding

A total of 30 patients (14 placebo and 16 SB 207499) had AEs of gastrointestinal bleeding (e.g., melena, hemorrhoids, feces discolored, and hemorrhage rectum) reported during the study. Of these patients, 6 who received placebo and 7 who were treated with SB 207499 did not have their AEs of GI bleeding reported as GIAE(s) of concern (Table 50). Brief narratives describing the GI bleeding events in these 13 patients are provided below (Sections 8.7.7.1 and 8.7.7.2).

[redacted]

Table 50 Summary of Patients with Gastrointestinal Bleeding

Treatment Group	N[a]	GI Bleeding[b] NOT Reported as GIAE of Concern n (%)	GI Bleeding[b] Reported as GIAE of Concern n (%)	Colonoscopy Performed n (%)[c]
Placebo	14	6 (42.9)	8 (57.1)	3 (21.4)
SB 207499[d]	16	7 (43.8)	9 (56.3)	3 (18.8)

a. Total represents the total number of patients with GI bleeding.
b. Includes preferred terms of melena, feces discolored, hemorrhage rectum, and hemorrhoids.
c. Table 49 captures the same patients with colonoscopies.
d. SB 207499 15mg BID.
Data Source: Appendix D, Listing 1, Listing 8, and Listing 14.

8.7.7.1. Placebo-treated Patients with Adverse Events of Gastrointestinal Bleeding Not Reported As GIAEs of Concern

[redacted] The patient completed the study.

[redacted] The patient completed the study.

[redacted] All FOB results were negative. The patient completed the study.

[redacted]

[redacted] The patient completed the study.

[redacted] The patient was withdrawn from the study as a result of the serious GIAEs. FOB tests were not assessed at the GIAE or early withdrawal visits. The patient had an anoscopy performed with follow-up colonoscopy. (Section 8.7.8.1).

8.7.7.2. SB 207499-treated Patients with Adverse Events of Gastrointestinal Bleeding Not Reported As GIAEs of Concern

[redacted] The patient completed the study.

[redacted] The patient withdrew consent on Day 84.

[redacted] The patient completed the study.

[redacted] The patient completed the study.

[redacted] The patient completed the study.

[redacted] All FOB results were negative and the patient completed the study.

[redacted] A colonoscopy was performed (Section 8.7.8.2).

8.7.8. Colonoscopy Results

Amendment #1 (March 2001) added a requirement of performing colonoscopies on patients with GIAEs of concern and a positive fecal occult blood test or melena during the randomized treatment phase of study 156. As a result, 12 patients had colonoscopies performed due to events that occurred during the study. A total of 7 patients (3 placebo-treated and 4 SB 207499-treated patients) who experienced one or more GIAEs of concern had a colonoscopy performed. Three SB 207499-treated and 2 placebo-treated patients with AEs of the gastrointestinal system or gastrointestinal symptoms that were not considered GIAEs of concern also had colonoscopies performed. Two additional patients with GIAEs of concern during the placebo run-in period had colonoscopies; however, these 2 patients were not randomized and are not included in the total number of colonoscopies performed during the study.

8.7.8.1. Colonoscopy Results in Patients with Gastrointestinal Adverse Events of Concern who Received Placebo

Of the 18 patients receiving placebo who had on-therapy GI adverse events of concern, 13 patients (72.2%) had fecal occult blood tests recorded specifically by the Investigator as a result of the event(s). [redacted] This patient with melena, as well as 2 other patients who received placebo and experienced a GIAE of concern, had a colonoscopy performed.

Brief narratives for these three patients are provided below, while full colonoscopy reports are provided in Section 15, Table 15.11E. [redacted]

[redacted]

[redacted]

[redacted] FOB tests were not assessed at the GIAE or early withdrawal visits. Although orthostatic vital signs were not assessed at the time of these GIAEs, there were no changes of concern noted at the early withdrawal visit. [redacted]

[redacted]

8.7.8.2. Colonoscopy Results in Patients with Gastrointestinal Adverse Events of Concern who Received SB 207499

Of the 51 patients receiving SB 207499 who had on-therapy GI adverse events of concern, 44 patients (86.3%) had fecal occult blood tests recorded specifically by the Investigator as a result of the event(s). [redacted]

[redacted] Brief narratives for these four patients are provided below, while full colonoscopy reports are provided in Section 15, Table 15.11E.

[redacted]

[redacted] No other findings were noted during the colonoscopy.

[redacted]

[redacted]

[redacted]

[redacted] All four patients tested positive for fecal occult blood at their last study assessment. However, none of these 4 patients had low hemoglobin and hematocrit or changes in orthostatic vital signs that reached a level of clinical concern during the study.

8.7.8.3. Colonoscopies and other GI procedures in patients with AEs in the GI body system or GI symptoms that were not considered GIAEs of Concern

A total of 6 patients who did not report GIAEs of concern had colonscopies (5 patients) or other GI procedures (1 patient) performed. Three patients with AEs in the GI body system that were not considered GIAEs of concern had colonoscopies (Appendix D, Listing 1). Brief narratives are presented below, while full colonoscopy reports are provided in Section 15, Table 15.11E.

[redacted] There were no orthostatic changes in vital signs of clinical concern at any time during the study and all fecal occult blood tests were negative. [redacted]

[redacted]

[redacted]

[redacted] Colonoscopy or other GI procedure reports can be found in Section 15, Table 15.11D. These unreported symptoms may be explained by pre-existing conditions, by patient underreporting of symptoms or by study conduct issues..

8.7.9. Orthostatic Vital Signs in Patients With Gastrointestinal Adverse Events of Concern

All 18 patients receiving placebo who had on-therapy GI adverse events of concern had orthostatic vital signs measured during a GI adverse event assessment. None of these patients had orthostatic changes of clinical concern at a GIAE assessment (see Table 55 for vital sign values and orthostatic changes of clinical concern).

All 51 patients receiving SB 207499 who had on-therapy GI adverse events of concern had orthostatic vital signs measured during a GI adverse event assessment. Hemoglobin or hematocrit values remained within normal levels for these three SB 207499-treated patients with GIAEs and orthostatic changes in vital signs of clinical concern. Neither increase was associated with a decrease in hemoglobin or hematocrit to below the normal range or to a level of clinical concern.

Table 51 Listing of Patients Receiving SB 207499 Who Experienced GIAEs of Concern and Orthostatic Changes in Vital Signs of Clinical Concern at the GIAE Assessment



a. Days relative to start of study medication (days relative to stop of study medication).
b. [+] indicates orthostatic change in vital signs of clinical concern recorded at a GIAE assessment. See Table 55 for clinical concern criteria.
Data Source: Appendix D, Listing 8; Appendix E, Listing 1C and Listing 1D.

8.7.10. Hemoglobin and Hematocrit Levels in Patients With Gastrointestinal Adverse Events of Concern

No patient in the SB 207499 treatment group who had GI adverse events of concern had low hemoglobin or hematocrit values that reached a level of clinical concern (see Table 68 for laboratory reference values) at any time during the study (Appendix D, Listing 8 and Appendix F, Listing 1 and Listing 2).

8.7.11. Gastrointestinal Adverse Events of Concern During Run-in and Post-therapy

During the run-in period, 5 patients had GI adverse events of concern reported as Baseline Signs and Symptoms (Appendix D, Listing 8A). None of these patients were withdrawn from the study prior to randomization due to these GIAEs.

Case report forms are provided for these patients in Appendix G.

8.8. Fecal Occult Blood Testing (All Patients)

Fecal occult blood tests were performed between Screening and Baseline, between Weeks 20 and 24, at early withdrawal, and in patients who experienced GI adverse events of concern. Fecal occult blood test results are presented in Appendix D, Listing 13.

Overall, a total of 288 (70.8%) of 407 patients who received placebo and 276 (66.0%) of 418 patients who received SB 207499 had fecal occult blood tests during double-blind treatment. Of these patients, 282 placebo-treated and 273 SB 207499-treated patients had negative FOB tests at baseline. A total of 3 (1.1%) of 282 patients who received placebo and 8 (2.9%) of 273 patients who received SB 207499 and who had negative baseline FOB tests, shifted to positive during double-blind treatment (Section 15, Table 15.12B). A total of 6 placebo-treated and 2 SB 207499-treated patients with baseline FOB test results recorded as “missing” had negative FOB tests during the double-blind treatment period.

These totals include fecal occult blood test results for patients with GI adverse events of concern detailed in Section 8.7.

A Summary of FOB tests for all patients at study end is presented in Table 52. Overall, 9 (1.6%) of 564 patients who had a FOB test performed, tested positive for fecal occult blood at their last study related visit.

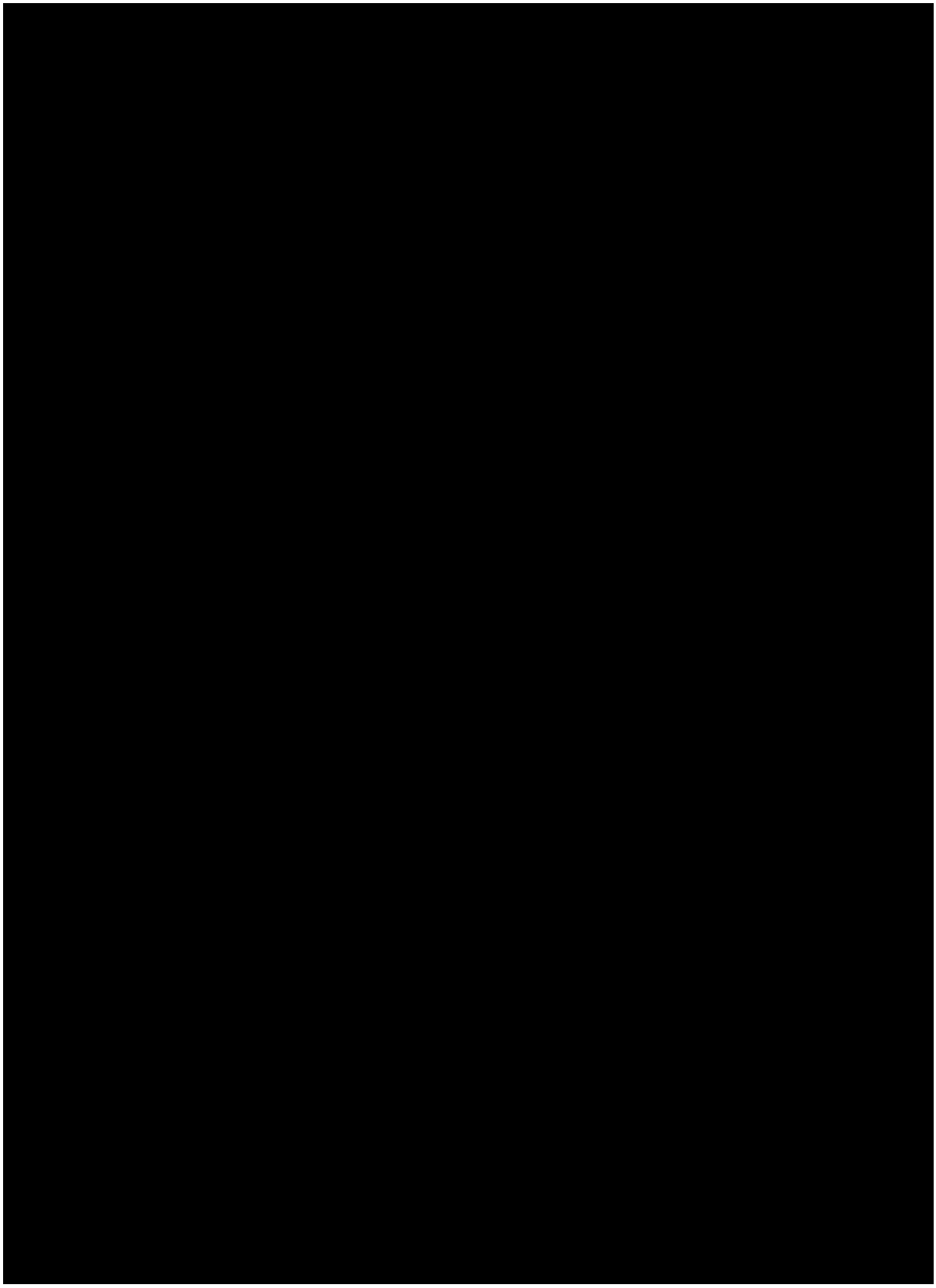
Table 52 Summary of Fecal Occult Blood Tests at Study End

Treatment Group	All Patients	
	N[a]	FOB Positive at Study End n (%)
Placebo	288	4 (1.4)
SB 207499[b]	276	5 (1.8)

a. Total represents the total number of patients who had a FOB test.
b. SB 207499 15mg BID.
Data Source: Appendix D, Listing 13, and Listing 14.

Table 53 presents all patients with a positive fecal occult blood test result during the double-blind treatment period, together with details of any GI adverse event of concern reported by the patient, and any other relevant history.

Table 53 Listing of Patients With a Positive Fecal Occult Blood Test Result During the Double-blind Treatment Period





a. Days relative to start of study medication (days relative to stop of study medication).
b.
c.
Appendix D, Listing 1, Listing 8, and Listing 13; Appendix B, Listing 5, Listing 6 and Listing 8A.

8.9. Vital Signs

Sitting systolic and diastolic blood pressure and heart rate were recorded at each study visit. Table 54 presents mean vital sign values and changes from Baseline at Week 24 by treatment group. Individual patient data on vital signs are available in Appendix E, Listing 1A.

Table 54 Summary of Mean Change in Vital Sign Values

Parameter and Time Point	Placebo N	Placebo mean (SD)		SB 207499 15mg BID N	SB 207499 15mg BID mean (SD)	
Systolic BP, mmHg						
Baseline[a]	407	128.5	(15.8)	418	128.9	(15.6)
Week 24	311	128.6	(15.7)	272	128.1	(15.5)
Change[b]	311	0.0	(16.0)	272	-0.8	(13.9)
Diastolic BP, mmHg						
Baseline[a]	407	76.6	(9.4)	418	76.2	(9.8)
Week 24	311	76.4	(8.7)	272	76.5	(9.3)
Change[b]	311	-0.4	(8.5)	272	0.1	(9.0)
Heart rate, bpm						
Baseline[a]	407	74.6	(10.7)	418	73.8	(10.0)
Week 24	311	74.4	(10.7)	272	75.1	(10.1)
Change[b]	311	0.3	(9.9)	272	1.0	(10.1)

SD = standard deviation
a. Includes all patients evaluated at Baseline.
b. Change is reported for patients (n) with both Baseline and Week 24 assessments.
Data Source: Section 15, Table 15.16; Appendix E, Listing 1A.

The mean changes from baseline to each study visit were small with no clinically meaningful differences between treatment groups.

In addition to sitting vital signs, orthostatic vital signs were also measured at Screening, Baseline, Week 24, early withdrawal, and at visits associated with gastrointestinal adverse events of concern. Vital sign values or orthostatic changes of clinical concern are defined in Table 55.

Narratives for patients receiving SB 207499 who had any on-therapy sitting or orthostatic vital sign values of high concern are provided in Section 15, Table 15.16A.

Table 55 Vital Sign Levels of Clinical Concern

Parameter	Low Concern	Low	Reference Range	High	High Concern
Sitting systolic BP	<75 mm Hg	75 - 89 mm Hg	90 - 139 mm Hg	140 - 180 mm Hg	>180 mm Hg
Sitting diastolic BP	<50 mm Hg	50 - 59 mm Hg	60 - 89 mm Hg	90 - 110 mm Hg	>110mm Hg
Sitting heart rate	<50 bpm	50 - 59 bpm	60 - 99 bpm	100 - 120 bpm	>120 bpm
Orthostatic change[a] in systolic BP	NA	NA	Decrease of <10 mm Hg	decrease of 10 - 19 mm Hg	decrease of ≥20 mm Hg
Orthostatic change[a] in diastolic BP	NA	NA	Decrease of <10 mm Hg	NA	decrease of ≥10 mm Hg
Orthostatic change[a] in heart rate	NA	NA	Increase of <10 bpm	NA	increase of ≥10 bpm

NA = Not Applicable.

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

Table 56 presents the number and percent of patients with transitions in sitting vital signs from within the normal range at baseline to outside the normal range or to values of clinical concern on-therapy. Transitions from baseline in sitting vital signs for all patients on-therapy and at endpoint are presented in Section 15, Table 15.17, and information for individual patients is listed in Appendix E, Listing 1B.

Table 56 Transitions from Normal Range at Baseline for Sitting Vital Signs - Time Point: On-therapy

		Double-Blind[a]				
Parameter	N[b]	Low Concern n (%)	Low n (%)	Normal n (%)	High n (%)	High Concern n (%)
Sitting systolic BP, mmHg						
Placebo	288	0	0	169 (58.7)	119 (41.3)	0
SB 207499	294	1 (0.3)	3 (1.0)	166 (56.5)	122 (41.5)	2 (0.7)
Sitting diastolic BP, mmHg						
Placebo	343	0	31 (9.0)	239 (69.7)	73 (21.3)	1 (0.3)
SB 207499	345	0	36 (10.4)	242 (70.1)	68 (19.7)	1 (0.3)
Heart rate, bpm						
Placebo	362	4 (1.1)	30 (8.3)	298 (82.3)	30 (8.3)	0
SB 207499	370	0	41 (11.1)	301 (81.4)	28 (7.6)	1 (0.3)

a. Patients are assigned to categories based on their highest and/or lowest on-therapy value. Patients with on-therapy values who meet criteria for both high and low values of interest and concern are reported in both categories, if applicable.
b. Number of patients with values within the normal range at baseline. Percentages are based on the number of patients with values within the normal range at baseline.

Data Source: Section 15, Table 15.17; Appendix E, Listing 1B.

The percentages of patients with transitions from normal vital sign values at baseline to values outside of the normal range on-therapy and at endpoint were comparable between the two treatment groups. The percentage of patients with transitions from normal vital sign values at baseline to values of high clinical concern on-therapy was low in both treatment groups. Transitions from baseline to endpoint were similar to the total on-therapy results (Section 15, Table 15.17).

Table 57 presents the number and percent of patients with transitions in on-therapy orthostatic vital signs from normal range at baseline to above normal range or to values of high clinical concern on-therapy. Transitions from baseline for all patients on-therapy and at endpoint are presented in Section 15, Table 15.13B, and information for individual patients is listed in Appendix E, Listing 1C.

Table 57 Transitions from Normal Range at Baseline for Orthostatic Vital Signs - Time Point: On-therapy

		Double-Blind[a]					
		Normal		High[b]		High Concern[c]	
Parameter	N	n	(%)	n	(%)	n	(%)
Orthostatic[d] change in systolic BP, mmHg							
Placebo	312	290	(92.9)	21	(6.7)	1	(0.3)
SB 207499	301	277	(92.0)	18	(6.0)	6	(2.0)
Orthostatic[d] change in diastolic BP, mmHg							
Placebo	339	331	(97.6)	NA	NA	8	(2.4)
SB 207499	323	315	(97.5)	NA	NA	8	(2.5)
Orthostatic[d] change in heart rate, bpm							
Placebo	334	323	(96.7)	NA	NA	11	(3.3)
SB 207499	322	314	(97.5)	NA	NA	8	(2.5)

NA = Not applicable.

a. Percentages are based on the number of patients with values within the normal range at baseline. Patients are assigned to categories based on their highest on-therapy change.

b. Orthostatic decrease of 10-19mmHg in systolic BP.

c. Orthostatic decrease of ≥20mmHg in systolic BP, orthostatic decrease of ≥10mmHg in diastolic BP, orthostatic increase of ≥10bpm in heart rate.

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

Data Source: Section 15, Table 15.13B; Appendix E, Listing 1C.

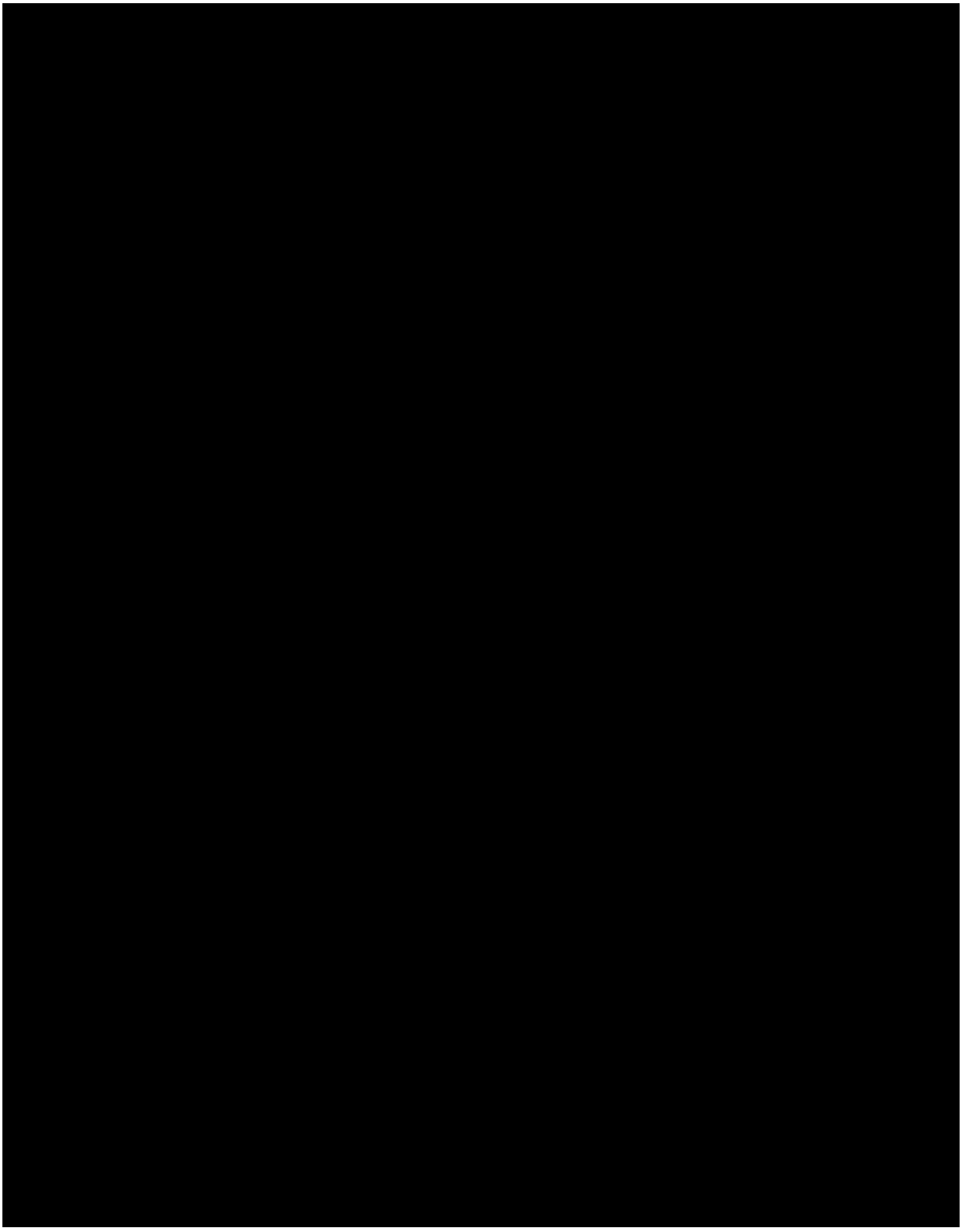
The percentages of patients who had orthostatic vital sign values within the normal range at baseline that changed to values above the normal range or to values of high concern on-therapy were small in both treatment groups. The incidence of orthostatic changes in systolic blood pressure greater than 10mm Hg in the SB 207499 treatment group was comparable with the placebo treatment group (SB 207499, 24 of 301 (7.8%); placebo, 22 of 312 (7.1%)). At least half of the patients in each treatment group who had orthostatic vital signs above the normal range or of high concern (placebo, 21 of 41 patients; SB 207499, 21 of 40 patients) were receiving cardiovascular medications that might affect postural vital signs (Appendix B, Listing 7 and Listing 8A; Appendix E, Listing 1C). Patients receiving SB 207499 who had on-therapy orthostatic vital sign changes of high clinical concern are listed in Table 58. Transitions from baseline in orthostatic changes at endpoint were similar to the total on-therapy results (Section 15, Table 15.13B).

Table 58 Patients Receiving SB 207499 Who Had On-therapy Orthostatic Vital Sign Changes of High Clinical Concern



Table 59 presents patients with vital signs reported as on-therapy adverse events. The most common of these adverse events in both treatment groups was hypertension. Patients may not necessarily have had an abnormal vital sign recorded in the CRF at the onset of the adverse event.

Table 59 Listing of Patients with Vital Signs Reported as On-therapy Adverse Events





1. Note 1: Bradycardia and Tachycardia AEs are also listed in Table 66.
2. Patients may not necessarily have had an abnormal vital sign recorded in the CRF at the onset of the adverse event.
3. Patient was withdrawn from study due to this adverse event.
4. Serious adverse event.

Data Source: Appendix D, Listing 1.

During double-blind treatment, 6.6% (27 of 407) of patients in the placebo treatment group and 5.5% (23 of 418) in the SB 207499 treatment group had vital signs reported as adverse events. Most of these adverse events were mild or moderate and considered not related or to have an unlikely relationship to study medication. In the placebo treatment group two adverse events were considered severe, one each of hypertension and hypotension. The latter was reported as serious and resulted in withdrawal of the patient from the study. In the SB 207499 treatment group two events were severe, one of bradycardia and one of hypertension. The bradycardia was reported as an SAE but did not result in withdrawal of the patient. Only one patient had a vital sign value of high clinical concern recorded at the time of the adverse event. No patients were withdrawn from SB 207499 due to a vital sign adverse event.

8.10. Electrocardiographic Data

8.10.1. ECG Assessments

Standard 12-lead ECGs were performed at all scheduled run-in and double-blind visits (except Week –2), at early withdrawal, at Safety Follow-up (if abnormal at the previous

visit), and 3 hours after administration of the first and last doses of double-blind study medication, i.e., at the approximate time of C_{max}.

Mean changes in ECG parameters from Baseline to Week 24 (trough) are presented in Table 60. Individual patient data on ECGs are available in Appendix E, Listing 2A.

Table 60 Summary of Mean Change in 12-lead ECG Values at Trough

Parameter and Time Point	Treatment Group: Placebo N	Placebo mean (SD)		SB 207499 15mg BID N	SB 207499 15mg BID mean (SD)	
Atrial rate (bpm)						
Baseline[a]	407	71.3	(20.6)	417	70.0	(10.9)
Week 24	296	70.7	(12.0)	265	72.6	(12.5)
Change[b]	296	-0.4	(22.6)	264	2.6	(9.2)
Ventricular rate (bpm)						
Baseline[a]	407	70.6	(12.3)	418	70.1	(10.9)
Week 24	299	70.8	(12.1)	268	72.5	(12.4)
Change[b]	299	0.8	(9.8)	268	2.5	(9.2)
QRS interval (msec)						
Baseline[a]	407	90.9	(16.4)	418	91.3	(15.5)
Week 24	299	90.5	(17.3)	268	91.8	(16.1)
Change[b]	299	-0.1	(6.5)	268	-0.6	(6.0)
PR interval (msec)						
Baseline[a]	398	159.8	(26.2)	411	160.4	(26.0)
Week 24	293	160.2	(27.4)	259	157.1	(25.7)
Change[b]	292	-0.5	(13.7)	259	-2.3	(14.3)
QT (uncorrected) (msec)						
Baseline[a]	407	394.1	(31.6)	418	394.9	(31.4)
Week 24	299	393.4	(32.7)	268	388.1	(33.2)
Change[b]	299	-1.8	(26.0)	268	-5.8	(24.3)
QTc (msec)[c]						
Baseline[a]	407	422.9	(21.5)	418	422.9	(20.6)
Week 24	299	422.7	(20.1)	268	422.1	(19.8)
Change[b]	299	0.5	(18.2)	268	0.4	(18.2)
QRS axis (degrees)						
Baseline[a]	407	38.9	(44.2)	418	39.6	(44.5)
Week 24	299	36.8	(44.5)	268	41.5	(44.1)
Change[b]	299	-0.4	(16.2)	268	0.3	(13.9)
T-wave axis (degrees)						
Baseline[a]	407	55.6	(36.7)	418	56.2	(31.6)
Week 24	299	56.8	(30.4)	268	53.6	(33.9)
Change[b]	299	2.0	(30.0)	268	-2.5	(26.2)

a. Includes all patients evaluated at Baseline.
b. Change is reported for patients (n) with both Baseline and Week 24 (trough) assessments.
c. QT corrected by Bazett's formula.
Data Source: Section 15, Table 15.18; Appendix E, Listing 2A.

There were small changes in trough ECG values from baseline to Week 24 in both treatment groups. No clinically meaningful differences were noted between groups.

Mean changes in ECG parameters from baseline to C_{max} on Day 1 and from baseline to C_{max} at Week 24 are presented in Table 61.

Table 61 Summary of Mean Change in 12-lead ECG Values at C_{max} at Day 1 and Week 24

	Treatment Group				
		Placebo		SB 207499 15mg BID	
Parameter	N	mean (SD)		N	mean (SD)	
C_{max}: Day 1						
Atrial rate (bpm)						
Baseline[a]	407	71.3	(20.6)	417	70.0	(10.9)
C_{max}, Day 1	373	73.0	(13.2)	396	73.0	(11.7)
Change from baseline[b]	373	1.6	(18.9)	396	2.9	(8.2)
Ventricular rate (bpm)						
Baseline[a]	407	70.6	(12.3)	418	70.1	(10.9)
C_{max}, Day 1	381	73.1	(13.2)	400	73.0	(11.7)
Change from baseline[b]	381	2.5	(8.2)	400	2.9	(8.1)
QRS interval (msec)						
Baseline[a]	407	90.9	(16.4)	418	91.3	(15.5)
C_{max}, Day 1	381	91.6	(16.4)	400	91.3	(15.4)
Change from baseline[b]	381	0.7	(5.8)	400	0.4	(5.2)
PR interval (msec)						
Baseline[a]	398	159.8	(26.2)	411	160.4	(26.0)
C_{max}, Day 1	371	159.4	(25.6)	392	158.3	(24.6)
Change from baseline[b]	371	-0.3	(10.5)	391	-1.8	(11.5)
QT (uncorrected) (msec)						
Baseline[a]	407	394.1	(31.6)	418	394.9	(31.4)
C_{max}, Day 1	381	390.4	(33.6)	400	390.5	(32.0)
Change from baseline[b]	381	-3.4	(23.1)	400	-4.0	(21.8)
QTc (msec)[c]						
Baseline[a]	407	422.9	(21.5)	418	422.9	(20.6)
C_{max}, Day 1	381	425.7	(21.1)	400	426.4	(21.0)
Change from baseline[b]	381	3.2	(15.3)	400	4.0	(15.9)
QRS axis (degrees)						
Baseline[a]	407	38.9	(44.2)	418	39.6	(44.5)
C_{max}, Day 1	381	39.8	(43.9)	400	40.2	(45.4)
Change from baseline[b]	381	0.4	(15.6)	400	-0.2	(21.0)
T-wave axis (degrees)						
Baseline[a]	407	55.6	(36.7)	418	56.2	(31.6)
C_{max}, Day 1	381	55.3	(36.0)	400	55.7	(32.4)
Change from baseline[b]	381	0.0	(28.8)	400	-0.8	(22.1)
C_{max}: Week 24						
Atrial rate (bpm)						
Baseline[a]	407	71.3	(20.6)	417	70.0	(10.9)
C_{max}, Week 24	286	72.7	(12.9)	257	74.8	(12.5)
Change from baseline[b]	286	1.6	(23.3)	256	4.8	(9.6)
Ventricular rate (bpm)						
Baseline[a]	407	70.6	(12.3)	418	70.1	(10.9)
C_{max}, Week 24	288	72.6	(12.9)	264	74.9	(12.5)
Change from baseline[b]	288	2.8	(11.3)	264	4.7	(9.7)

Parameter	Treatment Group: Placebo N	Placebo mean (SD)		Treatment Group: SB 207499 15mg BID N	SB 207499 15mg BID mean (SD)	
QRS interval (msec)						
Baseline[a]	407	90.9	(16.4)	418	91.3	(15.5)
C_{max}, Week 24	288	91.3	(16.9)	264	92.4	(16.4)
Change from baseline[b]	288	0.4	(6.4)	264	0.3	(7.0)
PR interval (msec)						
Baseline[a]	398	159.8	(26.2)	411	160.4	(26.0)
C_{max}, Week 24	280	159.5	(26.5)	256	156.8	(24.7)
Change from baseline[b]	279	-0.9	(13.0)	256	-2.2	(13.7)
QT (uncorrected) (msec)						
Baseline[a]	407	394.1	(31.6)	418	394.9	(31.4)
C_{max}, Week 24	288	390.0	(33.6)	264	385.6	(33.2)
Change from baseline[b]	288	-5.3	(28.6)	264	-8.2	(25.3)
QTc (msec)[c]						
Baseline[a]	407	422.9	(21.5)	418	422.9	(20.6)
C_{max}, Week 24	288	424.2	(20.2)	264	426.3	(22.7)
Change from baseline[b]	288	2.4	(19.6)	264	4.2	(19.4)
QRS axis (degrees)						
Baseline[a]	407	38.9	(44.2)	418	39.6	(44.5)
C_{max}, Week 24	288	34.7	(46.9)	264	40.8	(44.7)
Change from baseline[b]	288	-2.3	(16.9)	264	-0.3	(17.6)
T-wave axis (degrees)						
Baseline[a]	407	55.6	(36.7)	418	56.2	(31.6)
C_{max}, Week 24	288	56.2	(31.9)	264	57.4	(29.4)
Change from baseline[b]	288	1.1	(20.8)	264	1.4	(20.7)

a. Includes all patients evaluated at Baseline.
b. Change is reported for patients (n) with both Baseline and C_{max} assessments.
c. QT corrected by Bazett's formula.
Data Source: Section 15, Table 15.18, Appendix E, Listing 2A.

In general, there were small mean changes in the ECG parameters from baseline to C_{max} at Day 1 and C_{max} at Week 24, which were comparable between treatment groups.

The incidence of on-therapy ECG abnormalities that were not present on ECGs recorded pre-therapy at Screening or Baseline is presented in Table 62. New-onset ECG abnormalities that occurred in at least 1% of patients in either treatment group are included. ECG abnormalities are listed by patient in Appendix E, Listing 2C.

Table 62 New-Onset ECG Abnormalities Occurring in ≥1% of Patients in Either Treatment Group

ECG Abnormality	Placebo N[a]	Placebo n (%)[b]		SB 207499 15mg BID N[a]	SB 207499 15mg BID n (%)[b]	
T-Wave Abnormal NOS	305	54	(17.7)	325	63	(19.4)
Sinus Bradycardia	311	43	(13.8)	333	58	(17.4)
Sinus Arrhythmia	373	59	(15.8)	389	51	(13.1)
PVCs Unifocal	376	63	(16.8)	392	50	(12.8)
Poor R-Wave Progression	302	56	(18.5)	307	48	(15.6)
Premature Atrial Contractions NOS	379	56	(14.8)	387	48	(12.4)
S-T Changes Nonspecific	358	32	(8.9)	383	39	(10.2)
Decreased Voltage EKG	353	34	(9.6)	356	31	(8.7)
Q-T Interval Increased	381	30	(7.9)	393	30	(7.6)
Left Atrial Hypertrophy (P Mitrale)	375	23	(6.1)	391	27	(6.9)
Right Atrial Hypertrophy (P Pulmonale)	391	7	(1.8)	402	16	(4.0)
First Degree AV Block	382	10	(2.6)	397	14	(3.5)
Left Axis Deviation EKG	374	22	(5.9)	371	14	(3.8)
Sinus Tachycardia	396	21	(5.3)	406	14	(3.4)
Right Axis Deviation EKG	393	7	(1.8)	401	11	(2.7)
Left Anterior Hemiblock	374	16	(4.3)	371	10	(2.7)
Ectopic Rhythm NOS	397	11	(2.8)	408	9	(2.2)
Increased Ventricular Voltage NOS	400	5	(1.3)	411	9	(2.2)
Incomplete Bundle Branch Block	395	5	(1.3)	406	7	(1.7)
PVCs Multifocal	401	3	(0.7)	416	7	(1.7)
S-T Changes Segment Elevation	395	5	(1.3)	405	7	(1.7)
U-Wave	403	8	(2.0)	414	7	(1.7)
Intraventricular Block NOS	396	4	(1.0)	406	6	(1.5)
Left Ventricular Hypertrophy	403	4	(1.0)	410	5	(1.2)
Myocardial Infarction Inferior Old	395	5	(1.3)	406	5	(1.2)
Myocardial Infarction Septal Old	366	12	(3.3)	383	5	(1.3)
Left Ventricular S-T Changes	404	3	(0.7)	414	4	(1.0)
Premature Ventricular Contractions NOS	405	1	(0.2)	415	4	(1.0)
Myocardial Infarction Anterior Old	386	13	(3.4)	396	3	(0.8)
Myocardial Infarction Lateral Old	403	4	(1.0)	413	3	(0.7)
T-Wave Inversion	394	8	(2.0)	409	3	(0.7)
T-Wave Flat	402	11	(2.7)	412	1	(0.2)

a. Number of patients without the specific abnormality pre-therapy.
b. Percentages are based on the number of patients without the specific abnormality pre-therapy.
Data Source: Section 15, Table 15.20; Appendix E, Listing 2C.

There were few differences in the percentage of patients with specific new onset ECG abnormalities observed between treatment groups. Multifocal PVCs (1.7% vs. 0.7%), right atrial hypertrophy (4.0% vs. 1.8%) and sinus bradycardia (17.4% vs. 13.8%) were reported at a slightly higher rate in the SB 207499 treatment group compared with the placebo treatment group. Left anterior hemiblock (4.3% vs. 2.7%), left axis deviation (5.9% vs. 2.7%), old anterior myocardial infarction (3.4% vs. 0.8%), old septal myocardial infarction (3.3% vs. 1.3%), unifocal PVCs (16.8% vs. 12.8%), sinus tachycardia (5.3 vs. 3.4%), flat T-waves (2.7% vs. 0.7%) and T-wave inversion (2.0% vs. 0.7%) were reported at a slightly higher rate in the placebo treatment group. In addition

to premature atrial contractions and T-wave abnormal, the most common ECG abnormalities reported in the two groups (in at least 10% of patients in either group) were sinus bradycardia, sinus arrhythmia, unifocal PVCs, poor R-wave progression, and non-specific S-T changes. Treatment groups were comparable for percentages of patients reporting each of these ECG abnormalities.

ECG values of clinical concern are defined in Table 63.

Table 63 Electrocardiographic Values of Clinical Concern

Parameter	Low Concern	Low	Reference Range	High	High Concern
QRS interval	NA	NA	<120 msec	120 – 199 msec	≥200 msec
PR interval	NA	NA	<200 msec	200 – 249 msec	≥250 msec
Atrial rate	<50 bpm and 2 bpm lower than nadir from baseline	45–55 bpm	56–99 bpm	100 – 120 bpm	>120 bpm
Ventricular rate	<50 bpm and 2 bpm lower than nadir from baseline	45–55 bpm	56–99 bpm	100 – 120 bpm	>120 bpm
QT interval (corrected)[a]	NA	NA	Male <430 msec Female <450 msec	male 430 – 450 msec (borderline) female 450 – 470 msec (borderline)	male >450 msec (prolonged) female >470 msec (prolonged)
QT interval (uncorrected)	NA	NA	NA	NA	≥500 msec
QT interval (corrected)[a] change from baseline	NA	NA	Increase <30 msec	increase 30 – 60 msec	increase >60 msec
QRS axis	NA	NA	NA	NA	Change from baseline by >±30degrees, normal QRS axis at baseline (-30 to +90degrees), and QRS interval at baseline <120msec

a. QT corrected by Bazett's formula.

Transitions from baseline ECG parameters to values outside the normal range or to values of high or low clinical concern for all patients are presented by visit, total on-therapy, and at endpoint in Section 15, Table 15.19A and Table 15.19B. These tables include the 3-hour, post-dose ECGs at Day 1 and Week 24. Information for individual patients is listed in Appendix E, Listing 2A. Individual patients with ECG values of clinical concern are listed in Appendix E, Listing 2B. Narratives for patients receiving SB 207499 who had ECG values of concern are provided in Section 15, Table 15.20A.

As shown in Table 64, treatment groups were comparable for transitions from normal range at baseline to on-therapy, trough values outside the normal range and/or values of

clinical concern for atrial rate, ventricular rate, QRS interval, uncorrected QT interval, and QRS axis. Transitions from baseline at endpoint were similar to the total on-therapy results (Section 15, Table 15.19A). The percentage of patients with transitions in PR interval from normal range at baseline to above the normal range at trough on-therapy was slightly higher in the SB 207499 treatment group (5.3%) compared with the placebo treatment group (3.1%), although there was no difference between the groups at endpoint (placebo, 1.7%; SB 207499, 1.4%).

For patients with normal QTc (absolute, corrected by Bazett's formula) values at baseline, there was little difference between the treatment groups in the percentage of patients who reported on-therapy, trough QTc values that met the borderline (i.e., high) criteria (placebo, 27.2%; SB 207499, 25.8%), or for the percentage of these patients who reported on-therapy QTc values that met the prolonged criteria (i.e., high concern) (placebo, 6.1%; SB 207499, 6.9%). In addition, the treatment groups were comparable with regard to the percentages of patients with on-therapy QTc changes from baseline that were high (placebo, 17.3%; SB 207499, 19.6%) or of high concern (placebo, 2.0%; SB 207499, 2.3%). [redacted] At endpoint, the treatment groups were comparable with regard to transitions from normal QTc values at baseline and with regard to QTc changes from baseline.

Among patients with <120msec QRS interval at baseline, QRS axis transitions from normal at baseline to on-therapy high concern were comparable between the SB 207499 (12.5%) and placebo (13.1%) treatment groups.

Table 64 Transitions from Normal Range at Baseline for Trough ECG Parameters - Time Point: On-therapy

		Double-Blind[a]				
Parameter	N[b]	Low Concern n (%)	Low n (%)	Normal n (%)	High n (%)	High Concern n (%)
Atrial rate (bpm)						
Placebo	347	3 (0.9)	37 (10.7)	287 (82.7)	19 (5.5)	2 (0.6)
SB 207499	354	6 (1.7)	26 (7.3)	299 (84.5)	20 (5.6)	3 (0.8)
Ventricular rate (bpm)						
Placebo	349	3 (0.9)	38 (10.9)	289 (82.8)	19 (5.4)	1 (0.3)
SB 207499	355	6 (1.7)	26 (7.3)	300 (84.5)	20 (5.6)	3 (0.8)
QRS interval (msec)						
Placebo	365	NA NA	NA NA	358 (98.1)	7 (1.9)	0
SB 207499	367	NA NA	NA NA	359 (97.8)	8 (2.2)	0
PR interval (msec)						
Placebo	353	NA NA	NA NA	341 (96.6)	11 (3.1)	1 (0.3)
SB 207499	357	NA NA	NA NA	338 (94.7)	19 (5.3)	0
QT (uncorrected) (msec)						
Placebo	390	NA NA	NA NA	386 (99.0)	NA NA	4 (1.0)
SB 207499	388	NA NA	NA NA	385 (99.2)	NA NA	3 (0.8)
QTc (absolute values) (msec)[c]						
Placebo	293	NA NA	NA NA	195 (66.6)	80 (27.3)	18 (6.1)
SB 207499	305	NA NA	NA NA	205 (67.2)	79 (25.9)	21 (6.9)
QTc (change from baseline) (msec)[c,d]						
Placebo	294	NA NA	NA NA	237 (80.6)	51 (17.3)	6 (2.0)
SB 207499	306	NA NA	NA NA	239 (78.1)	60 (19.6)	7 (2.3)
QRS axis (degrees) (change from baseline)[e]						
Placebo	335	NA NA	NA NA	291 (86.9)	NA NA	44 (13.1)
SB 207499	321	NA NA	NA NA	281 (87.5)	NA NA	40 (12.5)

	N[b]	Left Axis Deviation n (%)	Normal n (%)	Right Axis Devation n (%)	Indeterminate n (%)
QRS axis (degrees)					
Placebo	348	17 (4.9)	319 (91.7)	13 (3.7)	0
SB 207499	332	9 (2.7)	305 (91.9)	18 (5.4)	0

a. Patients are assigned to categories based on their highest and/or lowest on-therapy value. Patients with on-therapy values who meet criteria for both high and low values of interest and concern are reported in both categories, if applicable.
b. Number of patients with values within the normal range at baseline. Percentages are based on the number of patients with values within the normal range at baseline.
c. QT corrected by Bazett's formula.
d. Number of patients with at least one on-therapy, change from baseline QTc measurement. Percentages for QTc change from baseline are based on this number.
e. In patients with a QRS interval <120msec at baseline.

Data Source: Section 15, Table 15.19A, Table 15.19B, and Table 15.19C; Appendix E, Listing 2B.

Table 65 presents the number and percent of patients with transitions from the normal range at baseline in ECG parameters measured at C_{max} 3 hours after the first dose on Day 1 and 3 hours after the last dose at Week 24. At both C_{max} assessments, the

treatment groups were comparable for transitions from normal range at baseline to values outside the normal range and/or values of clinical concern for atrial rate, ventricular rate, QRS interval, and uncorrected QT interval. PR interval changed from within the normal range to above the normal range on Day 1 at C_{max} in 6 patients (1.6%) in the SB 207499 treatment group vs. one patient (0.3%) in the placebo treatment group.

For the patients with normal QTc (absolute) values at baseline, a smaller percentage in the placebo treatment group (10.5%, 30 of 286) had QTc values that met the borderline (i.e., high) criteria at C_{max} Day 1 than in the SB 207499 treatment group (15.8%, 50 of 316). This difference in QTc transition was not seen at C_{max} Week 24 (placebo, 12.7%; SB 207499, 13.7%). Few patients in either group with normal QTc values at baseline met the criteria for prolonged (i.e., high concern) QTc at C_{max} Day 1 (placebo, 0.7%, 2 of 286; SB 207499, 1.6%, 5 of 316). A slightly higher proportion of patients in both treatment groups met the criteria for prolonged QTc at C_{max} Week 24 (placebo, 2.3%, 5 of 221; SB 207499, 4.4%, 9 of 204). In addition, the treatment groups were comparable with regard to the percentages of patients with QTc changes from baseline at C_{max} Day 1 that were high (placebo, 4.9%, 14 of 286; SB 207499, 4.7%, 15 of 316), while a slightly greater percentage of patients in the placebo treatment group (7.7%, 17 of 221) than in the SB 207499 treatment group (6.9%, 14 of 204) had high QTc changes from baseline at C_{max} Week 24. [redacted]

Table 65 Transitions from Normal Range at Baseline for ECG Parameters - Time Point: Post-dose (C_{max})

Parameter	N[b]	Double-Blind[a] Low Concern n (%)	Low n (%)	Normal n (%)	High n (%)	High Concern n (%)
C_{max}: Day 1						
Atrial rate (bpm)						
Placebo	331	0	9 (2.7)	314 (94.9)	8 (2.4)	0
SB 207499	357	0	6 (1.7)	345 (96.6)	6 (1.7)	0
Ventricular rate (bpm)						
Placebo	340	0	9 (2.6)	323 (95.0)	8 (2.4)	0
SB 207499	361	0	6 (1.7)	349 (96.7)	6 (1.7)	0
QRS interval (msec)						
Placebo	357	NA NA	NA NA	354 (99.2)	3 (0.8)	NA NA
SB 207499	379	NA NA	NA NA	376 (99.2)	3 (0.8)	NA NA
PR interval (msec)						
Placebo	342	NA NA	NA NA	341 (99.7)	1 (0.3)	0
SB 207499	366	NA NA	NA NA	360 (98.4)	6 (1.6)	0
QT (uncorrected) (msec)						
Placebo	380	NA NA	NA NA	379 (99.7)	NA NA	1 (0.3)
SB 207499	398	NA NA	NA NA	397 (99.7)	NA NA	1 (0.3)
QTc (absolute values) (msec)[c]						
Placebo	286	NA NA	NA NA	254 (88.8)	30 (10.5)	2 (0.7)
SB 207499	316	NA NA	NA NA	261 (82.6)	50 (15.8)	5 (1.6)
QTc (change from baseline) (msec)[c,d]						
Placebo	286	NA NA	NA NA	272 (95.1)	14 (4.9)	0
SB 207499	316	NA NA	NA NA	298 (94.3)	15 (4.7)	3 (0.9)
QRS axis (degrees) (change from baseline)[e]						
Placebo	328	NA NA	NA NA	316 (96.3)	NA NA	12 (3.7)
SB 207499	332	NA NA	NA NA	321 (96.7)	NA NA	11 (3.3)

	N[b]	Left Axis Deviation n (%)	Normal n (%)	Right Axis Devation n (%)	Indeter-minate n (%)
QRS axis (degrees)					
Placebo	341	6 (1.8)	333 (97.7)	2 (0.6)	0
SB 207499	343	7 (2.0)	331 (96.5)	4 (1.2)	1 (0.3)
C_{max}: Week 24					
Atrial rate (bpm)					
Placebo	251	0	8 (3.2)	237 (94.4)	5 (2.0)	1 (0.4)
SB 207499	234	1 (0.4)	5 (2.1)	221 (94.4)	7 (3.0)	0
Ventricular rate (bpm)						
Placebo	254	0	8 (3.1)	240 (94.5)	5 (2.0)	1 (0.4)
SB 207499	241	1 (0.4)	5 (2.1)	228 (94.6)	7 (2.9)	0
QRS interval (msec)						
Placebo	267	NA NA	NA NA	266 (99.6)	1 (0.4)	NA NA
SB 207499	246	NA NA	NA NA	243 (98.8)	3 (1.2)	NA NA
PR interval (msec)						
Placebo	257	NA NA	NA NA	254 (98.8)	3 (1.2)	0
SB 207499	239	NA NA	NA NA	234 (97.9)	5 (2.1)	0

Parameter	N[b]	Double-Blind[a] Low Concern n (%)	Low n (%)	Normal n (%)	High n (%)	High Concern n (%)
QT (uncorrected) (msec)						
Placebo	287	NA NA	NA NA	287 (100.0)	NA NA	0
SB 207499	261	NA NA	NA NA	261 (100.0)	NA NA	0
QTc (absolute values) (msec)[c]						
Placebo	221	NA NA	NA NA	188 (85.1)	28 (12.7)	5 (2.3)
SB 207499	204	NA NA	NA NA	167 (81.9)	28 (13.7)	9 (4.4)
QTc (change from baseline) (msec)[c,d]						
Placebo	221	NA NA	NA NA	203 (91.9)	17 (7.7)	1 (0.5)
SB 207499	204	NA NA	NA NA	188 (92.2)	14 (6.9)	2 (1.0)
QRS axis (degrees) (change from baseline)[e]						
Placebo	246	NA NA	NA NA	233 (94.7)	NA NA	13 (5.3)
SB 207499	220	NA NA	NA NA	211 (95.9)	NA NA	9 (4.1)

	N[b]		Left Axis Deviation n (%)	Normal n (%)	Right Axis Devation n (%)	Indeter-minate n (%)
QRS axis (degrees)						
Placebo	255	NA NA	9 (3.5)	245 (96.1)	1 (0.4)	0
SB 207499	229	NA NA	3 (1.3)	223 (97.4)	3 (1.3)	0

NA = Not applicable.

a. Patients are assigned to categories based on their highest and/or lowest on-therapy value. Patients with on-therapy values who meet criteria for both high and low values of interest and concern are reported in both categories, if applicable.

b. Number of patients with values within the normal range at baseline. Percentages are based on the number of patients with values within the normal range at baseline.

c. QT corrected by Bazett's formula.

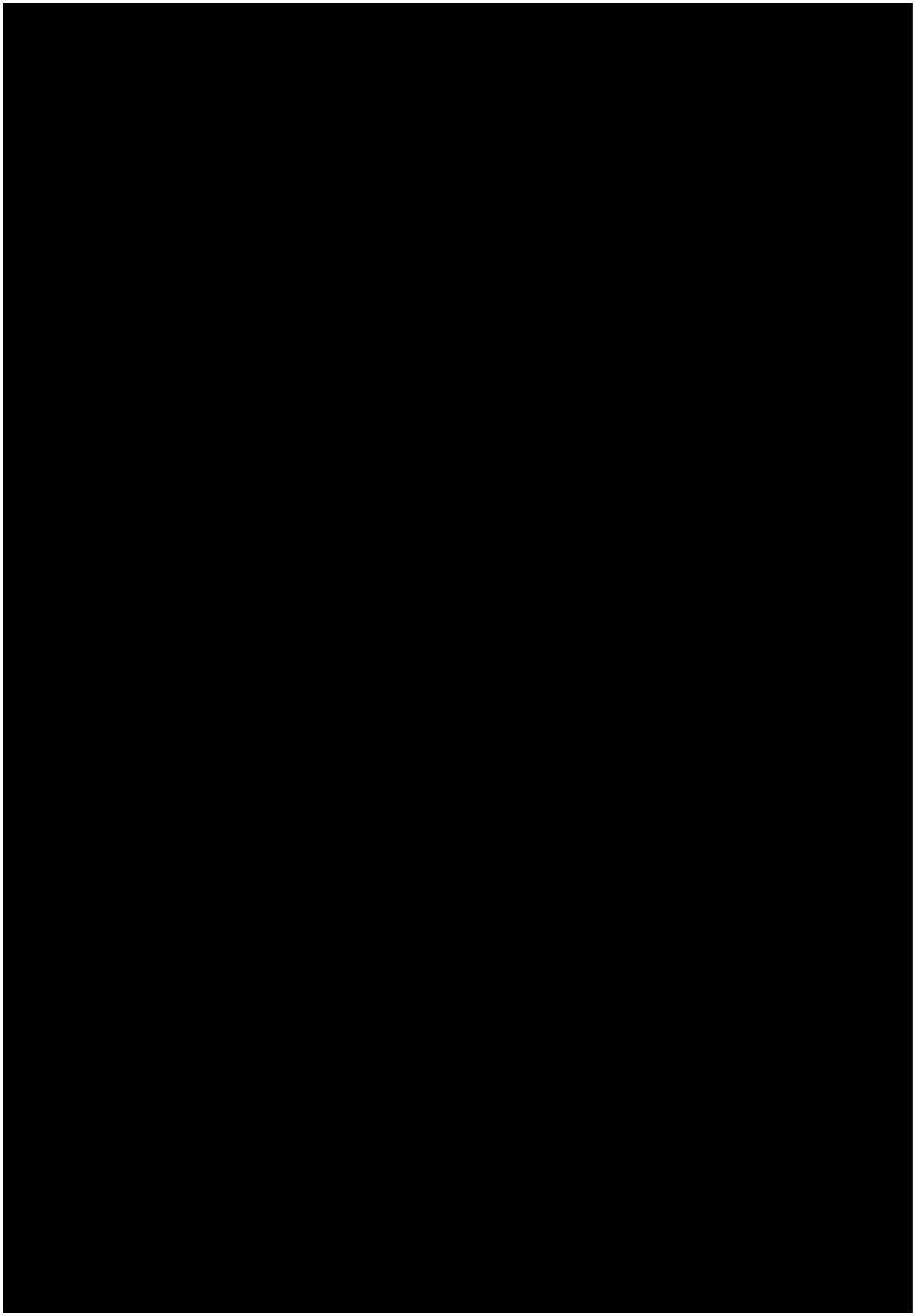
d. Number of patients with at least one on-therapy, change from baseline QTc measurement. Percentages for QTc change from baseline are based on this number.

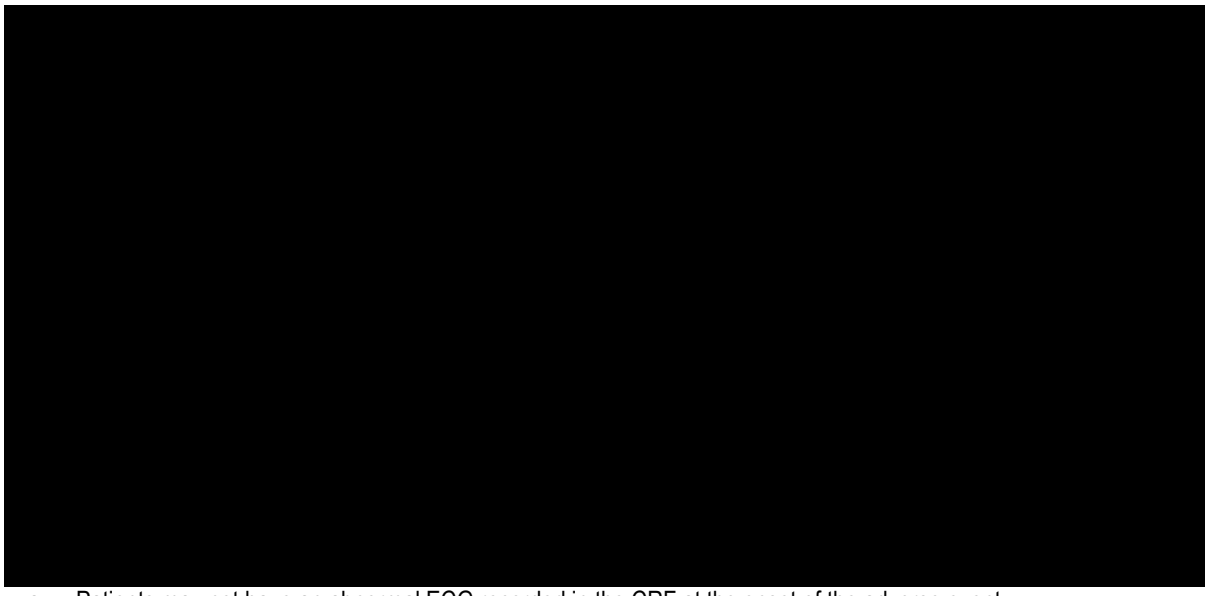
e. In patients with a QRS interval <120msec at baseline

Data Source: Section 15, Table 15.19A and Table 15.19B; Appendix E, Listing 2B.

Table 66 presents patients who had ECG abnormalities reported as adverse events during double-blind treatment. Patients may not necessarily have had an ECG abnormality recorded in the CRF at the time of onset of the adverse event.

Table 66 Listing of Patients With ECG Abnormalities Reported as On-therapy Adverse Events





a. Patients may not have an abnormal ECG recorded in the CRF at the onset of the adverse event.
b. Patient was withdrawn from study due to this adverse event.
c. Serious adverse event.
Data Source: Appendix D, Listing 1.

During double-blind treatment, 7.4% (30 of 407) of patients in the placebo treatment group and 5.5% (23 of 418) of patients in the SB 207499 treatment group had ECG abnormalities reported as adverse events. As a result of these adverse events 6 placebo-treated patients and 2 SB 207499-treated patients were withdrawn from the study. Five non-fatal, serious ECG adverse events were reported in the placebo treatment group, and 1 was reported in the SB 207499 treatment group. The majority of these adverse events in each treatment group were mild or moderate and considered not related or to have an unlikely relationship to study medication.

8.11. Laboratory Tests

Laboratory evaluations (hematology, clinical chemistry, and urinalysis) were performed at Screening, at all visits during double-blind treatment except Weeks 16 and 20, and at the Safety Follow-up Visit if abnormal results had been noted at the previous visit. Section 15, Table 15.14 presents mean values and mean change from baseline by week for all hematology and clinical chemistry tests. Urinalysis was performed by dipstick at the test site. If abnormalities were found, a urine sample was sent to the central laboratory (Quest). Only results of urinalysis performed by the central laboratory are included in the data listings. Data for individual patients are provided in Appendix F, Listing 2. Mean change from baseline at Week 24 for selected hematology and clinical chemistry parameters is presented in Table 67.

Narratives of SB 207499-treated patients with on-therapy laboratory values of high concern are presented in section 15, Table 15.15C.

Table 67 Summary of Mean Change in Selected Clinical Laboratory Parameters

	Treatment Group					
	Placebo			SB 207499 15mg BID		
Parameter and Time Point	N	Mean (SD)		N	Mean (SD)	
Hematology						
Hemoglobin (g/L)						
Baseline[a]	402	143.92	(13.85)	410	143.08	(13.01)
Week 24	306	143.49	(13.86)	267	142.88	(12.70)
Change[b]	306	0.08	(7.08)	267	-0.76	(8.05)
Hematocrit (%)						
Baseline[a]	402	43.29	(4.15)	410	43.03	(3.97)
Week 24	306	42.88	(4.15)	267	42.56	(3.76)
Change[b]	306	-0.18	(2.32)	267	-0.59	(2.61)
White Blood Cell Count (10^9/L)						
Baseline[a]	402	7.68	(2.14)	410	7.33	(2.02)
Week 24	306	7.36	(1.85)	267	7.41	(2.23)
Change[b]	306	-0.23	(1.75)	267	0.14	(1.68)
Neutrophil (10^9/L)						
Baseline[a]	402	4.90	(1.69)	410	4.56	(1.50)
Week 24	306	4.70	(1.47)	267	4.74	(1.72)
Change[b]	306	-0.16	(1.47)	267	0.21	(1.55)
Eosinophil (10^9/L)						
Baseline[a]	402	0.21	(0.17)	410	0.21	(0.16)
Week 24	306	0.21	(0.12)	267	0.20	(0.14)
Change[b]	306	0.00	(0.13)	267	-0.01	(0.13)
Platelets (10^9/L)						
Baseline[a]	401	249.92	(63.74)	410	252.35	(67.89)
Week 24	305	249.70	(61.27)	267	264.31	(77.84)
Change[b]	305	1.26	(38.22)	267	10.95	(43.43)
Clinical Chemistry						
AST (IU/L)						
Baseline[a]	403	21.86	(9.35)	413	21.78	(8.61)
Week 24	304	21.04	(8.31)	268	20.84	(11.45)
Change[b]	304	-0.54	(5.47)	268	-1.03	(8.43)
ALT (IU/L)						
Baseline[a]	403	19.68	(14.11)	413	19.14	(10.88)
Week 24	304	19.38	(11.95)	268	19.11	(13.84)
Change[b]	304	0.01	(8.09)	268	-0.34	(10.40
GGT (IU/L)						
Baseline[a]	403	34.68	(45.40)	413	31.42	(27.68)
Week 24	304	32.45	(27.61)	268	32.69	(36.02)
Change[b]	304	-0.59	(36.87)	268	1.30	(27.55)
Total Bilirubin (umol/L)						
Baseline[a]	403	8.97	(3.37)	413	9.17	(4.08)
Week 24	304	9.17	(3.90)	268	9.50	(4.03)
Change[b]	304	0.17	(3.04)	268	0.25	(2.93)
Alkaline Phosphatase (IU/L)						
Baseline[a]	403	81.11	(25.78)	413	78.18	(22.67)
Week 24	304	79.08	(20.67)	268	81.19	(23.65)
Change[b]	304	-1.16	(19.27)	268	1.57	(12.03)

Parameter and Time Point	Treatment Group: Placebo N	Placebo Mean (SD)		Treatment Group: SB 207499 15mg BID N	SB 207499 15mg BID Mean (SD)	
Creatinine (umol/L)						
Baseline[a]	403	79.85	(22.77)	412	80.55	(66.02)
Week 24	304	86.48	(108.2)	268	77.94	(19.34)
Change[b]	304	6.75	(106.5)	268	1.12	(12.57)
Blood Urea Nitrogen (mmol/L)						
Baseline[a]	403	5.81	(2.21)	413	5.79	(2.15)
Week 24	304	5.90	(3.01)	268	5.71	(2.03)
Change[b]	304	0.03	(2.70)	268	0.08	(1.48)
Sodium (mmol/L)						
Baseline[a]	387	140.78	(2.51)	393	140.89	(2.95)
Week 24	303	140.85	(2.57)	268	140.76	(2.97)
Change[b]	302	0.16	(2.73)	268	-0.12	(2.89)
Potassium (mmol/L)						
Baseline[a]	403	4.55	(0.45)	413	4.55	(0.44)
Week 24	303	4.55	(0.43)	268	4.54	(0.47)
Change[b]	303	-0.01	(0.46)	268	0.00	(0.47)

a. Includes all patients evaluated at Baseline.
b. Change is reported for patients (n) with both Baseline and Week 24 assessments.
Data Source: Section 15, Table 15.14; Appendix F, Listing 2.

Mean changes from baseline in clinical laboratory parameters were small and comparable between the treatment groups.

Laboratory values of clinical concern are defined in Table 68.

Table 68 Laboratory Values of Clinical Concern

Parameter	Reference Range	Low value of Concern	Low	High	High Value of Concern
Hemoglobin		<0.8 x LLN	0.8 x LLN-<LLN	> ULN-1.2 x ULN	>1.2 x ULN
male (18-64, ≥65 yrs)	138-172, 118-168 g/L				
female (18-64, ≥65 yrs)	120-156, 111-155 g/L				
Hematocrit		<0.8 x LLN	0.8 x LLN-<LLN	> ULN-1.2 x ULN	>1.2 x ULN
male (18-64, ≥65 yrs)	41.0-50.0, 36.0-49.0%				
female (18-64, ≥65 yrs)	35.0-46.0, 33.0-46.0%				
WBC	3.8-10.8 x 10^9/L	≤3.0 x 10^9/L	3.0 x 10^9/L -<LLN	> ULN- <20.0 x 10^9/L	≥20.0 x 10^9/L
Neutrophil	1.8-8.0 x 10^9/L	<0.8 x LLN	0.8 x LLN-<LLN	> ULN-1.5 x ULN	>1.5 x ULN
Eosinophil	0.05-0.55 x 10^9/L	----------	----------	> ULN- 2 x ULN	>2 x ULN
Platelet Count	130-400 x 10^9/L	<100 x 10^9/L	100 x 10^9/L-<LLN	> ULN- 500 x 10^9/L	>500 x 10^9/L
AST (SGOT)		----------	----------	> ULN -2 x ULN	>2 x ULN
(3-64, ≥65 yrs)	0-42, 0-55 IU/L				
ALT (SGPT)	0-48 IU/L	----------	----------	> ULN – 2 x ULN	>2 x ULN
GGT		----------	----------	> ULN – 2.5 x ULN	>2.5 x ULN
male (13-64, ≥65 yrs)	0-65, 0-75 IU/L				
female (13-64, ≥65 yrs)	0-45, 0-75 IU/L				
Total Bilirubin	0.0-22.1umol/L	----------	----------	> ULN – 1.5 x ULN	>1.5 x ULN
Alkaline Phosphatase	20-125 IU/L	----------	----------	> ULN – 2.0 x ULN	>2.0 x ULN
Creatinine	44-124 umol/L	<0.5 x LLN	0.5 x LLN-<LLN	> ULN – 1.5 x ULN	>1.5 x ULN
BUN (SI Units)		----------		> ULN – 17.85 mmol/L	>17.85 mmol/L
13-64, ≥65 yrs	2.5-8.9; 2.5-10.7 mmol/L				
Sodium (SI Units)	135-146 mmol/L	≤130 mmol/L	>130 mmol/L-<LLN	> ULN -<150 mmol/L	≥150 mmol/L
(non-SI Units)	135-146 mEq/L	≤130 mEq/L	>130 mEq/L-<LLN	> ULN - <150 mEq/L	≥150 mEq/L
Potassium (SI Units)	3.5-5.3 mmol/L	≤3.0 mmol/L	>3.0 mmol/L-<LLN	> ULN - <5.5 mmol/L	≥5.5 mmol/L
(non-SI Units)	3.5-5.3 mEq/L	≤3.0 mEq/L	>3.0 mEq/L-<LLN	> ULN - <5.5 mEq/L	≥5.5 mEq/L
Glucose		<2.0 mmol/L	2.0 mmol/L-<LLN	> ULN – 8.0 mmol/L	>8.0 mmol/L
(fasting/non-fasting)					
Uric Acid		----------	----------	> ULN – 1.4 x ULN	>1.4 x ULN
Male	238-506 umol/L				
Female	149-446 umol/L				

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

Table 69 shows the number and percent of patients with transitions in on-therapy hematology laboratory values from the normal range at baseline. The number and percent of all patients with transitions in hematology and clinical chemistry values on-therapy and at endpoint are presented by baseline result in Section 15, Table 15.15. All patients with on-therapy laboratory values of clinical concern are listed in Appendix F, Listing 1.

Table 69 Transitions from Normal Range at Baseline for Hematology Laboratory Values - Time Point: On-therapy

		Double-Blind[a]									
Parameter	N[b]	Low Concern n (%)		Low n (%)		Normal n (%)		High n (%)		High Concern n (%)	
Hemoglobin											
Placebo	349	0		32	(9.2)	306	(87.7)	11	(3.2)	0	
SB 207499	360	0		27	(7.5)	318	(88.3)	14	(3.9)	1	(0.3)
Hematocrit											
Placebo	331	0		30	(9.1)	262	(79.2)	39	(11.8)	0	
SB 207499	344	0		21	(6.1)	288	(83.7)	34	(9.9)	1	(0.3)
WBC											
Placebo	365	2	(0.5)	5	(1.4)	327	(89.6)	31	(8.5)	0	
SB 207499	372	0		11	(3.0)	326	(87.6)	35	(9.4)	0	
Neutrophil											
Placebo	371	5	(1.3)	3	(0.8)	333	(89.8)	27	(7.3)	3	(0.8)
SB 207499	374	0		4	(1.1)	341	(91.2)	27	(7.2)	2	(0.5)
Eosinophil											
Placebo	384	NA	NA	NA	NA	360	(93.8)	21	(5.5)	3	(0.8)
SB 207499	379	NA	NA	NA	NA	362	(95.5)	16	(4.2)	1	(0.3)
Platelet Count											
Placebo	381	0		6	(1.6)	366	(96.1)	8	(2.1)	1	(0.3)
SB 207499	377	0		4	(1.1)	356	(94.4)	14	(3.7)	3	(0.8)

a. Patients are assigned to categories based on their highest and/or lowest on-therapy value. Patients with on-therapy values who meet criteria for both high and low values of interest and concern are reported in both categories, if applicable.

b. Number of patients with values within the normal range at baseline. Percentages are based on the number of patients with values within the normal range at baseline.

Data Source: Section 15, Table 15.15; Appendix F, Listing 2.

Table 70 shows the number and percent of patients with transitions in on-therapy clinical chemistry laboratory values from the normal range at baseline.

Table 70 Transitions from Normal Range at Baseline for Clinical Chemistry Laboratory Values - Time Point: On-therapy

		Double-Blind[a]									
		Low Concern		Low		Normal		High		High Concern	
Parameter	N[b]	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
AST											
Placebo	385	NA	NA	NA	NA	371	(96.4)	13	(3.4)	1	(0.3)
SB 207499	386	NA	NA	NA	NA	375	(97.2)	10	(2.6)	1	(0.3)
ALT											
Placebo	376	NA	NA	NA	NA	361	(96.0)	15	(4.0)	0	
SB 207499	383	NA	NA	NA	NA	373	(97.4)	10	(2.6)	0	
GGT											
Placebo	363	NA	NA	NA	NA	341	(93.9)	21	(5.8)	1	(0.3)
SB 207499	364	NA	NA	NA	NA	348	(95.6)	14	(3.8)	2	(0.5)
Total Bilirubin											
Placebo	391	NA	NA	NA	NA	385	(98.5)	5	(1.3)	1	(0.3)
SB 207499	384	NA	NA	NA	NA	379	(98.7)	5	(1.3)	0	
Alkaline Phosphatase											
Placebo	376	NA	NA	NA	NA	363	(96.5)	13	(3.5)	0	
SB 207499	379	NA	NA	NA	NA	364	(96.0)	15	(4.0)	0	
Creatinine											
Placebo	373	0		4	(1.1)	352	(94.4)	14	(3.8)	3	(0.8)
SB 207499	381	0		5	(1.3)	364	(95.5)	11	(2.9)	1	(0.3)
BUN											
Placebo	379	NA	NA	NA	NA	352	(92.9)	26	(6.9)	1	(0.3)
SB 207499	383	NA	NA	NA	NA	366	(95.6)	15	(3.9)	2	(0.5)
Sodium											
Placebo	384	3	(0.8)	11	(2.9)	359	(93.5)	9	(2.3)	2	(0.5)
SB 207499	368	1	(0.3)	13	(3.5)	337	(91.6)	16	(4.3)	2	(0.5)
Potassium											
Placebo	368	0		3	(0.8)	314	(85.3)	11	(3.0)	40	(10.9)
SB 207499	369	0		5	(1.4)	316	(85.6)	14	(3.8)	34	(9.2)
Chloride											
Placebo	377	NA	NA	7	(1.9)	314	(83.3)	56	(14.9)	NA	NA
SB 207499	357	NA	NA	3	(0.8)	303	(84.9)	51	(14.3)	NA	NA
Protein											
Placebo	385	NA	NA	4	(1.0)	374	(97.1)	7	(1.8)	NA	NA
SB 207499	386	NA	NA	2	(0.5)	378	(97.9)	6	(1.6)	NA	NA
Albumin											
Placebo	391	NA	NA	2	(0.5)	388	(99.2)	1	(0.3)	NA	NA
SB 207499	387	NA	NA	1	(0.3)	385	(99.5)	1	(0.3)	NA	NA
Glucose Fasting											
Placebo	98	0		9	(9.2)	80	(81.6)	8	(8.2)	1	(1.0)
SB 207499	105	1	(1.0)	6	(5.7)	92	(87.6)	6	(5.7)	2	(1.9)

Parameter	N[b]	Double-Blind[a] Low Concern n (%)	Low n (%)	Normal n (%)	High n (%)	High Concern n (%)
Glucose Random						
Placebo	270	0	22 (8.1)	185 (68.5)	40 (14.8)	23 (8.5)
SB 207499	255	1 (0.4)	24 (9.4)	167 (65.5)	43 (16.9)	25 (9.8)
Uric Acid						
Placebo	384	NA NA	NA NA	364 (94.8)	19 (4.9)	1 (0.3)
SB 207499	378	NA NA	NA NA	363 (96.0)	15 (4.0)	0

NA = Not applicable.

a. Patients are assigned to categories based on their highest and/or lowest on-therapy value. Patients with on-therapy values who meet criteria for both high and low values of interest and concern are reported in both categories, if applicable.

b. Number of patients with values within the normal range at baseline. Percentages are based on the number of patients with values within the normal range at baseline.

Data Source: Section 15, Table 15.15; Appendix F, Listing 2.

The percentages of patients with transitions from normal range at baseline to outside the normal range and to a level of clinical concern were comparable in the two treatment groups with regard to hematology and clinical chemistry parameters.

Interestingly, there were a higher number of patients in both treatment groups that had transitions in laboratory values to high concern for glucose (random) compared to glucose (fasting). However, the threshold defined a priori in the analysis plan (8mmol/L) was used for both fasting and random states but is appropriate for fasting glucose levels only. A more appropriate threshold for glucose (random) would have been 11.1mmol/L (200mg/dL) [18].

Table 71 shows the most frequently reported adverse events (i.e., those occurring in >2 patients in either treatment group) related to lab results. The most common adverse events related to laboratory results were hyperglycemia, hematuria, and hyperkalemia which were reported in fewer than 3% of patients in either group. A complete listing of patients with adverse events related to laboratory results is provided in Appendix D, Listing 1.

Table 71 On-therapy Adverse Events Related to Laboratory Results Reported in at Least 2 Patients in Either Treatment Group

Adverse Event (Preferred Term)	Treatment Group: Placebo (N=407) n (%)		Treatment Group: SB 207499 15mg BID (N=418) n (%)	
Hyperglycemia	12	(2.9)	11	(2.6)
Hematuria	12	(2.9)	10	(2.4)
Hyperkalemia	9	(2.2)	10	(2.4)
Gamma-GT increased	7	(1.7)	2	(0.5)
Hypercholesterolemia	0		6	(1.4)
Hypoglycemia	2	(0.5)	5	(1.2)
Albuminuria	7	(1.7)	4	(1.0)
Glycosuria	1	(0.2)	4	(1.0)
Hyperlipemia	0		4	(1.0)
Amylase Increased	2	(0.5)	3	(0.7)
Leukocytosis	2	(0.5)	3	(0.7)
Polycythemia	2	(0.5)	3	(0.7)
Hypokalemia	0		3	(0.7)
SGPT increased	3	(0.7)	2	(0.5)
Hepatic enzymes increased	2	(0.5)	2	(0.5)
Thrombocytopenia	2	(0.5)	1	(0.2)
Alkaline phosphatase increased	3	(0.7)	0	

Data Source: Section 15, Table 15.2A; Appendix D, Listing 1.

9. PHARMACOKINETIC EVALUATION

The population pharmacokinetic evaluation of SB 207499 and SB 217493 is reported separately [18].

10. PHARMACODYNAMIC EVALUATION

The pharmacokinetic/pharmacodynamic evaluation of SB 207499 and SB 217493 is reported separately [18].

11. DISCUSSION/CONCLUSIONS

11.1. Discussion

This study was designed to evaluate the efficacy, safety and tolerability of SB 207499 15mg BID in patients with COPD. After a 4 week, single-blind, placebo run-in phase, eligible patients were randomized in a 1:1 ratio to receive either double-blind SB 207499 15mg BID (418 patients) or placebo (407 patients) for 24 weeks, followed by a one week safety follow-up visit.

The two treatment groups in the randomized patient population were well matched for demographic characteristics and for baseline characteristics of COPD. The treatment

groups were similar with respect to pulmonary function at screening, except that the placebo group had a mean FEV_1 that was 50mL greater than the SB 207499 treatment group (1.45L placebo vs. 1.40L SB 207499). This difference in FEV_1 is likely due to a gender effect since a higher number of female patients were enrolled in the SB 207499 treatment group (43.8%) compared to the placebo treatment group (38.1%). However, the % predicted FEV_1 for the patients randomized to placebo (50.0%) and SB 207499 (50.3%) were nearly identical. Overall, the patients were representative of a moderate COPD population. At screening, patients who were ultimately randomized to placebo and SB 207499 both had a mean FEV_1/FVC ratio of 0.53, poor reversibility to albuterol of 8.6%, and percent predicted DLCO of approximately 55%. In the placebo and SB 207499 treatment groups there were 33.7% and 32.3% of patients, respectively, with a current medical condition at screening of of chronic bronchitis. The most common current medical conditions in both groups (excluding respiratory disease) were hypertension (42.0% placebo vs. 39.2% SB 207499) and allergic rhinitis (20.9% placebo vs. 25.4% SB 207499). At entry, 45.9% and 46.7% of patients in the placebo and SB 207499 treatment groups, respectively, were current smokers, with few patients in either group changing smoking status during the study; the mean pack year smoking history was 61.8 and 58.9 years at screening for the placebo and SB 207499 treatment groups, respectively. The characteristics of the per protocol population were similar to those of the randomized population.

Patients were provided with albuterol metered dose inhalers for use on an 'as-needed' basis and were permitted to continue inhaled anticholinergic medication and mucolytics at a stable dose throughout the study; no other COPD medications were allowed except for the short-term treatment of exacerbations. The addition of new mucolytics was also not allowed. The use of albuterol was similar in both treatment groups (100% for placebo and 99.8% for SB 207499) and 30.7% and 32.8% of patients in the placebo and SB 207499 treatment groups, respectively, continued with a stable dose of ipratropium bromide during the study. Compliance with study medication was good as 95.3% of placebo-treated and 89.6% of SB 207499-treated patients were between 80% and 120% compliant at each week of double-blind treatment.

SB 207499 was shown to have a statistically significant ($p = 0.024$) effect on pulmonary function, preventing the decline in FEV_1 observed in the placebo treatment group over a six-month period. The mean change from baseline averaged over the 24 weeks of treatment for trough FEV_1 was significantly greater compared to placebo; the difference in the mean change from baseline in trough FEV_1 was 24mL. Progressive improvement over time in FEV_1 was observed for SB 207499 compared to placebo with statistically significant differences in FEV_1 at Week 16 (Δ=0.05L, $p = 0.001$), Week 20 (Δ=0.04L, $p = 0.028$), Week 24 (Δ=0.03L, $p = 0.047$), and at Endpoint (Δ=0.04L, $p = 0.013$).

In this study, patients who received placebo had a decline in pulmonary function consistent with that seen in previously published studies in patients with moderate COPD [22-24]. Patients who received SB 207499 remained close to baseline or improved during the course of the study. Consequently, SB 207499 appeared to maintain pulmonary function over the 24-week period compared to the decline observed in the placebo treatment group.

With the SGRQ (total score), an additional co-primary endpoint used to measure subjective improvements in patient health status, patients who received SB 207499 demonstrated statistically significant improvements over patients who received placebo (1.9 points; p = 0.017, CI -3.5 through -0.3).

The secondary efficacy endpoint of change from baseline in trough FVC was improved in SB 207499 patients compared to placebo patients. The SB 207499 treatment group showed an increase over baseline in trough FVC from Week 8 through Week 24 and at endpoint, ranging from 10mL to 50mL, while the placebo treatment group showed a decrease or no change from baseline in trough FVC at these time points. Exacerbation-free survival at 24 weeks and post-exercise breathlessness were comparable between the two treatment groups.

The tertiary endpoints also showed a numerical advantage favoring SB 207499 in pulmonary function (PEFR and FEF_{25-75}), COPD symptoms (overall breathlessness and use of rescue medication), quality of life measurements (activities score of SGRQ), post-exercise oxygen saturation, and exercise performance.

Measures of health economics were comparable between treatment groups.

The mean duration of exposure was 143.6 days for patients in the placebo treatment group and 128.2 days for patients in the SB 207499 treatment group.

The safety of SB 207499 was extensively assessed in this study with particular emphasis on cardiovascular and gastrointestinal monitoring. Gastrointestinal adverse events were closely monitored during this study; patients were instructed to report any gastrointestinal symptoms which caused them concern or interfered with their daily activities (referred to as GIAEs of concern).

The number of adverse events in the SB 207499 treatment group was not unexpected for a PDE4 inhibitor and was consistent with the known pharmacological profile of the drug. The percentages of patients who reported at least one adverse event were comparable between the two treatment groups, with overall incidences of 83.3% of 407 patients in the placebo treatment group and 87.1% of 418 patients in the SB 207499 treatment group. Adverse events associated with the gastrointestinal body system were reported more frequently in the SB 207499 treatment group (51.9%) as compared with the placebo treatment group (33.4%). In addition, a higher incidence of adverse events associated with the respiratory body system was observed in the placebo treatment group (47.2%) compared with the SB 207499 treatment group (39.7%). Review of the adverse event profile provided no evidence for an adverse effect of SB 207499 on other body systems including the cardiovascular system (including heart rate and rhythm), liver and biliary system, psychiatric, central and peripheral nervous system, resistance mechanism (i.e., infection) or reproductive system.

The most common adverse event reported overall was chronic obstructive airways disease, reported slightly less frequently in the SB 207499 treatment group (114 of 418 patients, 27.3%) compared with the placebo treatment group (125 of 407 patients, 30.7%). Among other commonly reported AEs, upper respiratory tract infection occurred more frequently in placebo-treated versus SB 207499-treated patients (15.0% vs. 11.0%)

while headache occurred more frequently in the SB 207499 treatment group versus the placebo treatment group (11.0% vs. 8.1%). The remaining common adverse events were associated with the gastrointestinal system and were reported more frequently in the SB 207499 treatment group as compared with placebo: nausea (6.6% placebo vs. 26.1% SB 207499), diarrhea (10.8% placebo vs. 19.6% SB 207499), abdominal pain (9.3% placebo vs. 12.4% SB 207499), dyspepsia (2.5% placebo vs. 9.1% SB 207499), and vomiting (2.7% placebo vs. 7.9% SB 207499). Other GI adverse events reported more frequently in the SB 207499 treatment group compared with the placebo included flatulence, anorexia, melena, constipation, and gastroesophageal reflux. Of note, dyspnea and coughing were reported in 7.1% and 8.4% of placebo-treated patients compared with 3.6% and 5.0% of SB 207499-treated patients, respectively

The majority of AEs in both treatment groups were mild to moderate in intensity (70.5% placebo and 70.8% SB 207499), with 12.8% of patients in the placebo treatment group and 16.3% of patients in the SB 207499 treatment group reporting severe AEs. The percentage of patients with adverse events considered by the Investigator to be related to study medication was higher in the SB 207499 treatment group (32.8%) compared with the placebo treatment group (14.5%). Related adverse events in the SB 207499 treatment group were predominately associated with the gastrointestinal body system including nausea, diarrhea, abdominal pain, dyspepsia, vomiting, and flatulence. In addition, headache considered related to study medication was reported more frequently in the SB 207499 treatment group than in the placebo treatment group (3.1% vs. 1.0%, respectively).

Analysis of the times to onset of specific adverse events showed that a majority (>50%) of SB 207499-treated patients reported the initial onset of nausea, diarrhea, abdominal pain, headache, dyspepsia, vomiting, fatigue, flatulence, insomnia, infection viral, dyspnea, myalgia, melena, constipation, hyperglycemia, asthenia, and gastroesophageal reflux during the first 4 weeks of double-blind treatment compared with the remaining 20 weeks. In general, early onset gastrointestinal intolerance was not unexpected and seen at a higher rate in SB 207499-treated patients during the first 4 weeks of therapy compared to placebo; however, incidences of GI intolerance were comparable between the two groups during the remainder of the study. Analysis of the initial time of onset of nausea, abdominal pain, diarrhea, and vomiting showed an overall gradual increase in incidence over the course of double-blind treatment in the placebo treatment group compared to a higher incidence during the first 4 weeks of treatment in the SB 207499 treatment group. Differences between the groups were clearly apparent within the first week of double-blind treatment.

There was a higher percentage of patients withdrawn due to adverse events in the SB 207499 treatment group (17.9%) compared with the placebo treatment group (9.8%). The incidence of nausea (0.7% placebo vs. 8.4% SB 207499), diarrhea (0.5% placebo vs. 3.8% SB 207499), and abdominal pain (0.7% placebo vs. 2.6% SB 207499) leading to withdrawal were higher in the SB 207499 treatment group compared to the placebo treatment group.

No patients died during the double-blind period or within 30 days following the last dose of study medication. A total of 3 patients died during the placebo run-in period. Two

patients died from myocardial infarction, while the third patient died of pneumonia, metastatic hepatic cancer, and bronchial carcinoma.

Thirty-eight (9.3%) patients in the placebo treatment group and 25 (6.0%) patients in the SB 207499 treatment group had non-fatal serious adverse events during double-blind treatment. [redacted] No serious adverse events were reported that were considered to have a probable relationship to study medication. [redacted] All serious GIAEs were considered unlikely related to study medication. The most common serious adverse event was chronic obstructive airways disease, which occurred in a similar percentage of patients in the SB 207499 and placebo treatment groups (1.4% vs. 1.7%, respectively). The nature of the adverse events and serious adverse events was not unexpected for a population of COPD patients with a significant smoking history.

Gastrointestinal adverse events of bloody or black stools, abdominal discomfort such as pain or cramps, diarrhea, or vomiting that concerned the patient or interfered with their daily activities were closely monitored during the study. During the double-blind treatment period, 18 (4.4%) of 407 placebo patients and 51 (12.2%) of 418 SB 207499 patients had gastrointestinal adverse events of concern. The most common of these were nausea, diarrhea, abdominal pain, and vomiting. All of the on-therapy GIAEs of concern (with the exception of rectum hemorrhage, diverticulitis, feces discolored, and hemorrhoids) were reported by a greater percentage of patients in the SB 207499 treatment group compared with the placebo treatment group. The majority of these adverse events were of mild to moderate intensity. A total of 4 (1.0%) patients in the placebo treatment group and 7 (1.7%) patients in the SB 207499 treatment group reported GIAEs of concern that were considered by the Investigator to be severe. There was a higher percentage of patients with GIAEs of concern considered by the Investigator to be related to study medication in the SB 207499 treatment group (8.1%, 34 of 418 patients) compared with the placebo treatment group (2.7%, 11 of 407 patients). GIAEs led to withdrawal of a higher percentage of patients from the SB 207499 treatment group (4.8%, 20 of 418 patients) compared with the placebo treatment group (1.0%, 4 of 407 patients).

A total of 564 of 825 patients (68.4%) had a fecal occult blood test during the double-blind period of the study. Only 11 of the 564 patients (3 placebo- and 8 SB 207499-treated patients) had at least one positive FOB result during double-blind treatment, and 9 (1.6%) of 564 patients (4 placebo and 5 SB 207499) tested positive for fecal occult blood at their last study related visit. Of the 18 placebo-treated patients and 51 SB 207499-treated patients who had on-therapy GI adverse events of concern, 13 patients (72.2%) who received placebo and 44 (86.3%) patients who received SB 207499 had fecal occult blood tests performed specifically by the Investigator as a result of the event(s). Of the patients assessed for fecal occult blood who had an on-therapy GIAE of concern, 1

(7.7%) of 13 placebo-treated patients and 7 (15.9%) of 44 SB 207499-treated patients had at least one positive FOB result during the double-blind or post-study periods. Overall, 12 patients had colonoscopies performed as a result of events that occurred during the study, including 5 placebo-treated and 7 SB 207499-treated patients. A total of 7 patients (3 placebo-treated and 4 SB 207499-treated patients) who experienced one or more GIAEs of concern had a colonoscopy performed. Three SB 207499-treated and 2 placebo-treated patients with AEs of the gastrointestinal system that were not considered GIAEs of concern also had colonoscopies performed. The colonoscopies did not identify any SB 207499 related safety concerns.



In summary, the intensive gastrointestinal monitoring performed in this study has not identified any serious, potentially drug-related effects of SB 207499 on the gastrointestinal tract. There was no evidence for a treatment effect of SB 207499 on fecal occult blood results or clinically important changes in orthostatic vital signs in patients experiencing GIAEs of concern. On-therapy fecal occult blood testing and orthostatic vital signs assessments did not reveal any evidence for acute or chronic blood loss associated with SB 207499.

All 12-lead ECGs in this study were interpreted centrally by a board certified cardiologist. Mean changes from baseline for 12-lead ECGs values performed at trough and C_{max} were similar between the placebo and SB 207499 treatment groups. There were few differences in either the incidence or pattern of new onset ECG abnormalities observed on-therapy between treatment groups. Multifocal PVCs (1.7% vs. 0.7%), right atrial hypertrophy (4.0% vs. 1.8%) and sinus bradycardia (17.4% vs. 13.8%) were reported at a slightly higher rate in the SB 207499 treatment group compared with the placebo treatment group. Left anterior hemiblock (4.3% vs. 2.7%), left axis deviation (5.9% vs. 2.7%), old anterior myocardial infarction (3.4% vs. 0.8%), old septal myocardial infarction (3.3% vs. 1.3%), unifocal PVCs (16.8% vs. 12.8%), sinus tachycardia (5.3% vs. 3.4%), flat T-waves (2.7% vs. 0.7%) and T-wave inversion (2.0% vs. 0.7%) were reported at a slightly higher rate in the placebo treatment group versus the SB 207499 treatment group. The number of patients having ECG abnormalities reported as adverse events was similar in the two treatment groups.

Overall, there was no difference between the treatment groups in the percentage of patients having transitions in QRS axis or QTc (absolute value) from within the normal range to a level of concern. Among patients with <120msec QRS interval at baseline, QRS axis transitions from normal at baseline to on-therapy high concern were comparable between the SB 207499 (12.5%) and placebo (13.1%) treatment groups. There were no marked differences in transitions from normal range at baseline to clinical concern for other trough ECG values on-therapy or C_{max} ECG values on Day 1 and Week 24. In summary, intensive 12-lead ECG monitoring did not raise any concerns about the cardiac safety of SB 207499, either at trough plasma levels of the drug or at C_{max}. There was no evidence for a treatment effect of SB 207499 on QTc prolongation or other evidence of a proarrhythmic effect.

Review of laboratory parameters revealed no differences in the mean changes from baseline between SB 207499 and placebo treatment groups. No differences were observed in the transitions from normal range at baseline to clinical concern on-therapy between the treatment groups. The percentages of patients who reported laboratory abnormalities as adverse events were at a comparably low level. Therefore, there was no evidence for an adverse effect of SB 207499 on laboratory parameters.

The efficacy demonstrated in this study coupled with the absence of evidence for a safety concern supports a positive risk:benefit ratio for SB 207499, particularly given the morbidity and mortality associated with COPD.

11.2. Conclusions

This study provides evidence of efficacy for SB 207499 15mg twice daily over a 24-week treatment period in patients with COPD. SB 207499 was shown to have statistically significant effects on both primary endpoints of FEV_1 and SGRQ. The decline in FEV_1 observed in the placebo treatment group was not seen in the SB 207499 treatment group and an improvement in quality of life was seen in the SB 207499 treatment group compared with placebo. Other measures confirming the treatment benefits of SB 207499 were noted in PEFR, FEF_{25-75}, overall breathlessness, use of rescue medication, post-exercise oxygen saturation, exercise performance, activities score of SGRQ, and change from baseline in trough FVC.

Based on the known pharmacology of the compound, gastrointestinal adverse events were not unexpected and occurred particularly early in treatment. However, these adverse events were generally mild or moderate in intensity. The gastrointestinal adverse event assessments, including fecal occult blood testing, assessment of orthostatic changes in vital signs, and laboratory assessments showed no untoward risk of hypovolemic events associated with these adverse events. Similarly, extensive cardiac monitoring confirmed the absence of cardiovascular safety concerns for SB 207499.

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13. SOURCE TABLES: STUDY POPULATION

13.0 Investigators, Center Number and the Investigator Affiliation and Location

13.1A Summary of Patient Disposition by Treatment Group

13.1B Summary of Patient Disposition by Center and Treatment Group

13.2 Distribution of Randomized Patients in Study by Visit/Week and Treatment Group

13.3 Reasons for Concluding the Run-in Period

13.4 Reasons for Concluding the Double-blind Period by Treatment Group

13.5 Summary of Early Withdrawals During the Double-blind Treatment Period by Time of Withdrawal, Reason and Treatment Group

13.6A Summary of Protocol Violations Resulting in Exclusion From Per-Protocol Analysis by Treatment Group

13.6B Summary of Protocol Violations Resulting in Exclusion From Per-Protocol Analysis by Treatment Group and Visit/Week

13.6C Summary of Conduct of Study Deviations by Treatment Group

13.7A Summary of Demographic Characteristics at Screening by Treatment Group – All Randomized Patients

13.7B Summary of Demographic Characteristics at Screening by Treatment Group - PP

13.7C Summary of Prior Systemic and Inhaled Steroid by Treatment Group - All Randomized Patients

13.7D Summary of Prior Systemic and Inhaled Steroid by Treatment Group - PP

13.8 Descriptive Statistics for Vital Signs at Screening by Treatment Group - All Randomized Patients

13.9A Descriptive Statistics for Pulmonary Function Parameters, and Percent Predicted DLCO at Screening by Treatment Group - All Randomized Patients

13.9B Descriptive Statistics for Pulmonary Function Parameters, and Percent Predicted DLCO at Screening by Treatment Group - PP

13.10 Descriptive Statistics for Distance Walked (Meters) During Screening and Run-in Visit by Treatment Group - All Randomized Patients

13.11 Summary of Pulmonary History by Treatment Group - All Randomized Patients

13.12A Descriptive Statistics for Smoking History, Alcohol Intake and Duration of COPD by Treatment Group – All Randomized Patients

13.12B Descriptive Statistics for Smoking History, Alcohol Intake and Duration of COPD by Treatment Group - PP

13.13A Summary of Prior Medical Conditions at Screening by Disease Code Level, Preferred Term and Treatment Group - All Randomized Patients

13.13B Summary of Current/Active Medical Conditions at Screening by Disease Code Level, Preferred Term and Treatment Group - All Randomized Patients

13.14 Summary of Baseline Signs and Symptoms by Body System and Preferred Term

13.15A Summary of Prior Medications by Generic Term and Treatment Group

13.15B Summary of Concomitant Medications by Generic Term and Treatment Group

13.15C Summary of Post-therapy Medications by Generic Term and Treatment Group

13.15D Summary of Medications Given for COPD Exacerbations by Generic Term and Treatment Group

13.16A Summary of Study Medication Compliance (%) by Treatment Group and Visit/Week

13.16B Descriptive Statistics for Study Medication Compliance (%) by Treatment Group and Visit/Week

13.17 Summary of Patient Smoking Status by Baseline Status, Treatment Group and Visit/Week

14. SOURCE TABLES: EFFICACY RESULTS

14.1A Summary of Average Change From Baseline Over 24 Weeks (Repeated Measures Analysis) in Trough FEV_1 (L) – ITT

14.1B Summary Statistics for Change From Baseline in Trough FEV_1 (L) by Week and Treatment Group – ITT

14.1C Descriptive Statistics for Change from Baseline in Trough FEV_1 (L) by Week and Treatment Group – ITT

14.1D Summary Statistics for Change From Pre-albuterol Baseline in FEV_1 (L) After First Dose by Time and Treatment Group – ITT

14.1E Descriptive Statistics for Change From Pre-albuterol Baseline in FEV_1 (L) After First Dose by Time and Treatment Group – ITT

14.1F Summary Statistics for Change From Week 24 Trough FEV_1 (L) After Last Dose by Time and Treatment Group – ITT

14.1G Descriptive Statistics for Change From Week 24 Trough FEV_1 (L) After Last Dose by Time and Treatment Group – ITT

14.1H Summary Statistics for Percent Change From Baseline in Trough FEV_1 (L) by Week and Treatment Group – ITT

14.1I Descriptive Statistics for Trough FEV_1 (L) at Endpoint by Center and Treatment Group – ITT

14.1J Descriptive Statistics for Trough FEV_1 (L) at Endpoint by Sex and Treatment Group – ITT

14.1K Descriptive Statistics for Trough FEV_1 (L) at Endpoint by ATS Severity and Treatment Group – ITT

14.1L Descriptive Statistics for Trough FEV_1 (L) at Endpoint by Race and Treatment Group – ITT

14.1M Descriptive Statistics for Trough FEV_1 (L) at Endpoint by Smoking Status and Treatment Group – ITT

14.1N Summary of Tests of Significance for Interaction Terms for Change From Baseline in Trough FEV_1 (L) – ITT

14.1O Summary of Tests of Significance for Prognostic Factors Effecting Change From Baseline in Trough FEV_1 (L) – ITT

14.1P Summary of Average Change From Baseline Over 24 Weeks (Repeated Measures Analysis) in Trough FEV_1 (L) – ITT

14.1T Descriptive Statistics For Trough FEV_1 (L) At Endpoint By Enrollment Period And Treatment Group - ITT

14.2A Summary of Average Change From Baseline Over 24 Weeks (Repeated Measures Analysis) in Total Score of the SGRQ – ITT

14.2B Summary Statistics for Change From Baseline in Total Score of the SGRQ by Week and Treatment Group – ITT

14.2C Descriptive Statistics for Change From Baseline in Total Score of the SGRQ by Week and Treatment Group – ITT

14.2I Descriptive Statistics for Total Score of the SGRQ at Endpoint by Center and Treatment Group – ITT

14.2J Descriptive Statistics for Total Score of the SGRQ at Endpoint by Sex and Treatment Group – ITT

14.2K Descriptive Statistics for Total Score of the SGRQ at Endpoint by ATS Severity and Treatment Group – ITT

14.2L Descriptive Statistics for Total Score of the SGRQ at Endpoint by Race and Treatment Group – ITT

14.2M Descriptive Statistics for Total Score of the SGRQ at Endpoint by Smoking Status and Treatment Group – ITT

14.2N Summary of Tests of Significance for Interaction Terms for Change From Baseline in Total Score of the SGRQ – ITT

14.2O Summary of Tests of Significance for Prognostic Factors Effecting Change From Baseline in Total Score of the SGRQ – ITT

14.3A Summary of Average Change From Baseline Over 24 Weeks (Repeated Measures Analysis) in Post-exercise Dyspnea – ITT

14.3B Summary Statistics for Change From Baseline in Post-exercise Dyspnea by Week and Treatment Group – ITT

14.3C Descriptive Statistics for Change from Baseline in Post-exercise Dyspnea by Week and Treatment Group – ITT

14.5A Summary of Average Change From Baseline Over 24 Weeks (Repeated Measures Analysis) in Trough FVC (L) – ITT

14.5B Summary Statistics for Change From Baseline in Trough FVC (L) by Week and Treatment Group – ITT

14.5C Descriptive Statistics for Change from Baseline in Trough FVC (L) by Week and Treatment Group – ITT

14.5D Summary Statistics for Change From Pre-albuterol Baseline in FVC (L) After First Dose by Time and Treatment Group – ITT

14.5E Descriptive Statistics for Change From Pre-albuterol Baseline in FVC (L) After First Dose by Time and Treatment Group – ITT

14.5F Summary Statistics for Change from Week 24 Trough FVC (L) After Last Dose by Time and Treatment Group – ITT

14.5G Descriptive Statistics for Change From Week 24 Trough FVC (L) After Last Dose by Time and Treatment Group – ITT

14.5H Summary Statistics for Percent Change From Baseline in Trough FVC (L) by Week and Treatment Group – ITT

14.6A Summary of Average Change From Baseline Over 24 Weeks (Repeated Measures Analysis) in Distance Walked (Meters) – ITT

14.6B Summary Statistics for Change From Baseline in Distance Walked (M) by Week and Treatment Group – ITT

14.6C Descriptive Statistics for Change from Baseline in Distance Walked (M) by Week and Treatment Group – ITT

14.7A Summary of Exacerbation-free Survival – ITT

14.7B Summary of Level 2/Level 3 Exacerbation-free Survival – ITT

14.7C Summary of COPD Exacerbations During the Double-blind Period by Level and Treatment Group – ITT

14.7D Summary of Proportional Hazards Regression of Time to First Exacerbation – ITT

14.7E Summary of Proportional Hazards Regression of Time to First Level 2/Level 3 Exacerbation – ITT

14.7F Summary of Marginal Regression Analysis of Time to Exacerbation – ITT

14.9A Summary of Average Change From Baseline Over 24 Weeks (Repeated Measures Analysis) in Trough PEF (L/Min) – ITT

14.9B Summary Statistics for Change From Baseline in Trough PEF (L/Min) by Week and Treatment Group – ITT

14.9C Descriptive Statistics for Change from Baseline in Trough PEF (L/Min) by Week and Treatment Group – ITT

14.9D Summary Statistics for Change From Pre-albuterol Baseline in PEF (L/Min) After First Dose by Time and Treatment Group – ITT

14.9E Descriptive Statistics for Change from Pre-albuterol Baseline in PEF (L/Min) After First Dose by Time and Treatment Group – ITT

14.9F Summary Statistics for Change from Week 24 Trough PEF (L/Min) After Last Dose by Time and Treatment Group – ITT

14.9G Descriptive Statistics for Change from Week 24 Trough PEF (L/Min) After Last Dose by Time and Treatment Group – ITT

14.9H Summary Statistics for Percent Change From Baseline in Trough PEF (L/Min) by Week and Treatment Group – ITT

14.10A Summary of Average Change From Baseline Over 24 Weeks (Repeated Measures Analysis) in Overall Dyspnea – ITT

14.10B Summary Statistics for Change From Baseline in Overall Dyspnea by Week and Treatment Group – ITT

14.10C Descriptive Statistics for Change from Baseline in Overall Dyspnea by Week and Treatment Group – ITT

14.11B Summary Statistics for Change From Baseline in Physical Composite Score of the SF-36 by Week and Treatment Group – ITT

14.11C Descriptive Statistics for Change from Baseline in Physical Composite Score of the SF-36 by Week and Treatment Group – ITT

14.12B Summary Statistics for Change From Baseline in Mental Composite Score of the SF-36 by Week and Treatment Group – ITT

14.12C Descriptive Statistics for Change from Baseline in Mental Composite Score of the SF-36 by Week and Treatment Group – ITT

14.13B Summary Statistics for Change From Baseline in Physical Functioning Score of the SF-36 by Week and Treatment Group – ITT

14.13C Descriptive Statistics for Change from Baseline in Physical Functioning Score of the SF-36 by Week and Treatment Group – ITT

14.14B Summary Statistics for Change From Baseline in Physical Role Functioning Score of the SF-36 by Week and Treatment Group – ITT

14.14C Descriptive Statistics for Change from Baseline in Physical Role Functioning Score of the SF-36 by Week and Treatment Group – ITT

14.15B Summary Statistics for Change From Baseline in Emotional Role Functioning Score of the SF-36 by Week and Treatment Group – ITT

14.15C Descriptive Statistics for Change from Baseline in Emotional Role Functioning Score of the SF-36 by Week and Treatment Group – ITT

14.16B Summary Statistics for Change From Baseline in Social Functioning Score of the SF-36 by Week and Treatment Group – ITT

14.16C Descriptive Statistics for Change from Baseline in Social Functioning Score of the SF-36 by Week and Treatment Group – ITT

14.17B Summary Statistics for Change From Baseline in Bodily Pain Score of the SF-36 by Week and Treatment Group – ITT

14.17C Descriptive Statistics for Change from Baseline in Bodily Pain Score of the SF-36 by Week and Treatment Group – ITT

14.18B Summary Statistics for Change From Baseline in Mental Health Score of the SF-36 by Week and Treatment Group – ITT

14.18C Descriptive Statistics for Change from Baseline in Mental Health Score of the SF-36 by Week and Treatment Group – ITT

14.19B Summary Statistics for Change From Baseline in Vitality Score of the SF-36 by Week and Treatment Group – ITT

14.19C Descriptive Statistics for Change from Baseline in Vitality Score of the SF-36 by Week and Treatment Group – ITT

14.20B Summary Statistics for Change From Baseline in General Health Perceptions Score of the SF-36 by Week and Treatment Group – ITT

14.20C Descriptive Statistics for Change from Baseline in General Health Perceptions Score of the SF-36 by Week and Treatment Group – ITT

14.21A Summary of Average Change From Baseline Over 24 Weeks (Repeated Measures Analysis) in Symptoms Score of the SGRQ – ITT

14.21B Summary Statistics for Change From Baseline in Symptoms Score of the SGRQ by Week and Treatment Group – ITT

14.21C Descriptive Statistics for Change from Baseline in Symptoms Score of the SGRQ by Week and Treatment Group – ITT

14.22A Summary of Average Change From Baseline Over 24 Weeks (Repeated Measures Analysis) in Impacts Score of the SGRQ – ITT

14.22B Summary Statistics for Change From Baseline in Impacts Score of the SGRQ by Week and Treatment Group – ITT

14.22C Descriptive Statistics for Change from Baseline in Impacts Score of the SGRQ by Week and Treatment Group – ITT

14.23A Summary of Average Change From Baseline Over 24 Weeks (Repeated Measures Analysis) in Activities Score of the SGRQ – ITT

14.23B Summary Statistics for Change From Baseline in Activities Score of the SGRQ by Week and Treatment Group – ITT

14.23C Descriptive Statistics for Change from Baseline in Activities Score of the SGRQ by Week and Treatment Group – ITT

14.24A Summary of Average Change From Baseline Over 24 Weeks (Repeated Measures Analysis) in Trough FEF_{25-75} (L/Sec) – ITT

14.24B Summary Statistics for Change From Baseline in Trough FEF_{25-75} (L/Sec) by Week and Treatment Group – ITT

14.24C Descriptive Statistics for Change from Baseline in Trough FEF_{25-75} (L/Sec) by Week and Treatment Group – ITT

14.24D Summary Statistics for Change From Pre-albuterol Baseline in FEF_{25-75} (L/Sec) After First Dose by Time and Treatment Group – ITT

14.24E Descriptive Statistics for Change from Pre-albuterol Baseline in FEF_{25-75} (L/Sec) After First Dose by Time and Treatment Group – ITT

14.24F Summary Statistics for Change from Week 24 Trough FEF_{25-75} (L/Sec) After Last Dose by Time and Treatment Group – ITT

14.24G Descriptive Statistics for Change from Week 24 Trough FEF_{25-75} (L/Sec) After Last Dose by Time and Treatment Group – ITT

14.24H Summary Statistics for Percent Change From Baseline in Trough FEF_{25-75} by Week and Treatment Group – ITT

14.25 Sputum Production Assessment by Week and Treatment Group – ITT

14.26 Cough Assessment by Week and Treatment Group – ITT

14.28B Summary Statistics for Change From Baseline in Post-exercise SaO_2 (%) by Week and Treatment Group – ITT

14.28C Descriptive Statistics for Change From Baseline in Post-exercise SaO_2 (%) by Week and Treatment Group – ITT

14.29B Summary Statistics for Change From Baseline in Resting SaO_2 (%) by Week and Treatment Group – ITT

14.29C Descriptive Statistics for Change From Baseline in Resting SaO_2 (%) by Week and Treatment Group – ITT

14.30B Summary Statistics for Change From Baseline in Optional PO_2 (mmHg) by Week and Treatment Group – ITT

14.30C Descriptive Statistics for Change From Baseline in Optional PO_2 (mmHg) by Week and Treatment Group – ITT

14.31B Summary Statistics for Change From Baseline in Optional PCO_2 (mmHg) by Week and Treatment Group – ITT

14.31C Descriptive Statistics for Change From Baseline in Optional PCO_2 (mmHg) by Week and Treatment Group – ITT

14.32B Summary Statistics for Change From Baseline in Optional pH by Week and Treatment Group – ITT

14.32C Descriptive Statistics for Change From Baseline in Optional pH by Week and Treatment Group – ITT

14.33B Summary Statistics for Change From Baseline in Optional HCO_3 (mmHg) by Week and Treatment Group – ITT

14.33C Descriptive Statistics for Change From Baseline in Optional HCO_3 (mmHg) by Week and Treatment Group – ITT

14.34B Summary Statistics for Change From Baseline in Optional Resting SaO_2 (%) by Week and Treatment Group – ITT

14.34C Descriptive Statistics for Change From Baseline in Optional Resting SaO_2 (%) by Week and Treatment Group – ITT

14.36 As Needed Albuterol Use by Week and Treatment Group – ITT

14.37B Summary Statistics for Change from Baseline in Post-exercise Heart Rate (bpm) by Week and Treatment Group – ITT

14.37C Descriptive Statistics for Change from Baseline in Post-exercise Heart-rate (bpm) by Week and Treatment Group – ITT

14.38 Investigator Global Assessments by Treatment Group – ITT

14.39 Patient Global Assessments by Treatment Group – ITT

14.40B Summary Statistics for Change in Post-albuterol FEV_1 (L) by Week and Treatment Group – ITT

14.40C Descriptive Statistics for Change from Baseline in Post-albuterol FEV_1 (L) by Week and Treatment Group – ITT

14.41B Summary Statistics for Change in Post-albuterol FVC (L) by Week and Treatment Group – ITT

14.41C Descriptive Statistics for Change from Baseline in Post-albuterol FVC (L) by Week and Treatment Group – ITT

14.42B Summary Statistics for Change in Post-albuterol PEF (L/Min) by Week and Treatment Group – ITT

14.42C Descriptive Statistics for Change from Baseline in Post-albuterol PEF (L/Min) by Week and Treatment Group – ITT

14.43B Summary Statistics for Change in Post-albuterol FEF_{25-75} (L/Sec) by Week and Treatment Group – ITT

14.43C Descriptive Statistics for Change from Baseline in Post-albuterol FEF_{25-75} (L/Sec) by Week and Treatment Group – ITT

14A.1A Summary of Average Change From Baseline Over 24 Weeks (Repeated Measures Analysis) in Trough FEV_1 (L) – PP

14A.1B Summary Statistics for Change From Baseline in Trough FEV_1 (L) by Week and Treatment Group – PP

14A.1C Descriptive Statistics for Change from Baseline in Trough FEV_1 (L) by Week and Treatment Group – PP

14A.1D Summary Statistics for Change From Pre-albuterol Baseline in FEV_1 (L) After First Dose by Time and Treatment Group – PP

14A.1E Descriptive Statistics for Change From Pre-albuterol Baseline in FEV_1 (L) After First Dose by Time and Treatment Group – PP

14A.1F Summary Statistics for Change from Week 24 Trough FEV_1 (L) After Last Dose by Time and Treatment Group – PP

14A.1G Descriptive Statistics for Change From Week 24 Trough FEV_1 (L) After Last Dose by Time and Treatment Group – PP

14A.2A Summary of Average Change From Baseline Over 24 Weeks (Repeated Measures Analysis) in Total Score of the SGRQ – PP

14A.2B Summary Statistics for Change From Baseline in Total Score of the SGRQ by Week and Treatment Group – PP

14A.2C Descriptive Statistics for Change From Baseline in Total Score of the SGRQ by Week and Treatment Group – PP

14A.3A Summary of Average Change From Baseline Over 24 Weeks (Repeated Measures Analysis) in Post-exercise Dyspnea – PP

14A.3B Summary Statistics for Change From Baseline in Post-exercise Dyspnea by Week and Treatment Group – PP

14A.3C Descriptive Statistics for Change From Baseline in Post-exercise Dyspnea by Week and Treatment Group – PP

14A.5A Summary of Average Change From Baseline Over 24 Weeks (Repeated Measures Analysis) in Trough FVC (L) – PP

14A.5B Summary Statistics for Change From Baseline in Trough FVC (L) by Week and Treatment Group – PP

14A.5C Descriptive Statistics for Change From Baseline in Trough FVC (L) by Week and Treatment Group – PP

14A.5D Summary Statistics for Change From Pre-albuterol Baseline in FVC (L) After First Dose by Time and Treatment Group – PP

14A.5E Descriptive Statistics for Change From Pre-albuterol Baseline in FVC (L) After First Dose by Time and Treatment Group – PP

14A.5F Summary Statistics for Change from Week 24 Trough FVC (L) After Last Dose by Time and Treatment Group – PP

14A.5G Descriptive Statistics for Change From Week 24 Trough FVC (L) After Last Dose by Week and Treatment Group – PP

14A.6A Summary of Average Change From Baseline Over 24 Weeks (Repeated Measures Analysis) in Distance Walked (Meters) – PP

14A.6B Summary Statistics for Change From Baseline in Distance Walked (Meters) by Week and Treatment Group – PP

14A.6C Descriptive Statistics for Change From Baseline in Distance Walked (Meters) by Week and Treatment Group – PP

14A.9D Summary Statistics for Change From Pre-albuterol Baseline in PEF (L/Min) After First Dose by Time and Treatment Group – PP

14A.9E Descriptive Statistics for Change From Pre-albuterol Baseline in PEF (L/Min) After First Dose by Time and Treatment Group – PP

14A.9F Summary Statistics for Change From Week 24 Trough PEF (L/Min) After Last Dose by Time and Treatment Group – PP

14A.9G Descriptive Statistics for Change From Week 24 Trough PEF (L/Min) After Last Dose by Time and Treatment Group – PP

14A.24D Summary Statistics for Change From Pre-albuterol Baseline in FEF_{25-75} (L/Sec) After First Dose by Time and Treatment Group – PP

14A.24E Descriptive Statistics for Change From Pre-albuterol Baseline in FEF_{25-75} (L/Sec) After First Dose by Time and Treatment Group – PP

14A.24F Summary Statistics for Change from Week 24 Trough FEF_{25-75} (L/sec) After Last Dose by Time and Treatment Group – PP

14A.24G Descriptive Statistics for Change from Week 24 Trough FEF_{25-75} (L/sec) After Last Dose by Time and Treatment Group – PP

14A.25 Sputum Production Assessment by Week and Treatment Group – PP

14A.26 Cough Assessment by Week and Treatment Group – PP

14A.36 As Needed Albuterol Use by Week and Treatment Group – PP

14A.38 Investigator Global Assessment by Treatment Group – PP

14A.39 Patient Global Assessments by Treatment Group – PP

14A.40B Summary Statistics for Change in Post-Albuterol FEV_1 (L) by Week and Treatment Group – PP

14A.40C Descriptive Statistics for Change in Post-Albuterol FEV_1 (L) by Week and Treatment Group – PP

14A.41B Summary Statistics for Change in Post-Albuterol FVC (L) by Week and Treatment Group – PP

14A.41C Descriptive Statistics for Change in Post-Albuterol FVC (L) by Week and Treatment Group – PP

14A.42B Summary Statistics for Change in Post-Albuterol PEF (L/Min) by Week and Treatment Group – PP

14A.42C Descriptive Statistics for Change in Post-Albuterol PEF (L/Min) by Week and Treatment Group – PP

14A.43B Summary Statistics for Change in Post-Albuterol FEF_{25-75} (L/Sec by Week and Treatment Group – PP

14A.43C Descriptive Statistics for Change in Post-Albuterol FEF_{25-75} (L/Sec by Week and Treatment Group – PP

15. SOURCE TABLES: SAFETY RESULTS

15.0 Narrative Location Table

15.1A Summary of Study Medication Exposure (Days) by Treatment Group

15.1B Descriptive Statistics for Study Medication Exposure (Days) by Treatment Group

15.2A Incidence of All On-therapy Adverse Experiences by Preferred Term, Descending Frequency of Occurrence and Treatment Group

15.2B Incidence of On-therapy Adverse Experiences by Body System, Preferred Term and Treatment Group

15.3 Incidence of On-therapy Adverse Experiences by Investigator-determined Relationship to Treatment, Body System, Preferred Term and Treatment Group

15.4 Incidence of On-therapy Adverse Experiences by Investigator-determined Intensity, Body System, Preferred Term and Treatment Group

15.5 Incidence of On-therapy Adverse Experiences (≥2%) by Initial Time of Onset, Body System, Preferred Term and Treatment Group

15.6 Incidence of On-therapy Adverse Experiences That Led to Dose Interruption by Body System, Preferred Term and Treatment Group

15.7 Incidence of On-therapy Adverse Experiences That Required Corrective Therapy by Body System, Preferred Term and Treatment Group

15.8A Incidence of Run-in Serious Adverse Experiences by Body System, Preferred Term and Treatment Group

15.8B Incidence of On-therapy Serious Adverse Experiences by Body System, Preferred Term and Treatment Group

15.8C Incidence of Post-therapy Serious Adverse Experiences by Body System, Preferred Term and Treatment Group

15.8D Narratives for Patients With Fatal Serious Adverse Experience

15.8E Narratives for Patients with Serious Adverse Experiences

15.9A	Incidence of On-therapy Adverse Experiences Leading to Patient Withdrawal By Preferred Term, Descending Frequency of Occurrence and Treatment Group
15.9B	Incidence of On-therapy Adverse Experiences Leading to Patient Withdrawal By Body System, Preferred Term and Treatment Group
15.9C	Narratives for Patients Withdrawn due to Non-serious On-therapy Adverse Experiences
15.10	Incidence of all Post-therapy Adverse Experiences by Body System, Preferred Term and Treatment Group
15.11A	Incidence of On-therapy Gastrointestinal Adverse Experiences of Concern by Preferred Term, Descending Frequency of Occurrence and Treatment Group
15.11B	Incidence of On-therapy Gastrointestinal Adverse Experiences of Concern That Led to Patient Withdrawal by Preferred Term, Descending Frequency of Occurrence and Treatment Group
15.11C	Incidence of On-therapy Gastrointestinal Adverse Experiences of Concern by Treatment Group, Preferred Term, Investigator-determined Intensity, and Descending Frequency of Occurrence
15.11D	Narratives of Patients Who Received SB 207499 With Non-serious Gastrointestinal Adverse Experiences of Concern That Did Not Lead to Withdrawal
15.11E	Colonoscopies and Other Gastrointestinal Test Reports
15.12A	Transitions From Baseline in FOB Results for Patients With GIAEs of Concern During Double-blind Period
15.12B	Transitions From Baseline in FOB Results for All Patients During Double-blind Period
15.13A	Transitions From Baseline in Orthostatic Vital Signs for Patients With Gastrointestinal Adverse Experiences of Concern
15.13B	Transitions From Baseline in Orthostatic Vital Signs
15.14	Descriptive Statistics for Clinical Laboratories by Visit/Week and Treatment Group
15.15	Transitions From Baseline in Laboratory Values by Analyte
15.15C	Narratives of Patients With On-therapy Laboratory Values of Concern
15.16	Descriptive Statistics for Standard Vital Signs by Visit/Week and Treatment

Group

15.16A Narratives of Patients with On-therapy Vital Sign Values of Concern

15.17 Transitions From Baseline in Sitting Vital Signs

15.18 Descriptive Statistics for ECGs by Visit/Week and Treatment Group

15.19A Transitions From Baseline in ECG Parameters

15.19B Change From Baseline in QTC

15.19C Change From Baseline in QRS Axis Obtained at Trough

15.20 Incidence of New-onset On-therapy ECG Abnormalities by Treatment Group

15.20A Narratives of Patients with On-therapy ECG Values of Concern

16. SOURCE TABLES: POPULATION PHARMACOKINETIC

Data from the population pharmacokinetic evaluation are reported separately. [18]

17. SOURCE TABLES: PHARMACODYNAMICS

Data from the pharmacokinetic/pharmacodynamic evaluation are reported separately. [18]

18. SOURCE TABLES: PHARMACOECONOMICS

18.1 Summary of COPD-related Healthcare Resource Utilization Prior to Screening by Treatment Group

18.2 Summary of Utilization-free Survival and Total Number of Utilizations by Type of Utilization and Treatment Group – ITT

18.3 Rates of Resource Utilization per 10,000 Treatment Exposure Days by Treatment Group – ITT

18.4 Summary of Poisson Regression of Utilization Rates by Type of Utilization – ITT

18.5 Summary Statistics for Percent of Time in Hospital by Treatment Group – ITT

18.6 Summary Statistics for Percent of Time in ICU by Treatment Group – ITT

18.7 Summary Statistics for Percent of Lost Days from Work by Treatment Group – ITT

18.8 Summary Statistics for Percent of Time with Restricted Leisure Activities by Treatment Group – ITT

18.9A Number and Percent of Patients by Average Weekly Hours of Unpaid Assistance and Treatment Group – ITT

18.9B Number and Percent of Patients by Average Weekly Hours of Paid Assistance and Treatment Group – ITT

18.10 Number and Percent of Patients by Days in Hospital and Treatment Group – ITT

18.11 Number and Percent of Patients by Days in ICU and Treatment Group – ITT

19. SOURCE FIGURES

19.1A Mean (SEM) Change From Baseline in Trough FEV_1 – ITT

19.1B Mean (SEM) Change From Baseline in Trough FEV_1 Averaged Over 24 Weeks – ITT

19.1C Change from Baseline in Trough FEV_1 versus Change From Baseline in Total Score of the SGRQ at Endpoint - ITT

19.1D Distribution of Change From Baseline in Trough FEV_1 at Endpoint for Placebo Patients – ITT

19.1E Distribution of Change From Baseline in Trough FEV_1 at Endpoint For SB 207499 Patients – ITT

19.1F Mean (SEM) Change From Baseline in FEV_1 After First Dose – ITT

19.1G Mean (SEM) Change From Week 24 Trough FEV_1 After Last Dose – ITT

19.2A Mean (SEM) Change From Baseline in Total Score of the SGRQ – ITT

19.2B Mean (SEM) Change From Baseline in Total Score of the SGRQ Averaged Over 24 Weeks – ITT

19.2D Distribution of Change From Baseline in Total Score of the SGRQ at Endpoint for Placebo Patients – ITT

19.2E Distribution of Change From Baseline in Total Score of the SGRQ at Endpoint for SB 207499 Patients – ITT

19.3A Mean (SEM) Change From Baseline in Post-exercise Dyspnea – ITT

19.3B Mean (SEM) Change From Baseline in Post-exercise Dyspnea Averaged Over 24 Weeks – ITT

19.5A Mean (SEM) Change From Baseline in Trough FVC – ITT

19.5B Mean (SEM) Change From Baseline in Trough FVC Averaged Over 24 Weeks – ITT

19.5F Mean (SEM) Change From Baseline in FVC After First Dose – ITT

19.5G Mean (SEM) Change From Week 24 Trough in FVC After Last Dose – ITT

19.6A Mean (SEM) Change From Baseline in Distance Walked – ITT

19.6B Mean (SEM) Change From Baseline in Distance Walked Averaged Over 24 Weeks – ITT

19.7A Kaplan-Meier Estimates of Percentage of Patients Exacerbation-free – ITT

19.7B Kaplan-Meier Estimates of Percentage of Patients Level II/III Exacerbation-free – ITT

19.9A Mean (SEM) Change From Baseline in Trough PEFR (L/Min) – ITT

19.9F Mean (SEM) Change From Baseline in PEFR After First Dose – ITT

19.9G Mean (SEM) Change From Week 24 Trough in PEFR After Last Dose – ITT

19.10A Mean (SEM) Change From Baseline in Overall Dyspnea – ITT

19.15 Cumulative Incidence of Nausea by Time of Initial Onset – ITT

19.16 Cumulative Incidence of Abdominal Pain by Time of Initial Onset – ITT

19.17 Cumulative Incidence of Diarrhea by Time of Initial Onset – ITT

19.18 Cumulative Incidence of Vomiting by Time of Initial Onset – ITT

19.19 Cumulative Incidence of Gastrointestinal Adverse Experiences of Concern by Time of Initial Onset – ITT

19.21A Mean (SEM) Change From Baseline in Symptoms Score of the SGRQ – ITT

19.22A Mean (SEM) Change From Baseline in Impacts Score of the SGRQ – ITT

19.23A Mean (SEM) Change From Baseline in Activities Score of the SGRQ – ITT

19.24A Mean (SEM) Change From Baseline in Trough FEF_{25-75} – ITT

19.24F Mean (SEM) Change From Baseline in FEF_{25-75} After First Dose – ITT

19.24G Mean (SEM) Change From Week 24 Trough in FEF_{25-75} After Last Dose – ITT

19.28A Mean (SEM) Change From Baseline in Post-exercise SaO2 – ITT

19.40B Mean (SEM) Change From Baseline in Post-Albuterol Trough FEV_1 at Week 24 – ITT

19.41B Mean (SEM) Change From Baseline in Post-Albuterol Trough FVC at Week 24 – ITT

19.42B Mean (SEM) Change From Baseline in Post-Albuterol Trough PEF at Week 24 – ITT

19.43B Mean (SEM) Change From Baseline in Post-Albuterol Trough FEF_{25-75} at Week 24 – ITT

19A.1A Mean (SEM) Change From Baseline in Trough FEV_1 – PP

19A.1B Mean (SEM) Change From Baseline in Trough FEV_1 Averaged Over 24 Weeks – PP

19A.1F Mean (SEM) Change From Baseline in FEV_1 After First Dose – PP

19A.1G Mean (SEM) Change From Week 24 Trough in FEV_1 After Last Dose – PP

19A.2A Mean (SEM) Change From Baseline in Total Score of the SGRQ – PP

19A.2B Mean (SEM) Change From Baseline in Total Score of the SGRQ Averaged Over 24 Weeks – PP

19A.3A Mean (SEM) Change From Baseline in Post-exercise Dyspnea – PP

19A.3B Mean (SEM) Change From Baseline in Post-exercise Dyspnea Averaged Over 24 Weeks – PP

19A.5A Mean (SEM) Change From Baseline in Trough FVC – PP

19A.5B Mean (SEM) Change From Baseline in Trough FVC Averaged Over 24 Weeks – PP

19A.5F Mean (SEM) Change From Baseline in FVC After First Dose – PP

19A.5G Mean (SEM) Change From Week 24 Trough in FVC After Last Dose – PP

19A.6A Mean (SEM) Change From Baseline in Distance Walked – PP

19A.6B Mean (SEM) Change From Baseline in Distance Walked Averaged Over 24 Weeks – PP

19A.9F Mean (SEM) Change From Baseline in PEF After First Dose – PP

19A.9G Mean (SEM) Change From Week 24 Trough in PEF After Last Dose – PP

19A.24F Mean (SEM) Change From Baseline in FEF_{25-75} After First Dose – PP

19A.24G Mean (SEM) Change From Week 24 Trough in FEF_{25-75} After Last Dose – PP

19A.40B Mean (SEM) Change From Baseline in Post-Albuterol Trough FEV_1 at Week 24 – PP

19A.41B Mean (SEM) Change From Baseline in Post-Albuterol Trough FVC at Week 24 – PP

19A.42B Mean (SEM) Change From Baseline in Post-Albuterol Trough PEF at Week 24 – PP

19A.43B Mean (SEM) Change From Baseline in Post-Albuterol Trough FEF_{25-75} at Week 24 – PP

20. APPENDICES

Appendix A Final Protocol, Sample (Blank) CRF, CVs of Investigators, Randomization Code, Certificates of Analysis, References, Audited Investigator Sites

Table of Contents

Table/ Appendix Number	Title	Number of Pages
A	Protocol (including Amendments) and Sample Informed Consent	
A	Sample (Blank) CRF	
A	Investigators Curriculum Vitae	
A.1	Treatment Randomization With Patient Number	
A	References	
A	Certificates of Analysis	
A	Audited Investigator Sites	

Appendix B Patient Data Listings of Demographic and Baseline Characteristics

Table of Contents

Listing Number	Title	Number of Pages
B.1	Reason for Study Conclusion, Days of Participating in the Study and Demographics by Patient Number	
B.2A	Exclusionary Medications and Visit Specific Protocol Violations by Patient Number	
B.2B	Violations of Eligibility Criteria by Patient Number	
B.2C	Conduct of Study Deviations by Patient Number	
B.3	FEV_1, FEV_1 % Predicted, PEF, FVC, FEF_{25-75}, Albuterol Reversibility and FEV_1/ FVC Ratio at Screening by Patient Number	
B.4	Alcohol Consumption, Cigarette Smoking History, and Percent Predicted DLCO at Screening by Patient Number	
B.5	Prior Medical Conditions by Patient Number	
B.6	Current/Active Medical Conditions by Patient Number and Disease Classification	
B.7	Prior Medications by Patient Number	
B.8A	Concomitant Medications by Patient Number	
B.8B	COPD Exacerbation Medications by Patient Number	
B.8C	Post-therapy Medications by Patient Number	
B.9	Medical Procedure Data by Patient Number	
B.10	Baseline Signs and Symptoms by Patient Number, Body System, Preferred Term and Verbatim Term	
B.11	Study Medication Compliance by Patient Number	
B.12	Study Medication Record by Patient Number	
B.13	Smoking Status by Patient Number	
B.14	Listing Of Supplemental Text For Patients Who Concluded The Study For A Reason = Other	

Appendix C Patient Data Listings of Efficacy

Table of Contents

Listing Number	Title	Number of Pages
C.1	Pulmonary Function Parameters by Patient Number	
C.2	Saint George's Respiratory Questionnaire by Patient Number	
C.3	Exercise Tolerance, Post-exercise Dyspnea, Overall Dyspnea, Post-exercise Heart Rate and Post-exercise SAO_2 by Patient Number	
C.4	COPD Exacerbations by Patient Number	
C.5	Arterial Blood Gases, pH and Resting SAO_2 by Patient Number	
C.6	COPD Symptom Parameters by Patient Number and Visit	
C.7A	Health Care Resource Utilization and Lost Work Days by Patient Number	
C.7B	Days of Restricted Leisure Activities and Weekly Hours of Paid and Unpaid Assistance by Patient Number	
C.8	SF-36 by Patient Number	

Appendix D Patient Data Listings of Safety

Table of Contents

Listing Number	Title	Number of Pages
D.1	On therapy Adverse Experiences by Patient Number, Body System, Preferred Term and Verbatim Term	
D.2A	On-therapy Adverse Experiences Possibly or Probably Related to Treatment by Patient Number, Body System, Preferred Term and Verbatim Term	
D.2B	On-therapy Adverse Experiences Unlikely or Not Related to Treatment by Patient Number, Body System, Preferred Term and Verbatim Term	
D.3	On-therapy Adverse Experiences That Led to Dose Interruption by Patient Number, Body System, Preferred Term and Verbatim Term	
D.4	On-therapy Adverse Experiences That Required Corrective Therapy by Patient Number, Body System, Preferred Term and Verbatim Term	
D.5A	Run-in Serious Adverse Experiences by Patient Number, Body System, Preferred Term and Verbatim Term	
D.5B	On-therapy Serious Adverse Experiences by Patient Number, Body System, Preferred Term and Verbatim Term	
D.5C	Post-therapy Serious Adverse Experiences by Patient Number, Body System, Preferred Term and Verbatim Term	
D.5D	Patient Fatalities by Patient Number	
D.6A	On-therapy Adverse Experiences That Led to Withdrawal by Patient Number, Body System, Preferred Term and Verbatim Term	
D.6B	Run-in Adverse Experiences That Led to Withdrawal by Patient Number, Body System, Preferred Term and Verbatim Term	
D.7	Post-therapy Adverse Experiences by Patient Number, Body System, Preferred Term and Verbatim Term	
D.8	Gastrointestinal Adverse Experiences of Concern by Patient Number, Body System, Preferred Term and Verbatim Term	

Listing Number	Title	Number of Pages
D.8A	Run-In Gastrointestinal Adverse Experiences of Concern by Patient Number, Body System, Preferred Term and Verbatim Term	
D.8B	Post-Therapy Gastrointestinal Adverse Experiences of Concern by Patient Number, Body System, Preferred Term and Verbatim Term	
D.9	Gastrointestinal Symptom Assessment by Patient Number	
D.10	Abdominal Pain Assessment by Patient Number	
D.11	Stool Assessment by Patient Number	
D.12	Physical Examination for Patients With Gastrointestinal Symptoms of Concern by Patient Number	
D.13	FOB Test Results by Patient Number	
D.14	Listing of Gastro-intestinal Adverse Experience of Concern with Associated FOB Results and Colonoscopy Findings by Patient Number	

Appendix E Patient Data Listings of Vital Signs and Electrocardiograms

Table of Contents

Listing Number	Title	Number of Pages
E.1A	Standard Vital Signs by Patient Number	
E.1B	Standard Vital Signs of Clinical Concern by Patient Number	
E.1C	Orthostatic Vital Sign Changes by Patient Number	
E.1D	Orthostatic Vital Sign Changes of Clinical Concern by Patient Number	
E.2A	ECG Intervals by Patient Number	
E.2B	ECGs of Clinical Concern by Patient Number	
E.2C	ECG Abnormalities by Patient Number	

Appendix F Patient Data Listings of Laboratory Values

Table of Contents

Listing Number	Title	Number of Pages
F.1	List of Patients with Laboratory Values of Clinical Concern by Treatment Group and Patient Number	
F.2	Clinical Laboratory Values by Treatment Group and Patient Number	

Appendix G CRFs and DRQs for GI Adverse Events of Concern, Non-fatal Serious Adverse Events, Withdrawals for Adverse Events and Death

Note: Please refer to Data Source Section 15, Table 15.8D, Table 15.8E, Table 15.9C, and Table 15.11D for location of patient narratives.

Appendix H CRF Tabulations by Patient ID

Case Report Form tabulations are available electronically.

Appendix I Statistical Report Listings

Table of Contents

Listing Number	Title	Number of Pages
I.1A	Repeated Measures Analysis Tests for Interactions for Trough FEV_1 (L) – ITT	
I.1B	Repeated Measures Analysis Test for Treatment Differences for Trough FEV_1 (L) – ITT	
I.1C	Analysis of Variance Test for Treatment Differences for Trough FEV_1 (L) at Endpoint – ITT	
I.2A	Repeated Measures Analysis Tests for Interactions for Total Score of the SGRQ – ITT	
I.2B	Repeated Measures Analysis Tests for Treatment Differences for Total Score of the SGRQ – ITT	
I.2C	Analysis of Variance Test for Treatment Differences for Total Score of the SGRQ at Endpoint – ITT	
I.4	Descriptive Statistics for Primary Efficacy Variables at Endpoint by Treatment Group – Withdrawals	
I.6A	Sensitivity Analysis of Assumed Covariance Structure on Treatment Differences for Trough FEV_1 (L) – ITT	
I.6B	Sensitivity Analysis of Assumed Covariance Structure on Treatment Difference for Total Score of the SGRQ – ITT	
I.7A	Repeated Measures Analysis Test for Covariate Effects on Treatment Differences for Trough FEV_1 (L) – ITT	
I.7B	Repeated Measures Analysis Test for Covariate Effects on Treatment Differences for Total Score of the SGRQ – ITT	
I.7C	Repeated Measures Analysis Test for Treatment Differences Adjusted for Significant Covariates for Trough FEV_1 (L) – ITT	
I.7D	Repeated Measures Analysis Test for Treatment Differences Adjusted for Significant Covariates for Total Score of the SGRQ – ITT	
I.8A	Repeated Measures Analysis Tests for Missing Data Pattern Effects for Trough FEV_1 (L) – ITT	

Listing Number	Title	Number of Pages
I.8B	Repeated Measures Analysis Tests for Missing Data Pattern Effects for Total Score of the SGRQ – ITT	
I.9A	Weighted Estimate of Treatment Effect From Pattern Mixture Model for Trough FEV_1 (L) – ITT	
I.9B	Weighted Estimate of Treatment Effect From Pattern Mixture Model for Total Score of the SGRQ – ITT	
I.10A	Summary of Demographic and Baseline Characteristics for All Withdrawn Patients	
I.10B	Summary of Demographic and Baseline Characteristics for All Completers	
I.11A	Summary of Average Change From Baseline Over 24 Weeks in Trough FEV_1 (L) – ITT (Repeated Measures Analysis Adjusted by Center, Time and Treatment-by-Time Interaction)	
I.11B	Summary of Average Change From Baseline From Week 16 to Week 24 (Repeated Measures Analysis) in Trough FEV_1 (L) – ITT	
I.12A	Summary of Average Change From Baseline Over 24 Weeks (Repeated Measures Analysis) in Trough FEV_1 (L) – Completers	
I.12B	Summary Statistics for Change From Baseline in Trough FEV_1 (L) by Week and Treatment Group – Completers	
I.13A	Summary of Average Change From Baseline Over 24 Weeks (Repeated Measures Analysis) in Total Score of the SGRQ – Completers	
I.13B	Summary Statistics for Change From Baseline in Total Score of the SGRQ by Week and Treatment Group – Completers	
I.14A	Summary of Exacerbation-free Survival – Completers	
I.14B	Summary of Proportional Hazards Regression of Time to First Exacerbation – Completers	
I.14C	Summary of Level 2/Level 3 Exacerbation-free Survival – Completers	
I.14D	Summary of Proportional Hazards Regression of Time to First Level 2/Level 3 Exacerbation – Completers	

Listing Number	Title	Number of Pages
I.15A	Summary of Average Change from Baseline Over 24 Weeks (Repeated Measures Analysis) in Trough FEV_1 (L) – ITT – Withdrawals Imputed with Worst FEV_1	
I.15B	Summary of Average Change From Baseline Over 24 Weeks (Repeated Measures Analysis) in Total Score of the SGRQ – ITT – Withdrawals Imputed with Worst Score	
I.16	Summary of Average Change from Baseline Over 24 Weeks (Repeated Measures Analysis) in Trough FEV_1 (L) by Centers in/not in Study 039 and Treatment Group – ITT	
I.17	Summary of Average Change from Baseline Over 24 Weeks (Repeated Measures Analysis) in Total Score of the SGRQ by Centers in/not in Study 039 and Treatment Group – ITT	
I.18	Summary of Average Change from Baseline Over 24 Weeks (Repeated Measures Analysis) in Trough FEV_1 (L) by Diagnosed Emphysema and Treatment Group – ITT	
I.19	Summary of Average Change from Baseline Over 24 Weeks (Repeated Measures Analysis) in Total Score of the SGRQ by Diagnosed Emphysema and Treatment Group – ITT	
I.20	Summary of Exacerbation-free Survival by Treatment Group – ITT Patients In Study 039 Centers	
I.21	Summary of Exacerbation-free Survival by Treatment Group – ITT Patients Not In Study 039 Centers	
I.22	Summary of Exacerbation-free Survival by Treatment Group – ITT Patients Diagnosed with Emphysema	
I.23	Summary of Exacerbation-free Survival by Treatment Group – ITT Patients Diagnosed without Emphysema	

Confidential

SmithKline Beecham

Ariflo (SB 207499)

A Randomized, 24-week, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy, Safety and Tolerability of Ariflo (15 mg BID) in Patients with Chronic Obstructive Pulmonary Disease (COPD)

SB 207499/156

Protocol

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Protocol Table of Contents

Protocol List of Tables 001562
Protocol List of Figures 001563
Protocol List of Appendices 001564
List of Abbreviations & Definitions 001565
Synopsis 001567
1 Introduction 001575
2 Objectives 001578
3 Study Design Overview 001579
3.1 Study Design 001579
3. 2 Schedule of Assessments 001582
3.3 Method of Randomization 001584
4 Study Population 001584
4.1 Number of Patients/Centers 001584
4.2 Inclusion Criteria 001584
4.3 Exclusion Criteria 001585
5 Conduct of the Study 001586
5.1 Ethical and Regulatory Considerations 001586
5.1.1 Ethics Review Committee (ERC)/Institutional Review Board (IRB) 001587
5.1.2 Informed Consent 001587
5.2 Outline of Study Procedures 001588
5.2.1 Study Visits 001588
5.3 Detailed Description of Study Stages/Visits 001589
5.3.1 Visit 1 (Week-4): Screening and Start of 4-week Single-blind run in 001589
5.3.2 Visit 2 (Week -2): Single-blind Run-in Period 001592
5.3.3 Visit 3 (Week 0): Baseline, Start of Double-blind Treatment Phase 001594
5.3.4 Visit 3a (End of Week 1): Double-blind Treatment Phase . . . 001599
5.3.5 Visit 4 (End of Week 2): Double-blind Treatment Phase 001601
5.3.6 Visit 5 (End of Week 4): Double-blind Treatment Phase 001603
5.3.7 Visit 6 (End of Week 8): Double-blind Treatment Phase 001605
5.3.8 Visit 7 (End of Week 12): Double-blind Treatment Phase . . . 001608
5.3.9 Visit 8 (End of Week 16): Double-blind Treatment Phase . . . 001610
5.3.10 Visit 9 (End of Week 20): Double-blind Treatment Phase . . 001613
5.3.11 Visit 10 (End of Week 24): End of Double-blind Treatment Phase 001615
5.3.12 Early Withdrawal Assessments 001619

5.3.13 Safety Follow-up Visit 001620
5.4 Clinical Observations and Procedures. 001621
5.4.1 Previous Medical History and Diagnosis 001621
5.4.2 Physical & Respiratory Examination and Vital Signs 001621
5.4.3 "As Needed" Albuterol Use 001622
5.4.4 Chest Radiograph 001622
5.4.5 Electrocardiograph (ECG) 001623
5. 4. 6 Breathlessness - Overall and Post-exercise 001623
5.4.7 Pulmonary Function Tests 001624
5.4.8 Laboratory Tests. 001626
5.4.9 Pharmacokinetic Sampling. 001628
5.4.10 Exercise Tolerance Test 001630
5.4.11 Diary Card 001631
5.4.12 Resting and Post-exercise Transcutaneous Oxygen Saturation 001631
5.4.13 Arterial Blood Gases 001631
5.4.14 Carbon Monoxide Diffusing Capacity (DLCO). 001631
5.4.15 Patient and Investigator Global Assessments. 001632
5.4.16 Cough and Sputum Production Assessments 001632
6 Study Medication and Administration 001633
6.1 Study Medication 001633
6.2 Dosage and Administration. 001634
6.3 Blinding. 001634
6.4 Packaging 001635
6.5 Labeling and Preparation 001636
6.6 Storage. 001637
6.7 Drug Accountability 001637
6.8 Assessment of Compliance 001638
6.9 Treatment of Study Medication Overdose 001638
6.10 Occupational Safety 001639
6.11 Concomitant Medication/Treatment 001639
6.11.1 Albuterol Use 001639
6.11.2 Anticholinergic Medication 001639
6.11.3 Prohibited Medications. 001640
6.11.4 Treatment of COPD Exacerbations 001641
6.11.5 Concomitant Medication 001642
7 Outcomes Research and Pharmacoeconomics 001642
7.1 Outcomes Measurement and Analysis 001642
7.2 Economic Data Collection and Analysis. 001642

7.3 Health Status Analyses 001643
8 Adverse Events 001644
8.1 Eliciting and Documenting Adverse Events 001644
8.1.1 Adverse Event Definition 001644
8.1.2 COPD Exacerbation Definitions 001645
8.1.3 Gastrointestinal Adverse Events 001646
8.1.4 Serious Adverse Event Definition 001647
8.2 Recording of Adverse Events 001649
8.2.1 Soliciting of Adverse Events 001650
8.2.2 Evaluating the Adverse Event 001650
8.3 Reporting and Recording of Serious Adverse Events 001651
8.3.1 Regulatory Responsibility 001651
8.3.2 Recording of Serious Adverse Events 001652
8.3.3 Reporting of Serious Adverse Events to SmithKline Beecham 001652
8.3.4 Follow-up of Serious AEs 001653
8.4 Overdose 001654
8.4.1 Reporting of Overdose 001654
8.4.2 Further Information on Overdose 001654
8.5 Treatment Failures 001654
8. 6 Post-study Events 001655
8.7 Pregnancy 001655
8.7.1 Reporting of Pregnancy 001655
8.7.2 Follow-up of Pregnancies 001655
8.7.3 Action Taken as a Result of Pregnancy 001656
8.8 Unblinding Treatment Codes 001656
8.9 Investigator Letters 001656
9 Subject Completion and Withdrawal 001656
9.1 Definitions 001656
9.2 Procedures for Handling Withdrawals 001657
9.3 Reasons for Withdrawal 001657
10 Statistical Issues: Design and Analysis 001658
10.1 Objectives 001658
10.2 Hypotheses 001659
10.3 Definition of Variables 001659
10.3.1 Primary Efficacy Variable 001659
10.3.2 Secondary Efficacy Variables 001659
10.3.3 Tertiary Efficacy Variables 001660
10.4 Comparisons of Interest 001661
10.4.1 Primary Comparison of Interest 001661

10.4.2 Secondary Comparisons of Interest 001661
10.5 Interim Analysis 001661
10.6 Target Sample Size 001662
10.6.1 Sample Size Assumption 001662
10.6.2 Sample Size and Sensitivity 001662
10.6.3 Sample Size Re-Estimation 001663
10.7 Methods of Analysis 001663
10.7.1 Populations of Interest 001663
10.7.2 Statistical Methods 001664
11 Administrative Matters. 001667
References 001668
Appendices 001670

Protocol List of Tables

Table 1 Treatment Differences for Ariflo Phase 3 Studies in Primary and Secondary Parameters Intent-to-Treat Population 001577
Table 2 Overall Incidence of Most Commonly Reported On-therapy Adverse Events in Ariflo Phase 3 Studies 001578
Table 3 Outline of Study Procedures 001583
Table 4 Study Medication Packaging 001636
Table 5 Prohibited Medications in Study SB 207499/156 001641

Protocol List of Figures

Figure 1 Schematic Representation of Study Design 001581
Figure 2 Order of Pulmonary Function Tests at Visit 3 001597
Figure 3 Order of Pulmonary Function Tests at Visit 10 001618

Protocol List of Appendices

Appendix A Declaration of Helsinki. 001671
Appendix B Administrative Matters 001675
Appendix C Sample Informed Consent (Written or Oral Witnessed as appropriate) 001680
Appendix D Predicted FEV 1 Equations. 001691
Appendix E The SF-36 Health Survey Questionnaire 001692
Appendix F The St. George's Respiratory Questionnaire 001699
Appendix G ATS Guidelines for the Diagnosis of COPD 001716
Appendix H Gastrointestinal Adverse Event Monitoring 001718

List of Abbreviations & Definitions

Abbreviations

AE	adverse event
ALP	alkaline phosphatase
ALAT (SGPT)	alanine aminotransferase
ASAT (SGOT)	aspartate aminotransferase
BID	twice daily
BP	blood pressure
BTPS	body temperature and pressure standard
cyclic AMP	cyclic adenosine monophosphate
CI	confidence interval
cm	centimeter
CO	carbon monoxide
COPD	chronic obstructive pulmonary disease
CRF	case report form
DLCO	carbon monoxide diffusing capacity
DMPK	drug metabolism and pharmacokinetics
ECG	electrocardiogram
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
HR	heart rate
IRB	institutional review board
ITT	intent-to-treat
IUD	intrauterine device
LTOT	long-term oxygen therapy
mcg	microgram
MDI	metered dose inhaler
mg	milligram
mL	milliliter
mmHg	millimeters of mercury
PCO_2	arterial carbon dioxide tension
PDE4	phosphodiesterase 4
PEFR	peak expiratory flow rate
PFT	pulmonary function test
PK	pharmacokinetic
PO_2	arterial oxygen tension
prn	pro re nata (as needed)
R&D	research and development
SaO_2	transcutaneous oxygen saturation

SB	SmithKline Beecham
SF-36	short form survey 36
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 unfavorable 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 hospitalization, 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 judgment

Synopsis

Compound/Protocol No.

SB 207499/156

Protocol Title

A Randomized, 24-week, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy, Safety and Tolerability of Ariflo™ (15 mg BID) in Patients with Chronic Obstructive Pulmonary Disease (COPD)

Rationale

COPD is a disorder characterized by reduced maximum expiratory flow and slow forced emptying of the lungs, features which do not change markedly over several months. [1] It is a major cause of morbidity and mortality. Fixed airflow limitation in COPD is due to three conditions: chronic bronchitis, emphysema, and small airways disease, which frequently co-exist in individual patients. [1]

Chronic Bronchitis is defined by the presence of chronic or recurrent increases in bronchial secretions sufficient to cause expectoration. [1] Cough is present for a minimum of 3 months a year, for at least two successive years, and can not be attributed to other pulmonary or cardiac causes. The site of most of the mucus hypersecretion is the large airways. Histological studies show enlargement of tracheobronchial submucosal glands and hyperplasia of tracheobronchial surface mucous (goblet) cells. *Emphysema* is defined as abnormal permanent enlargement of the air spaces distal to the terminal bronchioles, accompanied by destruction of their walls, and without obvious fibrosis. Airflow obstruction in COPD patients is progressive in nature, mostly irreversible and may be accompanied by airway hyperreactivity.

Recent data suggest that airway inflammation is a key feature of COPD, even in the early stages of the disease. It is characterized by the accumulation of increased numbers of mononuclear cells in the sub-mucosa and neutrophils in the airway lumen.[2]

The main risk factor for COPD is inhalation of tobacco smoke. Current treatment modalities for COPD include smoking cessation, symptomatic pharmacological

therapies for dyspnea and cough, and long-term oxygen therapy (LTOT). [1, 3] Presently, drug therapies can treat only the symptoms of COPD and not the underlying condition.

Ariflo (SB 207499) is a potent and selective phosphodiesterase type 4 (PDE4) inhibitor currently under development for the treatment of asthma and 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-hydrolyzing isozyme in these cells. [4]

Preclinical data suggest that Ariflo may have anti-inflammatory, bronchodilatory and neuromodulatory activities. Furthermore, the ability of Ariflo to inhibit airway smooth muscle cell proliferation suggests potential effects on airway remodeling. This unique combination of activities gives rise to the possibility that Ariflo may represent a new modality for the treatment of COPD, in that they may show short and long term benefit in the treatment of this disorder. [5]

As of 27 June 2000, 600 subjects have been treated with Ariflo in 27 Phase 1 clinical pharmacology studies; 1100 patients in six Phase 2 dose-ranging studies (633 and 467 patients, respectively with asthma and COPD); 1374 patients with COPD in three double-blind, placebo-controlled Phase 3 studies, 1054 patients in two ongoing, Phase 3 open-label extension studies; and 177 patients in three ongoing, Phase 2 mechanism of action studies.

The three Phase 3 randomized, double-blind, placebo-controlled studies (039, 042, and 091) have recently completed. Patients with COPD were characterized by a post-bronchodilator % predicted FEV_1 of ≥30% and ≤70%, a pre-bronchodilator FEV_1/FVC of ≤0.7, and fixed airway obstruction defined 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 3, placebo-controlled studies, patients with COPD entered a 4-week single-blind run-in phase and then were randomized to receive Ariflo 15 mg BID or placebo in a ratio of 2 to 1. A total of 1374 patients were treated with Ariflo 15 mg BID. Efficacy data from the three Phase 3 studies are presented in the following table.

Treatment Differences for Ariflo Phase 3 Studies in Primary and Secondary Parameters Intent-to-Treat Population*

	039		042		091	
Randomized Patients	**Placebo 213**	**Ariflo 425**	**Placebo 226**	**Ariflo 474**	**Placebo 242**	**Ariflo 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]	
Dyspnea	-0.24 (0.029) [-0.45, -0.02]		-0.20 (0.068) [-0.41, 0.01]		-0.16 (NS) [-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.
†† Ariflo relative to placebo.
NS not significant.

The following table displays the most common on-therapy adverse events reported in more than 5% of patients in decreasing frequency. Exacerbation of chronic obstructive pulmonary disease were more frequent in patients who received placebo, while diarrhea, nausea, abdominal pain, dyspepsia and vomiting were reported more frequently in patients who received Ariflo. The majority of the events were considered mild or moderate in severity by the Investigators. The gastrointestinal adverse events, reported more frequently in patients who received Ariflo, were generally mild and expected side effects of the known pharmacology of the drug. Most of these gastrointestinal adverse events were self-limited and occurred during the initial period of treatment. Few of the events were considered serious.

Overall Incidence of Most Commonly Reported On-therapy Adverse Events in Ariflo Phase 3 Studies

Adverse Event* (Preferred Term)	All Randomized Patients Placebo (N = 681) N	%	Ariflo (N = 1368) N	%
Chronic obstructive airways disease	265	38.9	421	30.8
Diarrhea	41	6.0	175	12.8
Nausea	28	4.1	170	12.4
Abdominal pain	39	5.7	155	11.3
Upper respiratory tract infection	51	7.5	111	8.1
Headache	43	6.3	101	7.4
Dyspepsia	17	2.5	83	6.1
Vomiting	7	1.0	76	5.6

* Includes adverse events reported for >5% of patients in either of the treatment groups.

There was no greater incidence of serious adverse events in patients who received 15 mg BID when compared with patients who received placebo. 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. [5]

Study 156 is being conducted as a pivotal Phase 3 study to assess the efficacy and safety of Ariflo versus placebo in patients with COPD. The present study has the goals of detecting a 50 mL treatment difference on FEV_1 and confirming the effects observed in Study 039 on health status. The study design of Study 156 is similar to that of Studies 039, 042, and 091.

Objectives

The primary objective of the study is to demonstrate the clinical efficacy of Ariflo (15 mg BID) versus placebo by assessment of forced expiratory volume in 1 second (FEV_1) at trough drug levels and the total score of the St. George's Respiratory Questionnaire (SGRQ) over 24 weeks in patients with COPD.

The secondary objectives of the study are to examine risk of exacerbations and to compare the clinical efficacy of Ariflo versus placebo on additional pulmonary function tests (clinic trough measurements) and other clinical evaluations (e.g. breathlessness).

The additional objective of the study is to further define the clinical safety and tolerability of Ariflo through the assessment of adverse events, vital signs, clinical laboratory tests, and electrocardiograms (ECGs).

Study Population

Up to 830 patients will be randomized to achieve 550 patients to satisfactorily complete the study. Approximately 140 centers in North America (United States and Canada) are expected to participate, with each center aiming to enroll between 6 and 24 patients.

Study Design

The study is a randomized, double-blind, placebo-controlled, parallel group study involving 12 visits over a 29-week period (Week-4 [Screening] through Week 25 [Safety Follow-up]). Double-blind study medication will be dispensed as tablets of either Ariflo (15 mg) or matched placebo, one tablet to be taken twice daily, immediately after breakfast and after the evening meal. (Previous clinical pharmacology studies have shown that Ariflo is better tolerated when administered in the fed state.)

The study will commence with a 4-week, single-blind, placebo run-in phase, after which the patients will be randomized in a double-blind manner to either Ariflo or matching placebo in a ratio of 1:1 for 24 weeks.

Pulmonary function tests will be performed at all visits (with the exception of one safety-only visit at Week 1). At the screening visit (Week -4), pulmonary function (FEV_1, FVC, FEF_{25-75} and PEFR) will be assessed before and after a standard dose of albuterol (180 mcg). At subsequent visits, pulmonary function will be measured at trough levels of study drug, in the absence of albuterol. In addition, the acute (first and last dose) effects of Ariflo (post-albuterol) on lung function will be assessed by hourly testing for a period of four hours. To ensure consistency and standardization of pulmonary function data, spirometry equipment, and interpretation will be standardized and centrally monitored.

Symptom based assessments, such as exercise tolerance and breathlessness (modified Borg scale) will also be performed at clinic visits.

The impact of COPD on patient health status will be assessed by the SGRQ at baseline, Week 12 and Week 24 and the SF-36 (health survey questionnaire) at

baseline and Week 24. An Investigator and Patient Global Assessments will be completed at Week 24.

Safety assessments will include adverse events, vital signs, ECGs, and clinical laboratory tests. As a prompt for reporting adverse events at clinic visits, patients will be asked to record in a diary if they feel differently since starting the study medication. 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, diarrhea, 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 standardized clinical and laboratory assessment will be completed, and patients will be followed daily until resolution of the adverse event. Any patient who has a gastrointestinal adverse experience of concern and a positive fecal occult blood test or melena during the randomized treatment phase of the study will be referred to a gastroenterologist for a **complete** colonoscopy that emphasizes visualization of the transverse colon. Biopsies should be taken if appropriate.

Patients who complete Study 156 or who withdraw before the end of Week 24 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:

- Change from baseline in trough pre-bronchodilator FEV_1.
- Change from baseline in total score of the SGRQ.

The **secondary** efficacy variables are listed below:

- Change from baseline in Clinic FVC at trough. FVC provides complementary information to FEV_1 with respect to lung function.
- Time to first COPD exacerbation.
- Time to first level 2 or level 3 COPD exacerbation. These are exacerbations associated with some form of physician contact including ER visits and hospitalization.
- Change from baseline in post-exercise breathlessness (modified Borg Scale).

The **tertiary** efficacy variables are listed below:

- First and last dose effect for FEV_1, FVC, PEFR and FEF_{25-75}.
- Post-bronchodilator effect for FEV_1, FVC, PEFR and FEF_{25-75}.
- Clinic trough PEFR.
- Clinic trough FEF_{25-75}.
- Use of 'as-required' (prn) albuterol recorded in CRF according to the following categories:
  - Much less than usual
  - Less that usual
  - About the same as usual
  - More than usual
  - Much more than usual
- SGRQ subscales (symptoms, activities and impacts).
- Health status assessment: SF-36.
- Health economic endpoints (impact on activities, healthcare utilization).
- Global Patient Assessment.
- Global Investigator Assessment.
- Exercise performance (distance walked) during the exercise tolerance test (6-minute walk with encouragement).
- Overall dyspnea (on a modified Borg scale) during usual activities.
- Exertional (post-exercise) dyspnea (on a modified Borg scale).
- Post-exercise SaO_2.
- SaO_2 at rest in patients with FEV_1 of <40% predicted for age, height and gender.
- Arterial blood gases, PO_2 and PCO_2 in patients with FEV_1 of <40% living at high altitudes or having a resting SaO_2 <88%.
- Cough assessment.
- Sputum assessment.

Safety Parameters

- Adverse Events (additional monitoring for gastrointestinal adverse events).
- Electrocardiogram (ECG) parameters at all double-blind visits.
- Vital signs.
- Laboratory assessments.

Statistical Evaluation

The primary endpoints will be analyzed using a repeated measures model to compare the average change over the 24-week double-blind period. Additional comparisons will be made at each individual timepoint. Continuous secondary and tertiary variables will be analyzed analogously. Exacerbation-free survival at 24 weeks will be estimated using the Kaplan-Meier product limit. Descriptive statistics will be provided for safety parameters.

Pharmacokinetic Parameters

Blood samples for pharmacokinetic analysis of SB-207499 and the metabolite SB-217493 plasma concentration data will be collected from all patients randomized into the study. Patients will be required to provide six samples during the 24-week period of double-blind treatment. At Visit 3 (Week 0) one sample will be drawn 3 hours post-dose. At Visit 5 (Week 4), pre-dose and post-dose (either between 0.5 and 2 hours or between 1.5 and 3 hours) samples will be drawn. At Visit 7 (Week 12), pre-dose and post-dose (either between 3 and 6 hours or between 5 and 10 hours) blood samples will be drawn. At Visit 10 (Week 24), a pre-dose blood sample will be drawn. A sample will also be collected from patients reporting to the clinic for an unscheduled visit triggered by a gastrointestinal adverse event (or a serious adverse event whenever practicable), to compliment the PK/PD analysis.

1 Introduction

Ariflo™ is a potent and selective phosphodiesterase type 4 (PDE4) inhibitor currently under development for the treatment of chronic obstructive pulmonary disease (COPD) and asthma.

COPD is a disorder characterized by reduced maximum expiratory flow and slow forced emptying of the lungs, features which do not change markedly over several months. [1] It is a major cause of morbidity and mortality. Fixed airflow limitation in COPD is due to three conditions: chronic bronchitis, emphysema, and small airways disease, which frequently co-exist in individual patients. [1]

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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]	
Dyspnea	-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.
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Table 2 displays the most common on-therapy adverse events reported in more than 5% of patients in decreasing frequency. Exacerbations of chronic obstructive pulmonary disease were more frequent in patients who received placebo, while diarrhea, nausea, abdominal pain, dyspepsia and vomiting were reported more frequently in patients who received Ariflo. The majority of the events were considered mild or moderate in severity by the Investigators. The gastrointestinal adverse events were reported more frequently in patients who received Ariflo, were generally mild and expected side effects of the known pharmacology of the drug. Most of these gastrointestinal adverse events were self-limited and occurred during the initial period of treatment. Few of the events were considered serious.

Table 2 Overall Incidence of Most Commonly Reported On-therapy Adverse Events in Ariflo Phase 3 Studies

	All Randomized Patients			
	Placebo		Ariflo	
Adverse Event*	**(N = 681)**		**(N = 1368)**	
(Preferred Term)	**N**	**%**	**N**	**%**
Chronic obstructive airways disease	265	38.9	421	30.8
Diarrhea	41	6.0	175	12.8
Nausea	28	4.1	170	12.4
Abdominal pain	39	5.7	155	11.3
Upper respiratory tract infection	51	7.5	111	8.1
Headache	43	6.3	101	7.4
Dyspepsia	17	2.5	83	6.1
Vomiting	7	1.0	76	5.6

* Includes adverse events reported for >5% of patients in either of the treatment groups.

There was no greater incidence of serious adverse events in patients who received 15 mg BID when compared with patients who received placebo. 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. [5]

Study 156 is being conducted as a pivotal Phase 3 study to assess the efficacy and safety of Ariflo versus placebo in patients with COPD. The present study has the goals of detecting a 50 mL treatment difference on FEV_1 and confirming the effects observed in Study 039 on health status. The study design of Study 156 is similar to that of Studies 039, 042, and 091.

2 Objectives

The primary objective of the study is to demonstrate the clinical efficacy of Ariflo (15 mg BID) versus placebo by assessment of forced expiratory volume in 1 second (FEV_1) at trough drug levels and the total score of the St. George's Respiratory Questionnaire (SGRQ) over 24 weeks in patients with COPD.

The secondary objectives of the study are to examine risk of exacerbations and to compare the clinical efficacy of Ariflo versus placebo on additional pulmonary function tests (clinic trough measurements) and other clinical evaluations (e.g. breathlessness).

The additional objective of the study is to further define the clinical safety and tolerability of Ariflo through the assessment of adverse events, vital signs, clinical laboratory tests, and electrocardiograms (ECGs).

3 Study Design Overview

3.1 Study Design

This is a Phase III, randomized, double-blind, placebo-controlled, parallel-group study involving 12 visits over a 29-week period (Week -4 [Screening] through Week 25). Double-blind study medication will be dispensed as tablets of either Ariflo (15 mg) or matched placebo, one tablet will be taken twice daily, immediately after breakfast and after the evening meal. (Previous clinical pharmacology studies have shown that Ariflo is better tolerated when administered in the fed state.)

The study will commence with a 4-week, single-blind, placebo run-in phase, after which the patients will be randomized in a double-blind manner to either Ariflo or matching placebo in a ratio of 1:1 for 24 weeks.

Pulmonary function tests (PFTs) will be performed at all visits (with the exception of one safety-only visit at Week 1). At the screening visit (Week -4), pulmonary function (FEV_1, FVC, forced expiratory flow at 25-75% vital capacity [FEF_{25-75}] and PEFR) will be assessed before and after a standard dose of albuterol (180 mcg). At subsequent visits, pulmonary function will be measured at trough levels of study drug, in the absence of albuterol. In addition, the acute (first and last dose) effects of Ariflo (post-albuterol) on lung function will be assessed by hourly testing for a period of four hours. To ensure consistency and standardization of pulmonary function data, spirometry equipment, and interpretation will be standardized and centrally monitored.

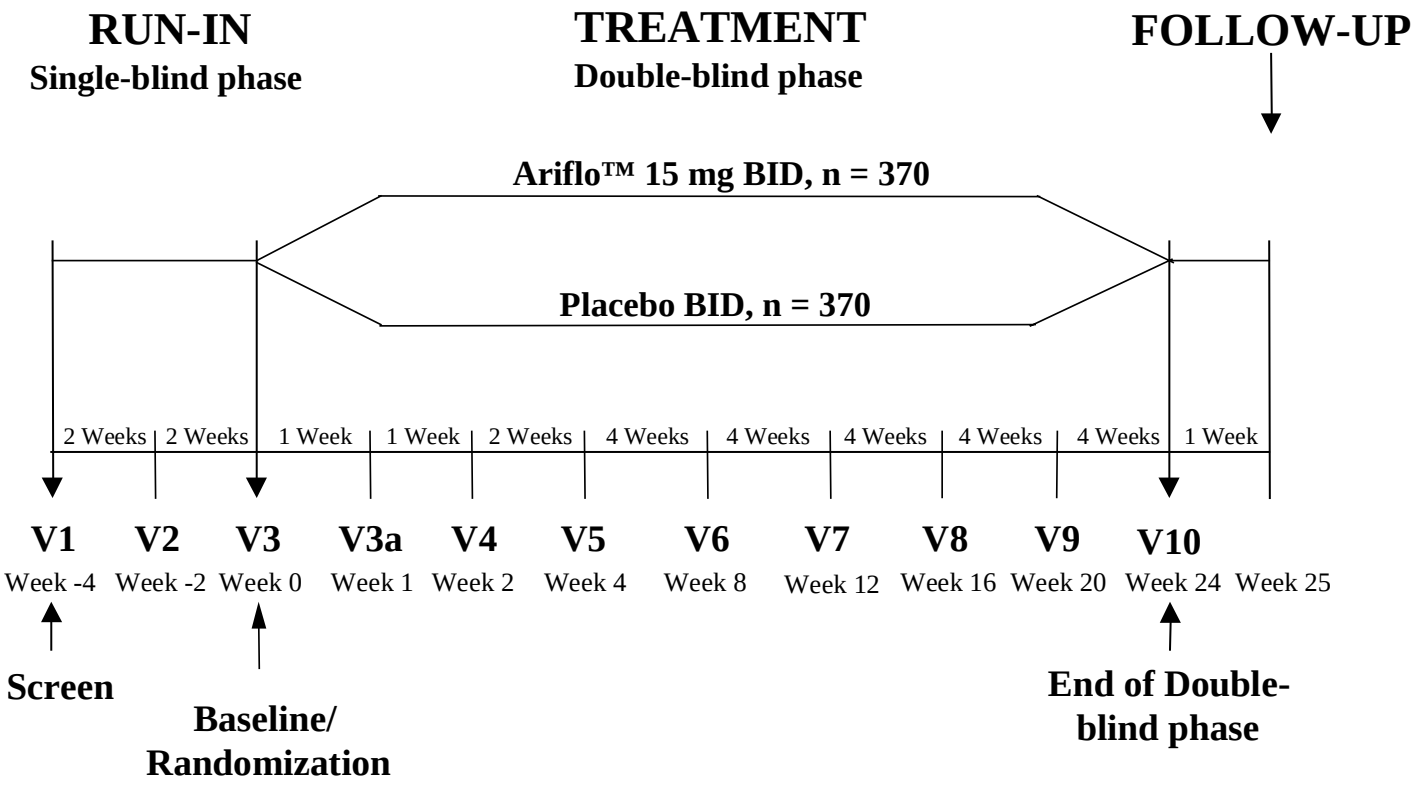
Symptom-based assessments, such as exercise tolerance and breathlessness (modified Borg scale) will also be performed at clinic visits.

The impact of COPD on patient health status will be assessed using the SGRQ at baseline, Week 12 and Week 24 and the SF-36 (health survey questionnaire) at baseline and Week 24. An Investigator and Patient Global Assessment will be completed at Week 24.

Safety assessments will include adverse events, vital signs, ECGs, and clinical laboratory tests. As a prompt for reporting adverse events at clinic visits, patients will be asked to record in a diary if they feel differently since starting the study medication. 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, diarrhea, 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 standardized clinical and laboratory assessment will be completed, and patients will be followed daily until resolution of the adverse event. Any patient who has a gastrointestinal adverse experience of concern and a positive fecal occult blood test or melena during the randomized treatment phase of the study will be referred to a gastroenterologist for a **complete** colonoscopy that emphasizes visualization of the transverse colon with reporting of positive or negative findings, irrespective of other identified pathology or causes for gastrointestinal bleeding. Biopsies should be taken if appropriate

Patients 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), albuterol (on an "as needed" basis) via MDI with or without a spacer (according to the patient's usual practice) and mucolytics are the only COPD medications permitted during the study (i.e., between Visits 1 and 10) with the exception of additional medication allowed for the treatment of exacerbations as outlined below. Combination products (e.g., a combined albuterol 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, inhaled/oral steroids or antibiotics may be administered for a short course (<14 days) for the treatment of an exacerbation of COPD. COPD exacerbations are categorized as Level 1, 2, or 3, based on the treatment received by the patient for the exacerbation (Section 8.1.2). Patients who experience more than three Level 2 or Level 3 exacerbations during the double-blind treatment period may need to be withdrawn after consultation with the SB Medical Monitor. Patients who take any corticosteroids or antibiotics for the treatment of a COPD exacerbation during the run-in phase will be withdrawn from the study prior to randomization (see Sections 6.11.4 and 8.1.2).

At **all** visits, the following restrictions apply: Patients should not have smoked for 2 hours or taken inhaler therapy (i.e., albuterol and/or anticholinergic agent) 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	3a	4	5	6	7	8	9	10		
	Screen		Baseline								End Double-blind	Early Withdrawal[1]	Final Safety Follow-up
Time relative to baseline (weeks)	-4	-2	0	+1	+2	+4	+8	+12	+16	+20	+24		+25
Signed written informed consent	x												
Medical & surgical history	x												
Physical examination[2]	x		x								x	x	x[3]
Pulmonary history & symptoms	x												
Postero-anterior chest radiograph[4]	x												
Exacerbation assessment/resource use	x	x	x	x	x	x	x	x	x	x	x	x	x
Medication history	x												
Overall breathlessness (modified Borg)	x	x	x		x	x	x	x	x	x	x		
Resting 12-lead ECG	x		x	x	x	x	x	x	x	x	x	x	x[3]
Vital signs (BP, HR)	x[5]	x	x[5]	x	x	x	x	x	x	x	x[5]	x[5]	x
Exercise Tolerance (6-Minute walk)	x	x	x			x	x	x	x	x	x	x	
Post-exercise SaO2 & breathlessness	x	x	x			x	x	x	x	x	x	x	
CO Diffusing Capacity (DLCO)[6]	x												
Albuterol reversibility[7]	x												
Laboratory tests	x		x[8]	x	x	x	x	x	x[9]	x[9]	x[8]	x[8]	x[3,9]
Dispense single-blind medication	x	x											
Albuterol Use		x	x	x	x	x	x	x	x	x	x		
Concomitant medication/medical procedures		x	x	x	x	x	x	x	x	x	x	x	x
PFTs (in absence of albuterol)[10]		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	
Baseline signs and symptoms/AEs[11]		x	x	x	x	x	x	x	x	x	x	x	x
Health status assessment: SGRQ			x					x			x	x	
Quality of life assessment: SF-36			x								x	x	
Cough and sputum assessments			x					x			x	x	
Pharmacokinetic evaluations[12]			x			x		x			x		
Arterial blood gas/SaO2[13]			x								x		
Hourly PFTs for 4 hrs post first/last dose [14]			x								x		
Dispense double-blind medication			x	x	x	x	x	x	x	x			
Investigator/Patient global assessment											x	x	
Study conclusion record												x	x

1 Patients who stop taking study medication between clinic visits will attend the clinic within 24 hours for an early withdrawal visit.

2 To include a respiratory examination.

3 If abnormalities at previous visit for patients who complete Visit 10 or withdraw from the study.

4 Postero-anterior chest X-ray must be performed at Visit 1 unless the film from a chest X-ray within the 12 weeks prior to Visit 1 is available to the Investigator.

5 Including Orthostatic vital signs.

6 DLCO should be done between Visit 1 and Visit 3 if not performed during the previous 24 weeks or if the results are unavailable.

7 Before and 15 to 30 (± 5) minutes after administration of 180 mcg albuterol via a MDI with a spacer to determine % predicted FEV_1, FVC, FEF_{25-75}, PEFR, and FEV_1: FVC.

8 In addition to usual laboratory tests, three fecal occult blood tests will be performed between Visits 1 and 3, between Visits 9 and 10, and at early withdrawal; amylase will be measured at Visit 3.

9 Urinary beta-HCG tests will be performed in females of childbearing potential. No other laboratory samples will be collected at Visits 8 and 9.

10 Includes FEV_1, FVC, FEF_{25-75}, PEFR, and FEV_1:FVC measured by centralized spirometry by the same person at each visit.

11 A diary will be used to record if patients feel different since starting study medication.

3.3 Method of Randomization

Patients will be randomized in a 1:1 ratio to receive either Ariflo 15 mg BID or placebo. The randomization code will be generated by the SB Biometrics Unit.

4 Study Population

4.1 Number of Patients/Centers

Up to 830 patients will be randomized to achieve 550 patients to satisfactorily complete the study. Approximately 140 centers in North America (United States and Canada) are expected to participate, with each center aiming to enroll between 6 and 24 patients.

A log of all patients considered for the study, and, if applicable, a reason for their exclusion will be maintained. In addition, an ongoing enrollment and visit tracking log for each patient will be updated by the sites on a weekly basis.

4.2 Inclusion Criteria

Only patients who fulfill **all** the following entry criteria will be eligible for inclusion in the study.

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. Patients with a clinical diagnosis of COPD, as defined by American Thoracic Society Guidelines (see Appendix G). [3]

3. Patients with a cigarette smoking history of ≥10 pack years (1 pack year = 20 cigarettes smoked per day for 1 year or the equivalent). Both current smokers and ex-smokers are eligible.

4. Patients with a pre-albuterol FEV_1 to FVC ratio (FEV_1:FVC) ≤0.7 at Visit 1 (Screening).

5. Patients with fixed airway obstruction, defined by ≤15% **or** ≤200 ml (or both) increase in FEV_1 after the administration of albuterol 180 mcg via MDI with a spacer at Visit 1 (Screening).

6. Patients with a post-albuterol FEV_1 between ≥30% and ≤70% of predicted normal for height, age and gender at Visit 1. Patients will be assessed 15 to 30 (± 5) minutes after receiving albuterol 180 mcg via MDI with a spacer.

7. Patients who give their signed written informed consent to participate.

4.3 Exclusion Criteria

Patients who fulfill **any** of the following criteria **will not be** eligible for the study.

1. Women who are pregnant or lactating.

2. Patients with asthma as the main component of their obstructive airways disease.

3. Patients with poorly controlled COPD, defined as the occurrence of any of the following in the 2 weeks prior to Visit 1: acute worsening of COPD that is managed by the patient at home by self-treatment with corticosteroids or antibiotics, that requires treatment prescribed by a physician, or for which the patient is hospitalized.

4. Patients with active tuberculosis, lung cancer, or clinically overt bronchiectasis.

5. Patients with clinically significant cardiovascular, neurological, renal, endocrine, or hematological abnormalities that are uncontrolled on permitted therapy.

6. Patients with clinically significant gastrointestinal or hepatic abnormalities.

7. Patients with a positive fecal occult blood test result between Visits 1 and 3.

8. Patients with clinically significant orthostatic changes in blood pressure or heart rate at Visit 1 or 3 (Section 5.4.2).

9. Patients with a history of hypersensitivity to PDE4 inhibitors.

10. Patients with a history (or suspected history) of alcohol misuse or any other recreational substance abuse.

11. Patients who require treatment with inhaled cromolyn sodium or nedocromil, inhaled long-acting beta$_2$-agonists, oral beta$_2$-agonists, nebulized beta$_2$-agonists, nebulized anticholinergics, xanthines, leukotriene modifiers or oral/inhaled corticosteroids beyond Visit 1. **All COPD medications except anticholinergic medication or albuterol via MDI should be withdrawn prior to or at Visit 1 (Screening) (**Section 6.11.3**).**

12. Patients receiving treatment with long term oxygen therapy (LTOT), patients who require supplemental oxygen more often than on an occasional (prn) basis, or patients who require nocturnal positive pressure for sleep apnea.

13. Patients who have participated in a Pulmonary Rehabilitation Program within 4 weeks prior to Visit 1 (Screening) or who will enter a Pulmonary Rehabilitation Program during the study.

14. Patients 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).

15. Patients who have previously participated in an Ariflo (SB 207499) study and who received randomized study medication.

16. Patients unable to comply with study procedures (including completion of the health status questionnaires).

5 Conduct of the Study

5.1 Ethical and Regulatory Considerations

The study will be conducted according to Good Clinical Practice, the World Medical Association Declaration of Helsinki (Appendix A), and the US 21 CFR Part 50 - Protection of Human Subjects, and Part 56 - Institutional Review Boards.

5.1.1 Ethics Review Committee (ERC)/Institutional Review Board (IRB)

Ethics Review Committees (ERCs)/Institutional Review Boards (IRBs) must be constituted according to US 21 CFR part 56 and the local laws/customs of each participating country.

This protocol will be submitted to an appropriate ERC or IRB and its written unconditional approval obtained and submitted to the sponsor before commencement of the study. SmithKline Beecham (SB) will supply relevant data for the Investigator to submit to the ERC/IRB for the protocol's review and approval. Verification of the ERC/IRB's unconditional approval of the protocol, the written informed consent statement and the written information to be given to the patients will be transmitted to the SB Study Monitor prior to shipment of drug supplies and Case Report Forms (CRFs) to the site. This approval must refer to the study by exact protocol title and number, identify the documents reviewed, and state the date of review.

The ERC/IRB must be informed by the Investigator of all subsequent protocol amendments and of serious or unexpected adverse events 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 SB 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.

Informed consent will be obtained in accordance with US 21 CRF 50.25. Written informed consent for the study must be obtained before protocol-specific procedures are carried out.

Information should be given in both oral and written form whenever possible and deemed appropriate by the ERC/IRB. Patients, their relatives, guardians or, if necessary, legal representatives must be given ample opportunity to inquire about details of the study.

The consent form generated by the Investigator with the assistance of SB, must be approved (along with the protocol) by the ERC/IRB and be acceptable to SB. Consent forms must be in a language fully comprehensible to the prospective patient. Where appropriate, informed consent shall be documented by the use of a

written consent form approved by the ERC/IRB and signed by the patient or the patient's legally authorized 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 patient or the patient's legally authorized representative, but, in any event, the Investigator shall give either the patient or the representative adequate opportunity to read it before it is signed.

Consent must be documented either by the dated signature of the patient or the patient's legally authorized representative. The signature confirms that the consent is based on information that has been understood. Each patient's signed informed consent form must be kept on file by the Investigator for possible inspection by Regulatory Authorities and/or SB professional and Regulatory Compliance 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 albuterol or anticholinergic medication during the 4-hour period preceding each visit. Patients who smoke must not smoke 2 hours prior to each visit.

For each scheduled study visit, patients will be required to attend the clinic in the morning, at the same time and after breakfast. Clinic visits should be scheduled at 10:00 a.m. ± 2 hours. Smoking and the use of albuterol or anticholinergic treatment must be avoided during the clinic stay if at all possible. Patients must **not** take their morning doses of study medication before attending morning clinic visits.

In exceptional circumstances, a patient may be allowed afternoon appointments at Visit 1 or for Visits 2, 3, 3a, 4, 6, 8, 9, and 10 only if ≥**8 hours have elapsed** since the last dose of study medication and the Investigator is capable of completing all visit assessments. This will ensure that trough measurements are obtained. For example, if the morning dose of study medication is taken after breakfast at 8:00 a.m., the patient's appointment may be scheduled after 4:00 p.m. the same day. If an afternoon visit is scheduled, patients will be instructed to take the morning dose of study medication after breakfast, which must be at least

8 hours before their clinic visit. If the baseline visit (Visit 3) is done in the afternoon, all subsequent visits should be done at this time, with the exception of Visits 5 and 7. Because of post-dose pharmacokinetic assessments, only morning assessments will be performed for Visits 5 and 7.

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 beta$_2$-agonist and anticholinergic medication for at least 4 hours prior to the visit and refrain 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.**

The following procedures will be conducted at Visit 1:

- Written informed consent will be obtained.
- A full medical and surgical history (including alcohol consumption) and physical examination (including respiratory examination), will be performed (Section 5.4.1 and Section 5.4.2). Cigarette smoking history and current smoking status will be documented. As per usual care, patients should be offered normal advice to stop smoking. (Note: Current smokers may participate in the study.)
- Pulmonary history and symptoms will be documented (Section 5.4.1).
- A current postero-anterior (PA) chest radiograph (performed within the 12 weeks prior to assessment) will be reviewed by the Investigator. If such a **film** is not available for review by the Investigator, a new film should be obtained. Review of written reports without the accompanying films is not acceptable (Section 5.4.4).
- An assessment of COPD exacerbations will be made. If the patient has experienced a Level 2 or Level 3 exacerbation of COPD during the two weeks prior to Visit 1, he is not eligible to participate in the study. Additionally, patients experiencing any level exacerbation who self medicate with

corticosteroids or antibiotics during the two weeks prior to Visit 1 are not eligible to participate (Section 8.1.2).

- All medication for COPD, including inhalers, taken during the 3 months preceding this visit will be recorded, together with all other medications taken within 2 weeks of the visit. Prohibited respiratory medications should be discontinued (Section 6.11.3).

- Overall breathlessness will be assessed using the modified Borg scale (Section 5.4.6).

Greater than 4 hours after the patient's last albuterol administration:

- A 12-lead electrocardiogram will be performed after the patient has been semisupine for 5 minutes (Section 5.4.5).

- Blood pressure and heart rate will be measured after the patient has been sitting for 5 minutes. Orthostatic changes in heart rate and blood pressure will be measured after 5 minutes in a supine position followed by sitting with legs dependent for 1 minute. 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 ≥10 beats/minute, he is not eligible to participate in the study (Section 5.4.2).

- An exercise tolerance test (6-minute walk) will be completed (Section 5.4.10).

- Breathlessness using the modified Borg scale, SaO_2 and heart rate will be assessed immediately after the exercise tolerance test (Section 5.4.6 and Section 5.4.12).

- Carbon monoxide diffusing capacity (DLCO) will be determined, if not assessed within the 24 weeks preceding Visit 1. DLCO may also be scheduled between Visits 1 and 3 (Section 5.4.14).

- Pulmonary function tests will be performed both before and 15 to 30 minutes after administration of albuterol. Albuterol reversibility will also be calculated. At least 10 minutes should elapse between the exercise tolerance test and pulmonary function testing so that the patient is fully rested (Section 5.4.7).

Following completion of the above procedures, a checklist of the inclusion and exclusion criteria will be completed. If the patient is eligible to enter the study the following should be performed:

- Blood and urine samples will be taken for routine hematology, biochemistry, (including beta-HCG for women of childbearing potential) and urinalysis (Section 5.4.8).

- Issue a 20-day supply (2 bottles) of single-blind study medication (Section 6), an albuterol MDI for 'as-needed' use and a spacer. The first morning dose of study medication should be taken in the clinic with food. Patients will be instructed to take one tablet in the morning immediately after breakfast and a second tablet immediately after the evening meal.

- Issue the diary card which will be used by the patient to record if they feel differently since starting the study (Section 5.4.11).

- Review the procedure for reporting gastrointestinal adverse events with the patient (Section 8.1.3).

- Issue a fecal occult blood kit and instruct the patient to follow the instructions on the kit (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 morning dose of study medication at home on the day of their next clinic visit if a morning appointment is scheduled.

- to refrain from using albuterol or anticholinergic medication during the 4 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 albuterol inhaler and spacer, and the diary card with them to Visit 2.

- to continue taking anticholinergic medication, if prescribed, at a constant dose.

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 albuterol or anticholinergic medication during the 4 hours immediately preceding the visit or smoked during the 2 hours immediately preceding the visit.

- Any changes or additions to the patient's concomitant medication will be recorded in the CRF (Section 6.11.5). Any changes in smoking status will also be documented (Section 5.4.1).

- Determine if the patient has entered a Pulmonary Rehabilitation Program since the last visit.

- Compliance in taking study medication will be determined (Section 6.8).

- Record the use of "as-required" (prn) albuterol in the CRF (Section 5.4.3).

- The diary card will be collected and reviewed. Any adverse events which have occurred will be recorded in the CRF on the Baseline Signs and Symptoms page and followed up, as appropriate (Section 8).

- A COPD exacerbation assessment will be made to determine if the patient has experienced any exacerbations during the period between Visits 1 and 2. Patients who take any corticosteroids or antibiotics for the treatment of a COPD exacerbation during the run-in phase will not be randomized 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.

- Overall breathlessness will be assessed using the modified Borg scale (Section 5.4.6).

Greater than 4 hours after the patient's last albuterol administration:

- Blood pressure and heart rate will be measured after the patient has been sitting for 5 minutes (Section 5.4.2).

- An exercise tolerance test (6-minute walk test) will be completed (Section 5.4.10).

- Breathlessness using the modified Borg scale, SaO_2 and heart rate will be assessed immediately after the exercise tolerance test (Section 5.4.6 and Section 5.4.12).

- Pulmonary function tests will performed in the absence of albuterol and before the administration of the next dose of study medication in the clinic. At least 10 minutes should elapse between the exercise tolerance test and pulmonary function testing so that the patient is fully rested (Section 5.4.7).

- All patients must demonstrate stability in clinic trough FEV_1 (i.e., the absolute value in the absence of albuterol must not have increased or decreased by >20% between Visits 1 and 2). Patients who fail this criterion must be withdrawn from the study (Section 9.2).

- Issue a 20-day supply (2 bottles) of single-blind study medication (Section 6). The next morning dose of study medication should be taken in the clinic with food. Patients will be reminded to take one tablet in the morning immediately after breakfast and a second tablet immediately after the evening meal.

- Issue a new diary card. The patient should be reminded to use the card to record if they feel differently since starting the study.

- Review the procedure for reporting gastrointestinal adverse 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 morning dose of study medication at home on the day of their next clinic visit.

- to refrain from using albuterol 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 albuterol inhaler and spacer, and the diary card with them to Visit 3.

- to continue taking their anticholinergic medication, if prescribed, at a constant dose.

5.3.3 Visit 3 (Week 0): Baseline, Start of Double-blind Treatment Phase

The following assessments will be made **BEFORE the first dose of double-blind study medication is administered in the clinic**.

- Document if the patient has taken albuterol or used anticholinergic medication during the 4 hours immediately preceding the visit or smoked during the 2 hours immediately preceding the visit.

- Two health status questionnaires (SF-36 and SGRQ) will be completed before all other assessments (Section 7.3, Appendix E and Appendix F). Patients unable or unwilling to complete the SGRQ questionnaire must be withdrawn from the study.

- Any changes or additions to the patient's concomitant medication will be recorded in the CRF (Section 6.11.5). Any changes in smoking status will also be documented (Section 5.4.1).

- Determine if the patient has entered a Pulmonary Rehabilitation Program since the last visit.

- Compliance in taking study medication since the previous visit will be determined (Section 6.8).

- Record the use of "as-required" (prn) albuterol in the CRF (Section 5.4.3).

- A physical examination, including a respiratory examination, will be performed (Section 5.4.2).

- The diary card will be collected. Any adverse events which have occurred since the last visit will be recorded on the Baseline Signs and Symptoms page of the CRF and followed up, as appropriate (Section 8).

- A COPD exacerbation assessment will be made to determine if the patient has experienced any exacerbations during the period between Visits 2 and 3. Patients who take any corticosteroids or antibiotics for the treatment of a COPD exacerbation during the run-in phase will not be randomized 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.

- Health economic factors will be assessed (Section 7.1 and Section 7.2).

- Overall breathlessness will be assessed using the modified Borg scale (Section 5.4.6).

- Cough and sputum production will be assessed (Section 5.4.16).

Greater than 4 hours after the patient's last albuterol administration:

- A 12-lead electrocardiogram will be performed after the patient has been semisupine for 5 minutes (Section 5.4.5).

- Heart rate and blood pressure will be measured after 5 minutes in a sitting position. Orthostatic changes in heart rate and blood pressure will be measured after 5 minutes in a supine position followed by sitting with legs dependent for 1 minute. 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 10 beats/minute) will not be randomized 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.

- An exercise tolerance test (6-minute walk) will be completed (Section 5.4.10).

- Breathlessness using the modified Borg scale, SaO_2 and heart rate will be assessed immediately after the exercise tolerance test (Section 5.4.6 and Section 5.4.12).

- Patients will perform a baseline pulmonary function test in the absence of albuterol and before taking the first dose of double-blind study medication. At least 10 minutes should elapse between the exercise tolerance test and pulmonary function testing so that the patient is fully rested (Section 5.4.7).

Randomization Criteria

Patients will only be randomized if the following criteria are met:

1. Stability in Pulmonary Function: Clinic trough FEV_1 (absolute value) in the absence of albuterol has not changed (i.e., increased or decreased) by >20% between Visits 1 and 3.

2. Medication Compliance: Patients must demonstrate ≥80% and ≤120% compliance since the previous visit in taking single-blind study medication (Section 6.8).

Patients who do not meet the randomization criteria must be withdrawn from the study.

If the patient meets the above Randomization Criteria, the following assessments will be made:

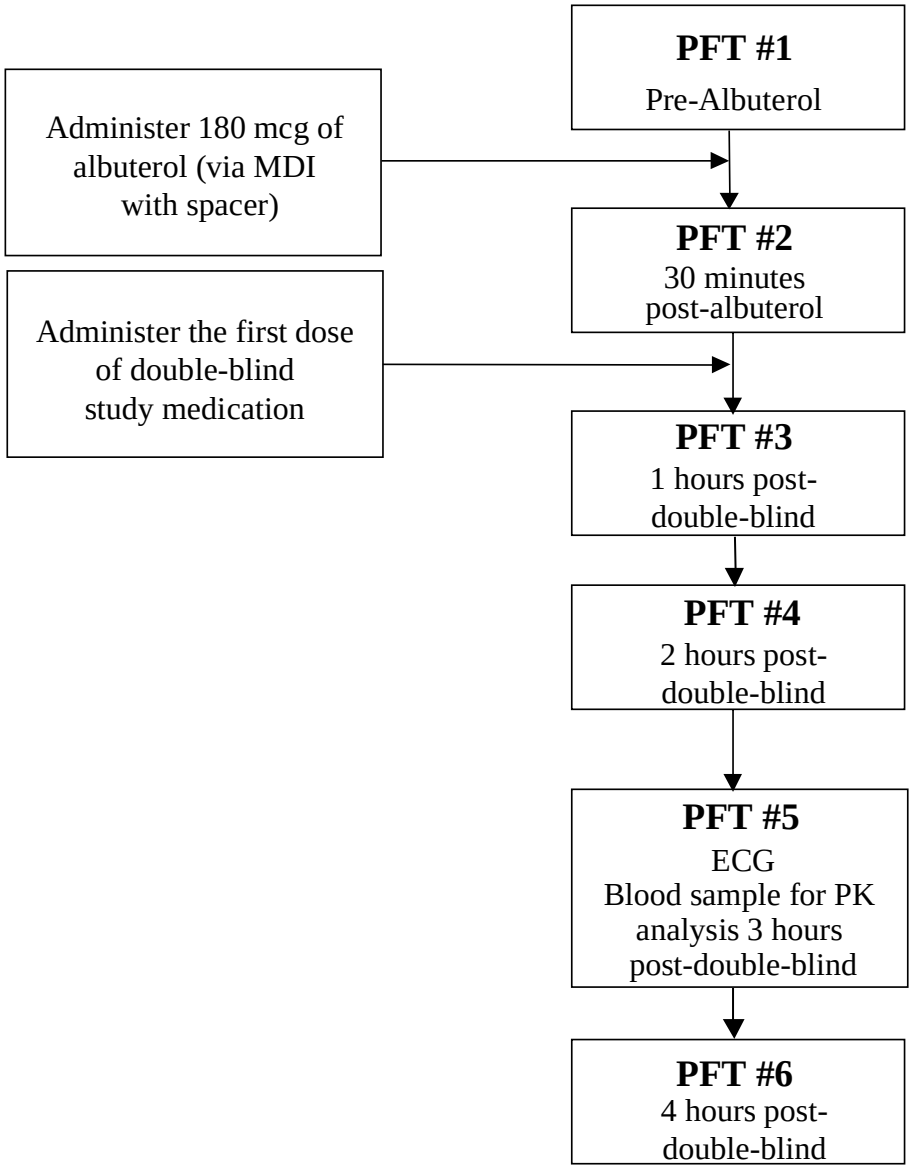
- Blood and urine samples will be obtained for routine hematology, biochemistry, (including beta-HCG for women of childbearing potential) and urinalysis (Section 5.4.8).

- Resting SaO_2 will be measured by pulse oximetry in severe patients (i.e., FEV_1 <40% of predicted at Visit 1). If SaO_2 <88% or if the patient lives at high altitude, arterial blood gases must be measured (Section 5.4.12 and 5.4.13).

Following completion of the above procedures, patients will be assigned the next available randomization number. Patients will also be assigned to the 'Early' or 'Late' pharmacokinetic sampling group (Section 5.4.9).

The patient will be given albuterol (180 mcg via MDI with spacer). Pulmonary function tests will be performed 30 (±5) minutes later. The first dose of double-blind study medication will then be taken in the clinic with food and the time of administration will be recorded in the CRF. The patient will remain in the clinic for the next 4 hours, during which the patient will be observed and will undergo post-dose pulmonary function testing every hour (Section 5.4.7). Refer to Figure 2.

Figure 2 Order of Pulmonary Function Tests at Visit 3



During the 4.5-hour observation period in the clinic, patients will be requested to avoid using additional albuterol or anticholinergic inhalers and to refrain from smoking if at all possible. If a patient uses albuterol or anticholinergic inhalers during the 4.5-hour post-dose period, all remaining pulmonary function tests should be abandoned.

If a patient withdraws during the observation period, they are to return in 7 (± 3) days for a Safety Follow-up visit (Section 5.3.13).

- Any adverse events which occur during the observation period will be recorded in the CRF and followed up as appropriate (Section 8).

- Prior to PFT #5 (3 hours post-dose), a 12-lead ECG will be performed after the patient has been supine for 5 minutes (Section 5.4.5), and a blood sample will be collected for pharmacokinetic analysis (Section 5.4.9).

After pulmonary function testing is complete:

- Issue a new diary card to the patient. The patient should be reminded to use the card to record if they feel differently since starting the study.

- Review the procedure for reporting gastrointestinal adverse events with the patient.

- Issue the patient a fecal occult blood kit to be used if the patient reports a gastrointestinal adverse event of concern (Section 8.1.3).

- Issue a 10-day supply (1 bottle) of double-blind study medication.

- The patient will be issued a new albuterol inhaler.

Visits 3a and 4 will be scheduled. Visit 4 will be scheduled at the same time of day in 14 (± 3) days. The patients will be instructed to return to the clinic in 7 (± 2) days for the safety visit, Visit 3a. Patients will also be reminded:

- to take the evening dose immediately after the evening meal.

- **not** to take the morning dose of study medication at home on the morning of the next clinic visit if a morning appointment is scheduled.

- to refrain from using albuterol 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 albuterol inhaler and spacer, and diary card with them to Visit 3a.

- to continue taking anticholinergic medication, if prescribed, at a constant dose.

Note: If results of any assessment made at Visit 3 are not available at the time of randomization and subsequently preclude continuation in the study, the patient must be withdrawn immediately and a Safety Follow-up Visit scheduled (Section 5.3.13).

5.3.4 Visit 3a (End of Week 1): Double-blind Treatment Phase

At this visit, the following procedures will be completed:

- Document if the patient has taken albuterol or anticholinergic medication during the 4 hours immediately preceding the visit or smoked during the 2 hours immediately preceding the visit.
- Compliance in taking study medication will be determined (Section 6.8). The Investigator will emphasize the importance of compliance to patients with compliance <80% or >120%.
- Record the use of "as-required" (prn) albuterol in the CRF (Section 5.4.3).
- Any changes or additions to the patient's concomitant medication will be recorded in the CRF (Section 6.11.5). Any changes in smoking status will also be documented (Section 5.4.1).
- Determine if the patient has entered a Pulmonary Rehabilitation Program since the last visit.
- The diary card will be collected. Any adverse events which have occurred will be recorded in the CRF and followed-up as necessary (Section 8).
- A COPD exacerbation assessment will be made to determine if the patient has experienced any exacerbations since the last visit (Section 8.1.2).
- Health economic factors will be assessed (Section 7.1 and Section 7.2).
- Blood and urine samples will be obtained for routine hematology, biochemistry and urinalysis (Section 5.4.8).

Greater than 4 hours after the patient's last albuterol administration:

- A 12-lead electrocardiogram will be performed after the patient has been semisupine for 5 minutes (Section 5.4.5).

- Blood pressure and heart rate will be measured after 5 minutes in a sitting position (Section 5.4.2).

Patients who withdraw from the study during the visit should complete all scheduled visit assessments along with pulmonary function tests, exercise tolerance tests, the SGRQ and SF-36 questionnaires, Investigator and Patient Global Assessment, a physical examination, assessments of cough and sputum production, orthostatic changes in blood pressure and heart rate and fecal occult blood (Section 5.3.12).

For patients continuing in the study:

- Issue a 10-day supply (1 bottle) of double-blind study medication. The next dose of study medication will be administered in the clinic with food.

- Issue a new diary card. The patient should be reminded to use the card to record if they feel differently since starting the study.

- Review reporting requirements for gastrointestinal symptoms (Section 8.1.3).

- Issue the patient a fecal occult blood kit to be used if the patient reports a gastrointestinal adverse event of concern and they have used the test kit previously provided (Section 8.1.3).

Patients will be instructed to return to the clinic for the previously scheduled Visit 4. Patients will also be reminded:

- to take the evening dose immediately after the evening meal.

- **not** to take the morning dose of study medication at home on the morning of the next clinic visit if a morning appointment is scheduled.

- to refrain from using albuterol 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 albuterol inhaler and spacer, and the diary card with them to Visit 4.

- to continue taking anticholinergic medication, if prescribed, at a constant dose.

5.3.5 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 albuterol or used anticholinergic medication during the 4 hours immediately preceding the visit or smoked during the 2 hours immediately preceding the visit.
- Compliance in taking study medication will be determined (Section 6.8). Patients who show <80% or >120% compliance in taking study medication on two consecutive visits may be withdrawn from the study after consultation with the SB Medical Monitor.
- Record the use of "as-required" (prn) albuterol in the CRF (Section 5.4.3).
- Any changes or additions to the patient's concomitant medication will be recorded in the CRF (Section 6.11.5). Any changes in smoking status will also be documented (Section 5.4.1).
- Determine if the patient has entered a Pulmonary Rehabilitation Program since the last visit.
- The diary card will be collected. Any adverse events which have occurred will be recorded in the CRF and followed-up as necessary (Section 8).
- A COPD exacerbation assessment will be made to determine if the patient has experienced any exacerbations since the last visit (Section 8.1.2).
- Health economic factors will be assessed (Section 7.1 and Section 7.2).
- Overall breathlessness will be assessed using the modified Borg scale (Section 5.4.6).
- Blood and urine samples will be obtained for routine hematology, biochemistry and urinalysis (Section 5.4.8).

Greater than 4 hours after the patient's last albuterol administration:

- A 12-lead electrocardiogram will be performed after the patient has been semisupine for 5 minutes (Section 5.4.5).
- Blood pressure and heart rate will be measured after 5 minutes in a sitting position (Section 5.4.2).

- Pulmonary function tests will be performed in the absence of albuterol and before administration of the next dose of study medication in the clinic (Section 5.4.7).

Patients who withdraw from the study during the visit should complete all scheduled visit assessments, the SGRQ and SF-36 questionnaires, Investigator and Patient Global Assessment, a physical examination, assessments of cough and sputum production, orthostatic changes in blood pressure and heart rate and fecal occult blood (Section 5.3.12).

For patients who are continuing in the study:

- Issue a 20-day supply (2 bottles of 20 tablets each) of double-blind study medication. The next morning dose of study medication will be administered in the clinic with food.

- A new diary card will be issued. The patient should be reminded to use the card to record if they feel differently since starting the study.

- Review the procedure for reporting gastrointestinal adverse events with the patient.

- Issue the patient a fecal occult blood kit to be used if the patient reports a gastrointestinal adverse event of concern and they have used the test kit previously provided (Section 8.1.3).

Patients will be asked to return to the clinic in the morning in 14 (± 3) days for Visit 5. They will also be reminded:

- to take the next dose immediately after the evening meal.

- **not** to take the morning dose of study medication at home on the day of their next clinic visit.

- to refrain from using albuterol 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 albuterol inhaler and spacer, and the diary card with them to Visit 5.

- to continue taking anticholinergic medication, if prescribed, at a constant dose.

- that they will have 2 blood samples drawn for the pharmacokinetic analysis at the next visit: one sample when they arrive in the clinic and the other 0.5 to 3 hours after the morning dose of study medication (Section 5.4.9).

5.3.6 Visit 5 (End of Week 4): Double-blind Treatment Phase

At this visit, the following assessments will be performed:

- Document if the patient has taken albuterol or used anticholinergic medication during the 4 hours immediately preceding the visit or smoked during the 2 hours immediately preceding the visit.

- Compliance in taking study medication will be determined (Section 6.8). Patients who show <80% or >120% compliance in taking study medication on two consecutive visits may be withdrawn from the study after consultation with the SB Medical Monitor.

- Record the use of "as-required" (prn) albuterol in the CRF (Section 5.4.3).

- Any changes or additions to the patient's concomitant medication will be recorded in the CRF (Section 6.11.5). Any changes in smoking status will also be documented (Section 5.4.1).

- Determine if the patient has entered a Pulmonary Rehabilitation Program since the last visit.

- The diary card will be collected. Any adverse events which have occurred will be recorded in the CRF and followed-up as necessary (Section 8).

- A COPD exacerbation assessment will be made to determine if the patient has experienced any exacerbations since the last visit (Section 8.1.2).

- Health economic factors will be assessed (Section 7.1 and Section 7.2).

- Overall breathlessness will be assessed using the modified Borg scale (Section 5.4.6).

- Blood and urine samples will be obtained for routine hematology, biochemistry (including beta-HCG for women of childbearing potential) and urinalysis (Section 5.4.8).

Greater than 4 hours after the patient's last albuterol administration:

- A 12-lead electrocardiogram will be performed after the patient has been semisupine for 5 minutes (Section 5.4.5).
- Blood pressure and heart rate will be measured after 5 minutes in a sitting position (Section 5.4.2).
- An exercise tolerance test (6-minute walk) will be completed (Section 5.4.10).
- Breathlessness using the modified Borg scale, SaO_2 and heart rate will be assessed immediately after the exercise tolerance test (Section 5.4.6 and Section 5.4.12).
- Pulmonary function tests will be performed in the absence of albuterol and before administration of the next dose of study medication in the clinic. At least 10 minutes should elapse between the exercise tolerance test and pulmonary function testing so that the patient is fully rested (Section 5.4.7).
- Pre-dose blood samples for pharmacokinetic analysis will be collected (Section 5.4.9).

Patients who withdraw from the study during the visit should complete all scheduled visit assessments (with the exception of post-dose PK), the SGRQ and SF-36 questionnaires, Investigator and Patient Global Assessment, a physical examination, assessments of cough and sputum production, orthostatic changes in blood pressure and heart rate and fecal occult blood (Section 5.3.12).

For patients who are continuing in the study:

- Issue 1 bottle of the 35-day supply (70 tablets) of study medication. The next morning dose of study medication will be administered in the clinic with food.
- Post-dose blood samples for pharmacokinetic analysis will be drawn (Section 5.4.9).
- An albuterol inhaler for 'as-needed' use will be issued.
- New diary cards will be issued. The patient should be reminded to use the card to record if they feel differently since starting the study.
- Review the procedure for reporting gastrointestinal adverse events with the patient.

- Issue the patient a fecal occult blood kit to be used if the patient reports a gastrointestinal adverse event of concern and they have used the test kit previously provided (Section 8.1.3).

Patients will be asked to return to the clinic at the same time of day in 28 (± 6) days for Visit 6. They will also be reminded:

- to take the next dose immediately after the evening meal.
- **not** to take the morning dose of study medication at home on the day of their next clinic visit if a morning appointment is scheduled.
- to refrain from using albuterol 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 with them any remaining study medication tablets, all study medication containers, the albuterol inhaler and spacer, and the diary cards.
- to continue taking anticholinergic medication, if prescribed, at a constant dose.

5.3.7 Visit 6 (End of Week 8): Double-blind Treatment Phase

The following procedures will be performed at this visit:

- Document if the patient has taken albuterol or used anticholinergic medication during the 4 hours immediately preceding the visit or smoked during the 2 hours immediately preceding the visit.
- Compliance in taking study medication will be determined (Section 6.8). Patients who show <80% or >120% compliance in taking study medication on two consecutive visits may be withdrawn from the study after consultation with the SB Medical Monitor.
- Record the use of "as-required" (prn) albuterol in the CRF (Section 5.4.3).
- Any changes or additions to the patient's concomitant medication will be recorded in the CRF (Section 6.11.5). Any changes in smoking status will also be documented (Section 5.4.1).

- Determine if the patient has entered a Pulmonary Rehabilitation Program since the last visit.

- Diary cards will be collected. Any adverse events which have occurred since the last visit will be recorded in the CRF and followed-up as necessary (Section 8).

- A COPD exacerbation assessment will be made to determine if the patient has experienced any exacerbations since the last visit (Section 8.1.2).

- Health economic factors will be assessed (Section 7.1 and Section 7.2).

- Overall breathlessness will be assessed using the modified Borg scale (Section 5.4.6).

- Blood and urine samples will be obtained for routine hematology, biochemistry (including beta-HCG for women of childbearing potential) and urinalysis (Section 5.4.8).

Greater than 4 hours after the patient's last albuterol administration:

- A 12-lead electrocardiogram will be performed after the patient has been semisupine for 5 minutes (Section 5.4.5).

- Blood pressure and heart rate will be measured after 5 minutes in a sitting position (Section 5.4.2).

- An exercise tolerance test (6-minute walk) will be completed (Section 5.4.10).

- Breathlessness using the modified Borg scale, SaO_2 and heart rate will be assessed immediately after the exercise tolerance test (Section 5.4.6 and Section 5.4.12).

- Pulmonary function tests will be performed in the absence of albuterol and before the next dose of study medication administered in the clinic. At least 10 minutes should elapse between the exercise tolerance test and pulmonary function testing so that the patient is fully rested (Section 5.4.7).

Patients who withdraw from the study during the visit should complete all scheduled visit assessments, the SGRQ and SF-36 questionnaires, Investigator and Patient Global Assessment, a physical examination, assessments of cough and sputum production, orthostatic changes in blood pressure and heart rate and fecal occult blood (Section 5.3.12).

For patients who are continuing in the study:

- Issue 1 bottle of the 35-day supply (70 tablets) of double-blind medication. Administer the next morning dose of study medication in the clinic with food.
- Give a new albuterol inhaler for 'as-needed' use to the patient.
- New diary cards will be issued. Patients should be reminded to use the card to record if they feel differently since starting the study.
- Review the procedure for reporting gastrointestinal adverse events with the patient.
- Issued the patient a fecal occult blood kit to be used if the patient reports a gastrointestinal adverse event of concern and they have used the test kit previously provided (Section 8.1.3).

Patients will be asked to return to the clinic in the morning in 28 (± 6) days for Visit 7. They will also be reminded:

- to take the first evening dose immediately after their evening meal.
- **not** to take their morning dose of study medication at home on the day of the next clinic visit.
- to refrain from using albuterol 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 albuterol inhaler and spacer, and the diary cards with them to the next visit.
- to continue taking anticholinergic medication, if prescribed, at a constant dose.
- that they will have 2 blood samples drawn for the pharmacokinetic analysis at the next visit: one sample when they arrive in the clinic and the other 3 to 10 hours after the morning dose of study medication (Section 5.4.9).

5.3.8 Visit 7 (End of Week 12): Double-blind Treatment Phase

At this visit, the following assessments will be made:

- Document if the patient has taken albuterol or used anticholinergic medication during the 4 hours immediately preceding the visit or smoked during the 2 hours immediately preceding the visit.
- The SGRQ will be completed prior to all other assessments (Section 7.3, Appendix F).
- Compliance in taking study medication will be determined (Section 6.8). Patients who show <80% or >120% compliance in taking study medication on two consecutive visits may be withdrawn from the study after consultation with the SB Medical Monitor.
- Record the use of "as-required" (prn) albuterol in the CRF (Section 5.4.3).
- Any changes or additions to the patient's concomitant medication will be recorded in the CRF (Section 6.11.5). Any changes in smoking status will also be documented (Section 5.4.1).
- Determine if the patient has entered a Pulmonary Rehabilitation Program since the last visit.
- Diary cards will be collected. Any adverse events which have occurred since the last visit will be recorded in the CRF and followed-up as necessary (Section 8).
- A COPD exacerbation assessment will be made to determine if the patient has experienced any exacerbations since the last visit (Section 8.1.2).
- Health economic factors will be assessed (Section 7.1 and Section 7.2).
- Overall breathlessness will be assessed using the modified Borg scale (Section 5.4.6).
- Cough and sputum production will be assessed (Section 5.4.16).
- Blood and urine samples will be obtained for routine hematology, biochemistry, (including beta-HCG for women of childbearing potential) and urinalysis (Section 5.4.8).

Greater than 4 hours after the patient's last albuterol administration:

- A 12-lead electrocardiogram will be performed after the patient has been semisupine for 5 minutes (Section 5.4.5).
- Blood pressure and heart rate will be measured after 5 minutes in a sitting position (Section 5.4.2).
- An exercise tolerance test (6-minute walk) will be completed (Section 5.4.10).
- Breathlessness using the modified Borg scale, SaO_2 and heart rate will be assessed immediately after the exercise tolerance test (Section 5.4.6 and Section 5.4.12).
- Pulmonary function tests will be performed in the absence of albuterol and before the next dose of study medication administered in the clinic. At least 10 minutes should elapse between the exercise tolerance test and pulmonary function testing so that the patient is fully rested (Section 5.4.7).
- Pre-dose blood samples for pharmacokinetic analysis will be collected (Section 5.4.9).

Patients who withdraw from the study during the visit should complete all scheduled visit assessments (with the exception of post-dose PK), the SF-36 questionnaire, Investigator and Patient Global Assessment, a physical examination, assessments of orthostatic changes in blood pressure and heart rate and fecal occult blood (Section 5.3.12).

For patients continuing in the study:

- Issue 1 bottle of the 35-day supply (70 tablets) of double-blind medication. The next morning dose of study medication will be administered in the clinic with food.
- Post-dose blood samples for pharmacokinetic analysis will be drawn (Section 5.4.9).
- Provide a new albuterol inhaler for 'as-needed' use to the patient.
- New diary cards will be issued. Patients should be reminded to use the card to record if they feel differently since starting the study.

- Review the procedure for reporting gastrointestinal adverse events with the patient.

- Issue the patient a fecal occult blood kit to be used if the patient reports a gastrointestinal adverse event of concern and they have used the test kit previously provided (Section 8.1.3).

Patients will be asked to return to the clinic at the same time of day in 28 (± 6) days for Visit 8. They will also be reminded:

- to take the first evening dose immediately after their evening meal.

- **not** to take their morning dose of study medication at home on the day of their next clinic visit if a morning visit is scheduled.

- to refrain from using albuterol 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 inhaler and spacer, and the diary card with them to the next visit.

- to continue taking anticholinergic medication, if prescribed, at a constant dose.

5.3.9 Visit 8 (End of Week 16): Double-blind Treatment Phase

The following procedures will be performed at this visit:

- Document if the patient has taken albuterol or used anticholinergic medication during the 4 hours immediately preceding the visit or smoked during the 2 hours immediately preceding the visit.

- Compliance in taking study medication will be determined (Section 6.8). Patients who show <80% or >120% compliance in taking study medication on two consecutive visits may be withdrawn from the study after consultation with the SB Medical Monitor.

- Record the use of "as-required" (prn) albuterol in the CRF (Section 5.4.3).

- Any changes or additions to the patient's concomitant medication will be recorded in the CRF (Section 6.11.5). Any changes in smoking status will also be documented (Section 5.4.1).

- Determine if the patient has entered a Pulmonary Rehabilitation Program since the last visit.

- Diary cards will be collected. Any adverse events which have occurred since the last visit will be recorded in the CRF and followed-up as necessary (Section 8).

- A COPD exacerbation assessment will be made to determine if the patient has experienced any exacerbations since the last visit (Section 8.1.2).

- Health economic factors will be assessed (Section 7.1 and Section 7.2).

- Overall breathlessness will be assessed using the modified Borg scale (Section 5.4.6).

- Urine samples will be obtained to determine beta-HCG levels in women of childbearing potential.

Greater than 4 hours after the patient's last albuterol administration:

- A 12-lead electrocardiogram will be performed after the patient has been semisupine for 5 minutes (Section 5.4.5)

- Blood pressure and heart rate will be measured after 5 minutes in a sitting position (Section 5.4.2).

- An exercise tolerance test (6-minute walk) will be completed (Section 5.4.10).

- Breathlessness using the modified Borg scale, SaO_2 and heart rate will be assessed immediately after the exercise tolerance test (Section 5.4.6 and Section 5.4.12).

- Pulmonary function tests will be performed in the absence of albuterol and before the next dose of study medication administered in the clinic. At least 10 minutes should elapse between the exercise tolerance test and pulmonary function testing so that the patient is fully rested (Section 5.4.7).

Patients who withdraw from the study during the visit should complete all scheduled visit assessments, the SGRQ and SF-36 questionnaires, laboratory

assessments, Investigator and Patient Global Assessment, a physical examination, assessments of cough and sputum production, orthostatic changes in blood pressure and heart rate and fecal occult blood (Section 5.3.12).

For patients continuing in the study:

- Issue 1 bottle of the 35-day supply (70 tablets) of double-blind medication. The next morning dose of study medication will be administered in the clinic with food.
- Provide a new albuterol inhaler for 'as-needed' use to the patient.
- New diary cards will be issued. Patients should be reminded to use the card to record if they feel differently since starting the study.
- Review the procedure for reporting gastrointestinal adverse events with the patient.
- Issue the patient a fecal occult blood kit to be used if the patient reports a gastrointestinal adverse event of concern and they have used the test kit previously provided (Section 8.1.3).

Patients will be asked to return to the clinic at the same time of day in 28 (± 6) days for Visit 9. They will also be reminded:

- to take the first evening dose immediately after their evening meal.
- **not** to take their morning dose of study medication at home on the day of their next clinic visit if a morning visit is scheduled.
- to refrain from using albuterol 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 albuterol inhaler and spacer, and the diary cards with them to the next visit.
- to continue taking anticholinergic medication, if prescribed, at a constant dose.

5.3.10 Visit 9 (End of Week 20): Double-blind Treatment Phase

At this visit, the following assessments will be made:

- Document if the patient has taken albuterol or used anticholinergic medication during the 4 hours immediately preceding the visit or smoked during the 2 hours immediately preceding the visit.
- Compliance in taking study medication will be determined (Section 6.8). Patients who show <80% or >120% compliance in taking study medication on two consecutive visits may be withdrawn from the study after consultation with the SB Medical Monitor.
- Record the use of "as-required" (prn) albuterol in the CRF (Section 5.4.3).
- Any changes or additions to the patient's concomitant medication will be recorded in the CRF (Section 6.11.5). Any changes in smoking status will also be documented (Section 5.4.1).
- Determine if the patient has entered a Pulmonary Rehabilitation Program since the last visit.
- Diary cards will be collected. Any adverse events which have occurred since the last visit will be recorded in the CRF and followed-up as necessary (Section 8).
- A COPD exacerbation assessment will be made to determine if the patient has experienced any exacerbations since the last visit (Section 8.1.2).
- Health economic factors will be assessed (Section 7.1 and Section 7.2).
- Overall breathlessness will be assessed using the modified Borg scale (Section 5.4.6).
- Urine samples will be obtained to determine beta-HCG levels in women of childbearing potential.

Greater than 4 hours after the patient's last albuterol administration:

- A 12-lead electrocardiogram will be performed after the patient has been semisupine for 5 minutes (Section 5.4.5)

- Blood pressure and heart rate will be measured after 5 minutes in a sitting position (Section 5.4.2).
- An exercise tolerance test (6-minute walk) will be completed (Section 5.4.10).
- Breathlessness using the modified Borg scale, SaO_2 and heart rate will be assessed immediately after the exercise tolerance test (Section 5.4.6 and Section 5.4.12).
- Pulmonary function tests will be performed in the absence of albuterol and before the next dose of study medication administered in the clinic. At least 10 minutes should elapse between the exercise tolerance test and pulmonary function testing so that the patient is fully rested (Section 5.4.7).

Patients who withdraw from the study during the visit should complete all scheduled visit assessments, the SGRQ and SF-36 questionnaires, laboratory assessments, Investigator and Patient Global Assessment, a physical examination, assessments of cough and sputum production, orthostatic changes in blood pressure and heart rate and fecal occult blood (Section 5.3.12).

For patients continuing in the study:

- Issue 1 bottle of the 35-day supply (70 tablets) of double-blind medication. The next morning dose of study medication will be administered in the clinic with food.
- Provide a new albuterol inhaler for 'as-needed' use to the patient.
- New diary cards will be issued. Patients should be reminded to use the card if they feel differently since starting the study.
- Review the procedure for reporting gastrointestinal adverse events with the patient.
- Issue a fecal occult blood kit and instruct the patient to follow the instructions on the kit and return the completed test by Visit 10. Issue a second fecal occult blood kit to be used if the patient reports a gastrointestinal adverse event of concern and they have used the test kit previously provided (Section 8.1.3).

Patients will be asked to return to the clinic at the same time of day in 28 (± 6) days for Visit 10. They will also be reminded:

- to take the first evening dose immediately after their evening meal.
- **not** to take their morning dose of study medication at home on the day of their next clinic visit.
- to refrain from using albuterol 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 albuterol inhaler and spacer, and the diary cards with them to the next visit.
- to continue taking anticholinergic medication, if prescribed, at a constant dose.

5.3.11 Visit 10 (End of Week 24): End of Double-blind Treatment Phase

At this visit, the following procedures will be completed:

- Document if the patient has taken albuterol or used anticholinergic medication during the 4 hours immediately preceding the visit or smoked during the 2 hours immediately preceding the visit.
- Two health status questionnaires (SF-36 and SGRQ) will be completed before all other assessments (Section 7.3, Appendix E and Appendix F).
- Investigator and Patient Global Assessment (Section 5.4.15).
- Compliance in taking study medication will be determined (Section 6.8).
- Record the use of "as-required" (prn) albuterol in the CRF (Section 5.4.3).
- Any changes or additions to the patient's concomitant medication will be recorded in the CRF (Section 6.11.5). Any changes in smoking status will also be documented (Section 5.4.1).
- Determine if the patient has entered a Pulmonary Rehabilitation Program since the last visit.
- Diary cards will be collected. Any adverse events which have occurred will be recorded in the CRF and followed-up as necessary (Section 8).

- A COPD exacerbation assessment will be made to determine if the patient has experienced any exacerbations since the last visit (Section 8.1.2).
- Health economic factors will be assessed (Section 7.1 and Section 7.2).
- Overall breathlessness will be assessed using the modified Borg scale (Section 5.4.6).
- Cough and sputum production will be assessed (Section 5.4.16).
- A physical examination, including a respiratory examination, will be performed (Section 5.4.2).
- Blood and urine samples will be obtained for routine hematology, biochemistry, (including beta-HCG for women of childbearing potential) and urinalysis (Section 5.4.8).

Greater than 4 hours after the patient's last albuterol administration:

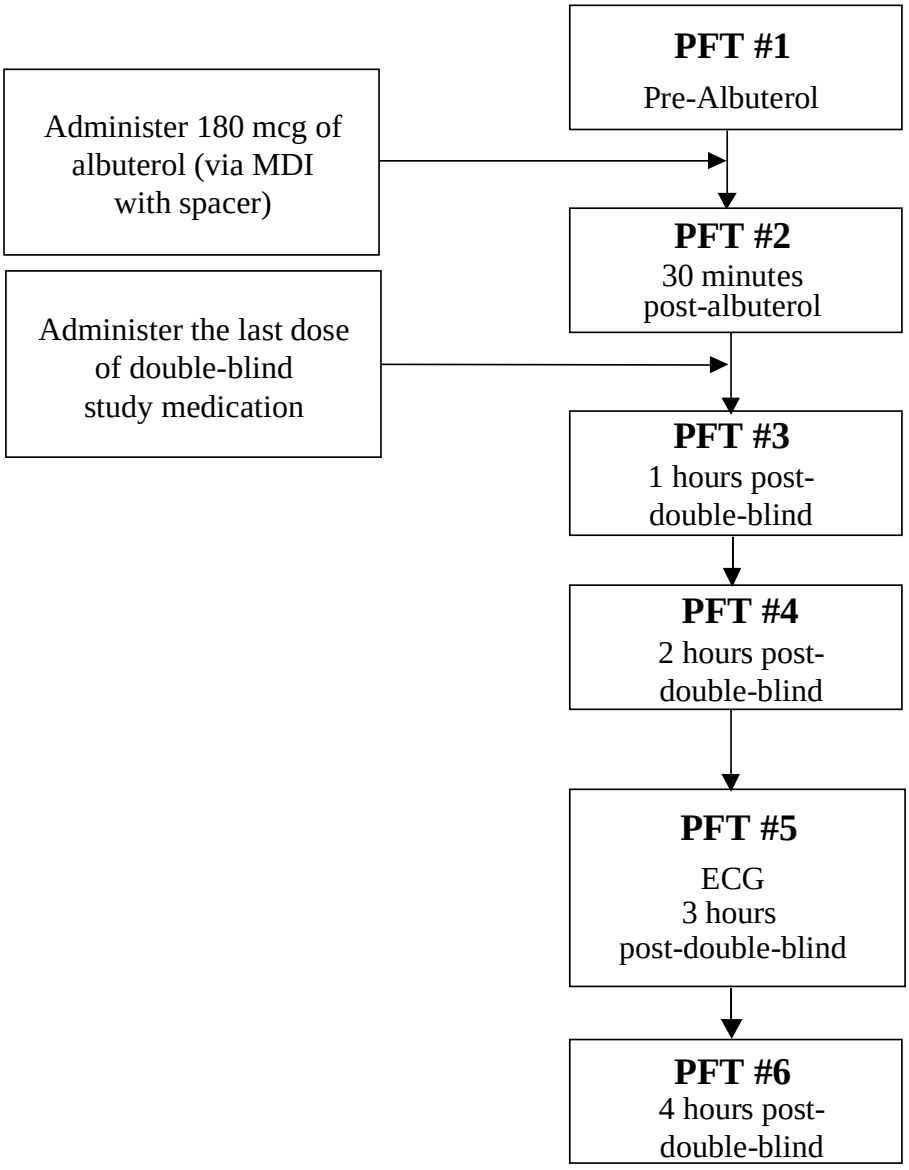
- A 12-lead electrocardiogram will be performed after the patient has been semisupine for 5 minutes (Section 5.4.5).
- Heart rate and blood pressure will be measured after 5 minutes in a sitting position. Orthostatic heart rate and blood pressure will be measured after 5 minutes in a supine position followed by sitting with legs dependent for 1 minute (Section 5.4.2).
- An exercise tolerance test (6-minute walk) will be completed (Section 5.4.10).
- Breathlessness using the modified Borg scale, SaO_2 and heart rate will be assessed immediately after the exercise tolerance test (Section 5.4.6 and Section 5.4.12).
- A pre-dose blood sample will be collected for pharmacokinetic analysis (Section 5.4.9).
- Resting SaO_2 will be measured by pulse oximetry in severe patients (i.e., FEV_1 <40% of predicted at Visit 1). If SaO_2 <88% or if the patient lives at high altitude, arterial blood gases must be measured (Section 5.4.12 and Section 5.4.13).

Patients will perform a pre-albuterol pulmonary function test before taking the last dose of albuterol and double-blind study medication in the clinic. At least

10 minutes should elapse between the exercise tolerance test and pulmonary function testing so that the patient is fully rested (Section 5.4.7).

Albuterol (180 mcg via MDI with spacer) will be administered to the patient. Pulmonary function tests will be performed 30 (±5) minutes later. The last dose of double-blind study medication will then be taken in the clinic with food and the time of administration will be recorded in the CRF. The patient will remain in the clinic for the next 4 hours. During this time, the patient will be observed and will undergo post-dose pulmonary function testing every hour (Section 5.4.7). Refer to Figure 3 .

Figure 3 Order of Pulmonary Function Tests at Visit 10



During the 4.5-hour observation period in the clinic, patients will be requested to avoid using additional albuterol or anticholinergic inhalers and to refrain from smoking if at all possible. If the patient uses albuterol or anticholinergics during the 4.5-hour post-dose period, all remaining pulmonary function tests should be abandoned.

If a patient withdraws during the observation period they will be asked to return in 7 (± 3) days for a Safety Follow-up Visit (Section 5.3.13).

- Any adverse events which occur during the observation period will be recorded in the CRF and followed up as appropriate (Section 8).

- Prior to PFT #5 (3 hours post-dose) a 12-lead electrocardiogram will be performed after the patient has been semisupine for 5 minutes (Section 5.4.5).

Patients will be asked to return in 7 (± 3) days for a Safety Follow-up Visit (Section 5.3.13). Patients may resume their previous COPD medications.

All patients will be issued a fecal occult blood kit to be used if the patient reports a gastrointestinal adverse event of concern and they have used the test kit previously provided (Section 8.1.3).

5.3.12 Early Withdrawal Assessments

Patients who withdraw from the study at a scheduled visit should complete the assessments scheduled at that visit (with the exception of any post-dose assessments). A physical examination, including a respiratory exam and orthostatic vital signs (Section 5.4.2) and laboratory assessments including fecal occult blood (Section 5.4.8) will be performed and the SGRQ and SF-36 questionnaires (Sections 7.3), Investigator and Patient Global Assessments (Section 5.4.15), and cough and sputum assessments (Section 5.4.16) will be completed, if not already included in the scheduled visit assessments. Pulmonary function tests (without albuterol, Section 5.4.7) and exercise tolerance tests (Section 5.4.10) will be performed if a patient withdraws from the study at Visit 3a.

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 withdrawal assessments. At this clinic visit, patients will complete trough pulmonary function tests, exercise tolerance tests, the SGRQ and SF-36 questionnaires, Investigator and Patient Global Assessments, cough and sputum assessments, and safety assessments (adverse events, COPD exacerbations, laboratory including fecal occult blood, ECG, physical examination, vital signs including orthostatic vital signs). Medication compliance, concomitant medications, medical procedures, entry into pulmonary rehabilitation programs, smoking status, and diary cards will be evaluated.

A Safety Follow-up Visit is required for all patients who withdraw from the study following the start of double-blind medication and before completion of the assessments up to and including those scheduled at Visit 10. This includes

patients who withdraw from the study at a scheduled visit or between visits. This assessment should be performed 7 (± 3) days after discontinuation of study medication (Section 5.3.13).

5.3.13 Safety Follow-up Visit

A Safety Follow-up visit is required for all patients including patients who complete Visit 10 and any patients who **withdraw** from double-blind therapy prior to completion of Visit 10 (either at a scheduled visit or between visits). This visit will occur 7 ± 3 days after Visit 10 or withdrawal from study medication. Patients will be asked to refrain from using albuterol or anticholinergics (or other COPD medications) and from smoking during the 2 hours immediately preceding the follow-up visit.

The following procedures will be performed at this visit:

- Document if the patient has taken albuterol or used anticholinergic medication during the 4 hours immediately preceding the visit or smoked during the 2 hours immediately preceding the visit.
- Any changes or additions to the patient's concomitant medication since the previous visit (including the resumption of any COPD medications) will be recorded in the CRF (Section 6.11.5). Any changes in smoking status will also be documented (Section 5.4.1).
- Any adverse events which have occurred since the last visit will be recorded in the CRF and followed-up as necessary (Section 8).
- A COPD exacerbation assessment will be made to determine if the patient has experienced any exacerbations since the last visit (Section 8.1.2).
- A physical examination, including a respiratory examination, will be performed if abnormal findings were observed at the last visit.
- In women of child-bearing potential, urine pregnancy tests will be performed.
- Blood and urine samples will be obtained for routine hematology and biochemistry and urinalysis only if abnormal findings were observed at the last visit.

Greater than 4 hours after the patient's last albuterol administration:

- A 12-lead electrocardiogram will be performed after the patient has been semisupine for 5 minutes if abnormal findings were observed at the last visit.
- Blood pressure and heart rate will be measured after 5 minutes in a sitting position (Section 5.4.2).
- Pulmonary function tests will be performed in the absence of albuterol (Section 5.4.7).

5.4 Clinical Observations and Procedures

Visit 3a is a safety-only visit. Unless specifically noted, the following assessments will not be performed at Visit 3a.

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, 10, Safety Follow-up, 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, 10 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 Visits 10, Safety Follow-up or early withdrawal.

Greater than 4 hours after the patient's last albuterol 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 and 10, early withdrawal and at visits associated with gastrointestinal adverse events, heart rate and blood pressure will be obtained after the patient has been supine for 5 minutes and then after the patient sits up with legs dependent for 1 minute. 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 ≥10 beats/minute at Visits 1 or 3, he 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 H.

5.4.3 'As Needed' Albuterol Use

Visits 2 - 10

During Visits 2 - 10, the Investigator will be required to record the patient's daily albuterol use via MDI according to the following:

- Much less than usual
- Less than usual
- About the same as usual
- More than usual
- Much more than usual

5.4.4 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. If the X-ray is not performed at Visit 1, the **film** must be available to the Investigator at Visit 1. Abnormal findings not consistent with the

diagnosis of COPD should be documented in the CRF and followed-up as appropriate.

5.4.5 Electrocardiograph (ECG)

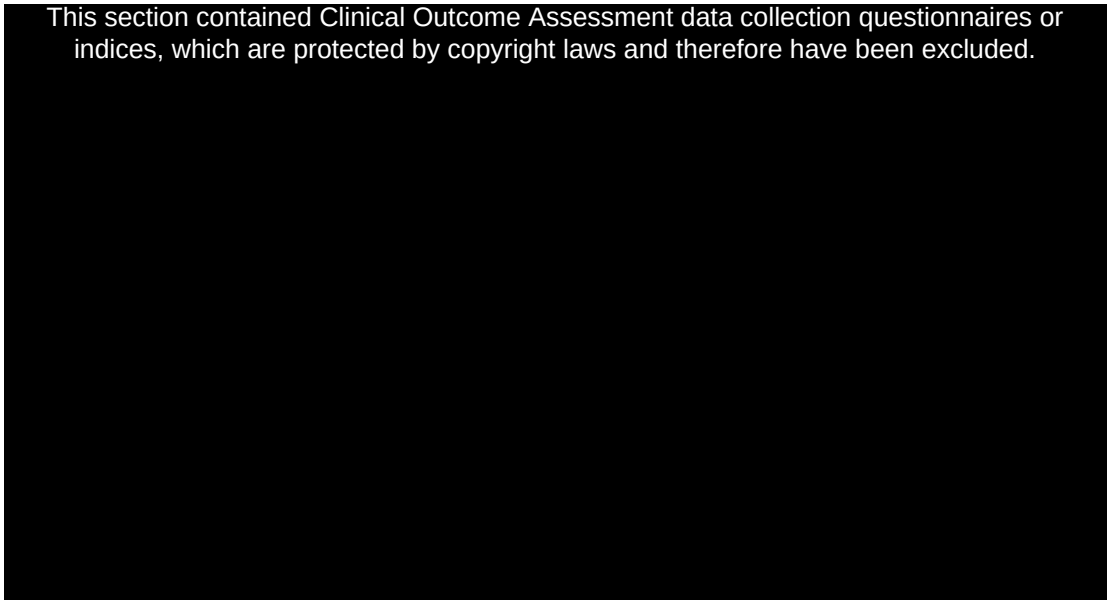
Visits 1, 3-10, Safety Follow-up, Early Withdrawal

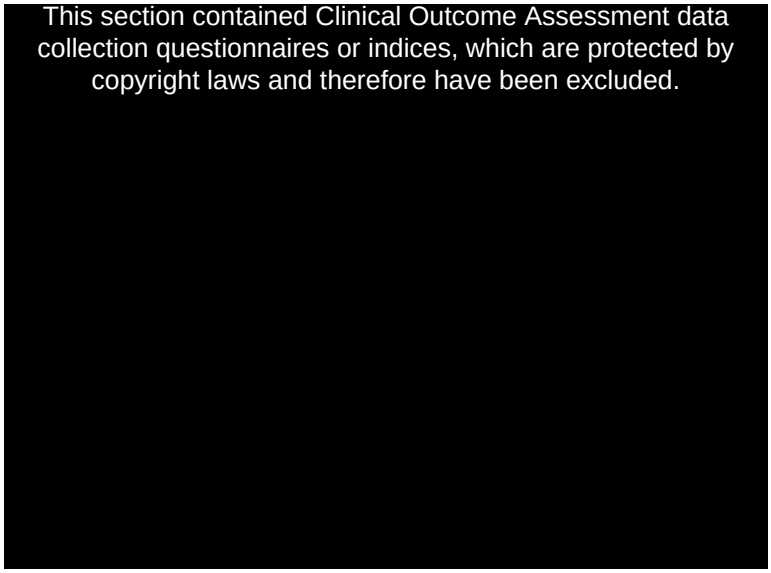
Greater than 4 hours after the patient's last albuterol administration, a 12-lead ECG will be performed at Visits 1, 3, 3a, 4-10, and Safety Follow-up (if abnormal at the previous visit) or upon early withdrawal after the patient has been semisupine for 5 minutes. At Visit 3 and 10 an ECG will also be recorded 3 hours after administration of study medication during the 4.5-hour PFT tests. Each ECG recording will be clearly labeled with patient initials, patient identification number, protocol number, center number and date performed. The ECGs will be reviewed by the Investigator for clinically significant abnormalities. ECGs will be transferred to a centralized facility for complete analysis.

5.4.6 Breathlessness - Overall and Post-exercise

Overall: Visits 1 - 10 and Early Withdrawal; Post-exercise: Visits 1 - 3, 5 - 10 and Early Withdrawal

Overall breathlessness will be assessed before exercise, using the modified Borg scale. [7] The patient will be asked the following question:





5.4.7 Pulmonary Function Tests

All Visits (except 3a)

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 SB **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. Pulmonary function tests will be performed after the patient has been at rest for at least 10 minutes after an exercise tolerance test.

Forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), peak expiratory flow rate (PEFR), 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 SB, which is suitable for research purposes, calibrated and maintained to acceptable respiratory function laboratory standards. [8] Pulmonary function tests will be repeated up to 8 times to obtain three acceptable readings according to ATS guidelines. [8] For each set of three FEV_1 measurements, one FEV_1 must be within 10% of the highest.

All visits: Pulmonary function tests (PFTs) will be assessed greater than 4 hours after the last dose of inhaled albuterol or anticholinergic agent. Patients will also be asked to refrain from smoking in the 2 hours prior to PFTs.

At all visits, PFTs will be performed in the absence of albuterol and will be performed at trough (pre-dose) plasma levels of study medication. Additional PFTs are performed at Visits 1, 3 and 10.

Visit 1: PFTs will be conducted before and 15 to 30 (± 5) minutes after administration of 2 puffs (180 mcg) of albuterol via metered dose inhaler (MDI) with a spacer. Patients will be provided with a spacer which they will be asked to bring to each visit.

Albuterol reversibility will be calculated with the formula below:

$$\text{Reversibility} = \frac{\text{Highest post - albuterol } FEV_1 - \text{Highest pre - albuterol } FEV_1}{\text{Highest pre - albuterol } FEV_1} \times 100$$

Percentage predicted FEV_1 will be calculated according to the Crapo equation (Appendix D).

Visits 3 and 10: PFTs will be assessed **6 times:**

- Before a dose of albuterol is administered in the clinic.

Note: Prior to randomization at Visit 3, patients must demonstrate stability in pulmonary function. Clinic FEV_1 (absolute value) in the absence of albuterol must not change (i.e., increase or decrease) by more than 20% between Visits 1 and 3. If the patient meets randomization criteria, the first dose of study medication will be administered.

Post-albuterol PFTs will be performed:

- 30 (±5) minutes after the administration of albuterol.

The first and last dose (Visits 3 and 10, respectively) of double-blind medication is administered in the clinic and post-dose PFTs will be performed:

- 1 hour after the dose of double-blind study medication.
- 2 hours after the dose of double-blind study medication.

- 3 hours after the dose of double-blind study medication.
- 4 hours after the dose of double-blind medication.

The hourly post-dose PFTs will assess the acute bronchodilator effects of Ariflo after the first and last doses of double-blind study medication.

During the observation period in the clinic, patients will be requested to avoid additional use of albuterol or anticholinergic medications and to refrain from smoking. If a patient uses albuterol or anticholinergics during the 4.5-hour period, all remaining PFTs for the visit should be abandoned.

Any adverse events which occur during the clinic stay will be recorded and followed up as appropriate (Section 8).

5.4.8 Laboratory Tests

Visits 1, 3, 3a, 4, 5, 6, 7, 10, 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 10 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 their 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:

Hematology: Hemoglobin concentration, hematocrit, red cell count, white cell count with differential, platelet count

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).

Feces: Fecal occult blood tests between Visits 1 and 3, between Visits 9 and 10 and at early withdrawal (three tests collected on consecutive bowel movements, if possible). The tests are to be performed according to the instructions provided with the fecal 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 hemorrhoids 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.

Fecal 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 hemorrhoids, blood in the urine, medications, vitamins, or foods.

Urinalysis: Blood, glucose, protein, ketones.

Pregnancy: Serum beta-HCG for women of childbearing potential Visits 1, 3, 5, 6, 7, and 10
Urinary beta-HCG for women of child bearing potential at Visits 8, 9 and 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 or sleep (see Section 8.1.3).

A central laboratory, Quest Laboratories, will be used for the routine hematological and biochemical assessments. All centers will send their samples to the Quest. Information on the Quest requisition form will include the patient number, patient initials, protocol number, center number, visit number and date. Samples will be labeled with the patient number, patient initials, and the account and requisition numbers. Full details for the preparation and shipment of samples will be provided by Quest to the Investigator before the start of the study.

Pregnancy testing at Visits 8 and 9 and the Safety Follow-up Visit will be performed locally using kits provided by Quest.

Reference ranges for all parameters will be obtained from the laboratory prior to starting the study and the tests should not be changed unless absolutely necessary during the study. If a change is unavoidable, the new reference range should be clearly identified in the CRFs concerned.

All clinically significant abnormal laboratory findings are to be repeated until the values return to normal. If such values do not return to normal within a period judged reasonable by the Investigator, the 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 fecal 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 Pharmacokinetic Sampling

Sample Collection

Blood samples for pharmacokinetic analysis of SB-207499 and SB-217493 plasma concentration data will be collected from all randomized patients. Each of these patients will be required to provide six samples during the 24-week double-blind treatment period, according to the schedule below.

Following randomization at Visit 3, patients will be assigned (in approximately equal numbers at each center) to either the 'Early' sampling group or the 'Late' sampling group. These designations define post-dose time intervals during which a blood sample is to be drawn at Visits 5 and 7. Centers are encouraged to scatter patients throughout the designated time intervals, rather than sample all patients in each group at the same time.

Visit 3 (Week 0): One sample will be drawn (post-dose)

A blood sample will be collected after the first dose of double-blind study medication, during the 4.5-hour post-dose PFTs. Blood will be drawn immediately after the ECG procedures, and prior to the 3-hour PFT.

Visit 5 (Week 4): Two samples will be drawn (one pre-dose and one post-dose).

After a pre-dose blood sample is collected, the patient will take the morning dose of study medication in the clinic with a snack. A patient in the 'Early' group will have a post-dose blood sample drawn between 0.5 and 2 hours after double-blind study medication is administered in the clinic. A patient in the 'Late' group will have a post-dose blood sample drawn between 1.5 and 3 hours after the dose of study medication.

The time (actual clock time) and date of the study medication dose administered in the clinic, along with the previous 2 doses, will be recorded in the CRF. The exact time and date of the blood samples will also be documented in the CRF.

Visit 7 (Week 12): Two samples will be drawn (one pre-dose and one post-dose).

After a pre-dose blood sample is drawn, the patient will take the morning dose of study medication in the clinic with a snack. A patient in the 'Early' group will return for a post-dose blood sample between 3 and 6 hours after double-blind study medication is administered in the clinic. A patient in the 'Late' group will have a post-dose blood sample drawn between 5 and 10 hours after the dose of study medication.

The time (actual clock time) and date of the study medication dose administered in the clinic, along with the previous 2 doses, will be recorded in the CRF. The exact time and date of the blood samples will also be documented in the CRF.

Visit 10 (Week 24): One sample will be drawn (pre-dose).

After a pre-dose blood sample is collected, and the trough pulmonary function tests have been performed (Section 5.4.8), the patient will take the final morning dose of study medication in the clinic with a snack.

The time (actual clock time) and date of the study medication dose administered in the clinic, along with the previous 2 doses, will be recorded in the CRF. The exact time and date of the blood sample will also be documented in the CRF.

Unscheduled samples: In every patient attending the clinic for an unscheduled "safety-monitoring" visit triggered by a gastrointestinal adverse event (see Section 8.1.3) or a serious adverse event, where feasible, a blood sample will be collected as soon as possible following presentation to the clinic.

Sample Treatment

Blood samples (5 ml each) for pharmacokinetic analysis will be collected into tubes containing EDTA and immediately placed on ice. Plasma will be separated within 30 minutes of collection by centrifugation (1000-1300 g for 10 minutes) and transferred into appropriately labeled polypropylene tubes (label is attached to the Quest requisition form). Plasma must be frozen immediately after centrifugation and stored at approximately -20°C until transported for analysis via Quest. Details for the preparation and shipment of samples will be provided by Quest before the start of the study.

Analytical Methodology

Plasma samples will be assayed for SB-207499 and the metabolite SB-217493 using the currently approved assay methodology. These analyses will be performed intermittently throughout the study in order to provide Quality Assured analytical results in an ongoing fashion.

The randomization code may be provided to DMPK in order to avoid analyzing samples from patients receiving placebo, and to allow real-time analysis of pharmacokinetic data to begin. This information will not be communicated to anyone outside DMPK, except to staff performing the drug analyses, until the database is released. Sample analysis will be the responsibility of Pharma-Bio (Holland).

5.4.10 Exercise Tolerance Test

All visits (except Visit 3a, 4, and Safety Follow-up)

A 6-minute walk test, as described by G. H. Guyatt and colleagues, will be used to assess the functional capacity of the patient. [9,10]

The 6-minute walk will be conducted **greater than 4 hours after the patients last albuterol administration** and where possible should be administered by the same person to avoid variability. The patient will be instructed to walk from one end of a course to the other, covering as much ground as they can during 6 minutes. The patient will be encouraged to perform during the tests; the supervisor will face the patient every 30 seconds and deliver one of the following encouraging phrases:

"You're doing well!" or "Keep up the good work!"

At the end of the test, the supervisor will call out "Stop" and the distance walked by the patient will be measured and recorded on the CRF.

5.4.11 Diary Card

All Visits (except Visit 1 and Safety Follow-up)

Diary cards will be issued at Visits 1 – 9. The diary will provide space for the patient to record if they feel differently since starting the study medication. This will help the patient to remember events that occur between visits that they want to discuss with the Investigator at the next visit.

5.4.12 Resting and Post-exercise Transcutaneous Oxygen Saturation

Resting: Visit 3 and 10 (severe patients), Post-exercise: All visits (except Visits 3a, 4, and Safety Follow-up)

Oxygen saturation (SaO_2) will be measured by ear or finger oximetry and heart rate will be measured immediately at the end of the exercise test.

Resting oxygen saturation will be measured by pulse oximetry at Visits 3 and 10 for severe COPD patients (i.e., those with a FEV_1 <40% of predicted at Visit 1).

5.4.13 Arterial Blood Gases

Visits 3 and 10 (severe patients)

If resting SaO_2 <88% or if the patient lives at high altitude, arterial blood gas assessments must be performed at Visit 3 and 10 for severe COPD patients (i.e., those with a FEV_1 <40% of predicted at Visit 1). PO_2, PCO_2, pH and bicarbonate will be measured from whole arterial blood by an arterial blood gas analyzer. The blood gas analyzer will be properly calibrated and maintained to acceptable laboratory standards.

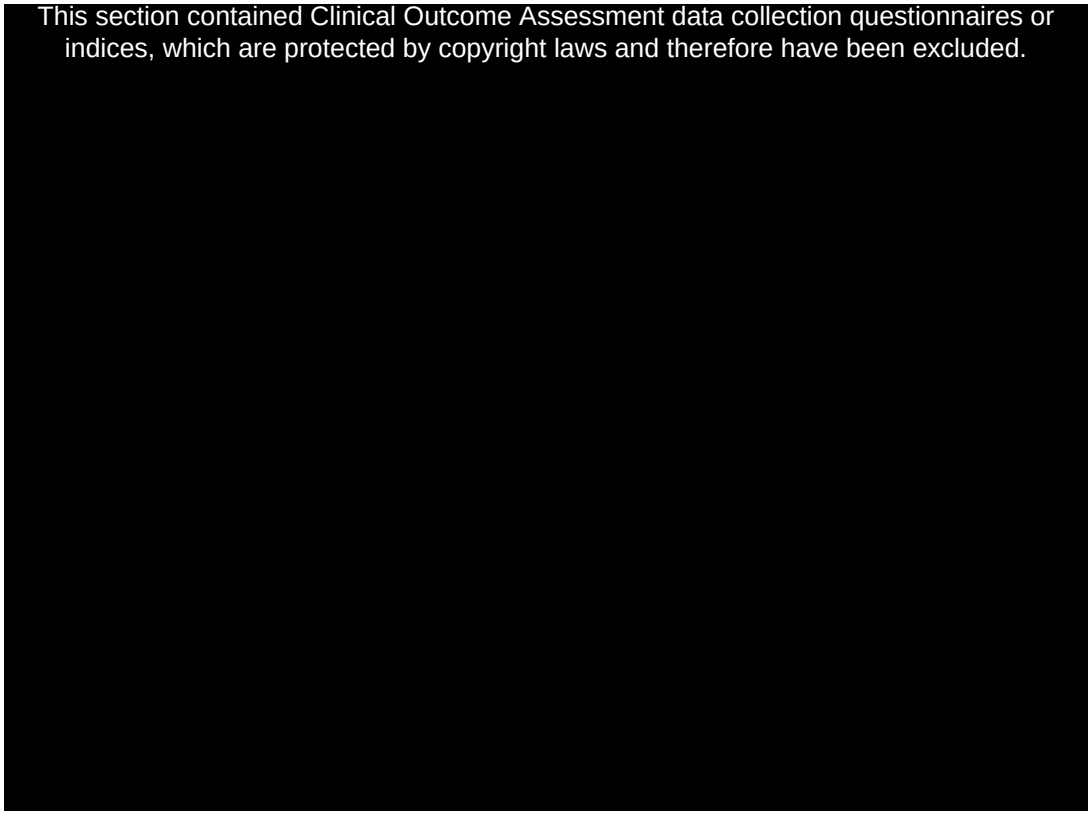
5.4.14 Carbon Monoxide Diffusing Capacity (DLCO)

Visit 1

Single-breath carbon monoxide diffusing capacity (DLCO) will be determined at Visit 1, if not assessed in the 24 weeks prior to Visit 1 or if the results are not available to the Investigator. Alternatively, DLCO assessment may be scheduled between Visits 1 and 3.

The assessment will be performed twice (at least 4 minutes apart) after the patient has been seated for at least 5 minutes. [11] Mean DLCO will be recorded in the CRF.

5.4.15 Patient and Investigator Global Assessments



5.4.16 Cough and Sputum Production Assessments

Visits 3, 7 and 10

Cough and sputum production will be rated according to the following scales:

COUGH

"How troubled have you been by cough today?"

0	No symptoms at all
1	Some symptoms, but hardly noticeable
2	Symptoms noticeable and a little uncomfortable
3	Symptoms definitely noticeable and uncomfortable
4	Symptoms very bad and extremely uncomfortable

SPUTUM PRODUCTION

"How much sputum have you produced today?"

0	No sputum at all
1	Some sputum, but not as much as usual
2	As much as usual
3	More than usual
4	A lot more than usual

6 Study Medication and Administration

6.1 Study Medication

Ariflo will be provided as a yellow, round, convex tablet containing 15 mg of Ariflo (SB 207499). Matching placebo tablets will also be provided.

Canisters (MDIs) of albuterol (90 mcg/actuation, 200 actuation's per canister) will be provided for on-demand (prn) use during the study. Spacers will also be provided for use at Visits 1, 3 and 10. Patients may employ these for on-demand use if this their customary inhalation method. Albuterol is not considered study medication.

Double-blind study medication will be assigned to patients through SmithKline Beecham's Registration and Medication Ordering System (RAMOS). The toll-free number is [redacted] 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 randomized to a treatment group through a call to RAMOS. 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 patent pack of double-blind medication that should be assigned to the patient from the investigator's inventory; and 2) a 5-digit randomization number which must be written in the patient's CRF. The patient pack assigned during the randomization call will contain all of the double-blind study medication for the assigned patient. Although study medication will be stored at each site, the investigator (or designee) must phone into RAMOS to

obtain study medication assignments. 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.

6.2 Dosage and Administration

Patients who fulfill the entry criteria will enter a 4-week single-blind placebo run-in phase. During the run-in phase, patients will take one Ariflo-matched placebo tablet twice daily, in the morning immediately after breakfast and in the evening immediately after a meal. *Patients must not take the morning dose of study medication before attending morning clinic visits. On the day of clinic visits, the first dose of study medication will be administered in the clinic with food.*

Patients who fulfill the Randomization Criteria will enter a 24-week double-blind treatment phase. Patients will receive either Ariflo 15 mg or matching placebo. 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 the morning dose of study medication before attending morning clinic visits. On the day of clinic visits, the first dose of study medication will be administered in the clinic with food.*

6.3 Blinding

Ariflo 15 mg tablets and Ariflo-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 randomization number will be provided during the randomization call to RAMOS.

The randomization 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.

All run-in medication will be blinded to the patient, and all medication for randomized patients will be blinded to both the Investigator and the patient. Labels on all double-blind bottles will be coded. The blind will be maintained by SmithKline Beecham who will maintain an updated copy of the master randomization code.

The labels on each bottle of double-blind medication will include an unblinding panel on the tear-off portion of the label. This tear-off panel will be affixed to the

CRF at the time that the medication is dispensed. Alcohol swabs are required to remove the blinding panel and reveal the contents of the bottle. The unblinding panel is provided for Investigators to use in emergency situations only. SB must be notified of any case of unblinding of study medication.

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 SB 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 SB Medical Monitor as soon as possible.

6.4 Packaging

For the single-blind placebo run-in phase, Ariflo-matched placebo tablets will be supplied in bottles containing 20 tablets. Each bottle will provide a 10-day supply of study medication. Therefore, two bottles of run-in medication (a 20-day supply) should be dispensed to eligible patients at Visits 1 and 2 to allow for some flexibility in the interval between visits. Placebo medication for the single-blind run-in period will be supplied separately from the double-blind study medication as individual unallocated bottles.

Study medication for the 24-week double-blind treatment period will be presented in double-blind patient packers. Each patient packer will contain 9 bottles. Four of these bottles will contain 20 tablets (a 10-day supply) of either Ariflo (SB 207499) 15 mg or matching placebo. These bottles are for use at the initial visits during the double-blind phase (Visits 3, 3a, and 4). Therefore, one bottle should be dispensed for visits scheduled one week apart and two bottles should be dispensed for visits scheduled two weeks apart. An overage of tablets is included in each bottle to allow for flexibility in the interval between visits.

Five additional bottles will contain 70 tablets (a 35-day supply) of either Ariflo (SB 207499) 15 mg or matching placebo. These bottles are for use at the later visits during the double-blind phase (Visits 5, 6, 7, 8, and 9). Therefore, one bottle should be dispensed at these visits which will be scheduled 4 weeks apart. An overage of tablets is included in each bottle to allow for flexibility in the interval between visits.

While all of the bottles in a patient packer contain the same medication (Ariflo 15 mg or matching placebo tablets), it is important to dispense the weekly bottles

first in order to ensure that patients receive the proper quantity of tablets between visits. Weekly and monthly bottles will be segregated in each patient packer. The number of days of study medication provided at each visit and the number of days in each inter-visit period are provided in the Table 4.

Table 4 Study Medication Packaging

Visit	Medication Dispensed for	Study Medication
1	2 weeks (run-in)	A 20-day supply of Ariflo-matched placebo tablets (2 bottles of 20 tablets)
2	2 weeks (run-in)	A 20-day supply of Ariflo-matched placebo tablets (2 bottles of 20 tablets)
3	1 week	A 10-day supply of Ariflo 15 mg or placebo tablets (1 bottle of 20 tablets)
3a	1 week	A 10-day supply of Ariflo 15 mg or placebo tablets (1 bottle of 20 tablets)
4	2 weeks	A 20-day supply of Ariflo 15 mg or placebo tablets (2 bottles of 20 tablets)
5	4 weeks	A 35-day supply of Ariflo 15 mg or placebo tablets (1 bottle of 70 tablets)
6	4 weeks	A 35-day supply of Ariflo 15 mg or placebo tablets (1 bottle of 70 tablets)
7	4 weeks	A 35-day supply of Ariflo 15 mg or placebo tablets (1 bottle of 70 tablets)
8	4 weeks	A 35-day supply of Ariflo 15 mg or placebo tablets (1 bottle of 70 tablets)
9	4 weeks	A 35 day supply of Ariflo 15 mg or placebo tablets (1 bottle of 70 tablets)

6.5 Labeling and Preparation

A two-panel label consisting of a fixed portion and a tear-off portion will be attached to the run-in medication bottles. The Investigator (or designate) will remove the tear-off portion of the label from the bottle at the time of dispensing and attach it to the appropriate page in the CRF. Labels on the run-in medication will include the protocol number, packaging job number, fill count, batch number (on tear-off portion only), dosing directions, storage conditions, caution statements, and SB company address. There will also be prompts for patient initials, date dispensed, and visit number on the fixed portion of the label.

The double-blind patient packer will be labeled with a single panel label. This label will include the protocol number, six-digit container number, contents (4 bottles x 20 tablets and 5 bottles x 70 tablets), storage conditions, caution statements, and SB company address. There will also be a prompt for the patient's initials.

The weekly and monthly bottles will be segregated within each patient packer and labeled with a single panel label. This label will include the protocol number, six-digit container number (the same number that appears on the patient packer label), contents (either 4 bottles x 20 tablets or 5 bottles x 70 tablets), storage conditions, caution statements, and SB company address.

Each bottle in the double-blind patient packer will be labeled 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 bottle at the time of dispensing and attach it to the appropriate page in the CRF. Labels on the double-blind medication bottles will include the protocol number, six-digit container number (the same number that appears on the patient packer label), fill count, blinded disclosure panel (on tear-off portion only), dosing directions, storage conditions, caution statements, and SB company address. There will also be prompts for patient initials, date dispensed, and visit number 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 SB.

The Investigator (or designate) will record all study medication dispensed on a Drug Accountability Form. At the conclusion of the study, reconciliation must be made between the amount of medication supplied, dispensed and subsequently returned to SB. Any discrepancies must be accounted for. A certificate of return must be signed incorporating the assurance from the Investigator (or designate) that all unused investigational products have been returned. Supplies will, in the majority of cases, be returned to the local SB site for subsequent destruction. In exceptional cases, supplies may be destroyed at the center. Destruction should only be performed by authorized personnel who are aware of any possible hazardous effects, and following receipt of written approval from the local SB 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 10. 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 patients 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. If the patient shows <80% or >120% compliance at 2 consecutive visits, the patient may be withdrawn from the study after consultation with the SB Medical Monitor.

6.9 Treatment of Study Medication Overdose

To date, there have been no cases of confirmed overdose with Ariflo. 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 SB 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 by phoning Corporate Environmental Safety at [redacted] 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 Albuterol Use

The use of albuterol 90 mcg/actuation, 200 actuations per canister, 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 SB and not their own devices. The Investigator should issue a new inhaler every 4 weeks.

Between Visits 1 and 10, patients should NOT use any additional bronchodilators that they possess at home, with the exception of a stable dose of anticholinergic medication by MDI if prescribed for the patient. *If the patient experiences symptoms which do not respond adequately to rescue medication (e.g., albuterol, two actuations every four hours), the patient must contact the Investigator.* If a patient occasionally uses albuterol 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.

6.11.2 Anticholinergic Medication

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 6.11.3). The dose of the anticholinergic medication should remain stable from Visit 1 to Visit 10. The use of inhaled anticholinergic medication must be recorded in the concomitant medication section of the CRF.

6.11.3 Prohibited Medications

Except in the short-term management of COPD exacerbations, the use of corticosteroids (inhaled or oral), xanthines, inhaled cromolyn sodium or nedocromil, inhaled long acting beta$_2$-agonists, inhaled short-acting beta$_2$-agonists other than albuterol, oral or nebulized beta$_2$-agonists, nebulized anticholinergics, and/or leukotriene modifiers is **not allowed between Visits 1 and 10**.

All COPD medications except anticholinergic agents and albuterol via MDI, and mucolytics must be withdrawn prior to or at Visit 1.

This protocol does not permit the use of combined beta$_2$-agonist/ipratropium therapy (e.g., Combivent®). Combination therapies (beta$_2$-agonist/ anticholinergic mix) must be changed to separate single therapy inhalers prior to or at Visit 1. Patients should maintain equivalent doses of the component bronchodilators. Patients who use mucolytics may continue to do so during the study at a stable dose; mucolytics should not be started during the study.

Table 5 provides a list of prohibited medications, along with selected trade names.

Note: This table is intended to provide examples of drugs in each class; it is not a complete list of trade names.

Table 5 Prohibited Medications in Study SB 207499/156

Medication Class	Selected Trade Names
Inhaled corticosteroids	Aerobid®, Azmacort®, Flovent®, Pulmicort®, Vanceril®
Oral corticosteroids	prednisone, Medrol®, Decadron®, Sterapred®
Combination of inhaled short-acting beta$_2$-agonists & anticholinergics	Combivent®
Selected short-acting inhaled beta$_2$-agonists	All **except** Ventolin®
Long-acting inhaled beta$_2$-agonists	Serevent®
Oral beta$_2$-agonists	Proventil®, Ventolin®, Volmax®, Brethine®
Nebulized beta$_2$-agonists	albuterol, metaproterenol, Alupent®, Isuprel®, Proventil®, Tornalate®, Ventolin®
Nebulized anticholinergics	Atrovent®
Inhaled cromolyn sodium	Intal®
Inhaled nedocromil	Tilade®
Oral xanthines	Slo-Bid®, Theo-Dur®
Leukotriene modifiers	Accolate®, Zyflo®, Singulair®
Mucolytics*	Mucomyst®, Mucosal®
Long-term oxygen therapy (LTOT)**	N/A

* Mucolytic administration should not be started during the study. Stable doses of mucolytics taken prior to study start may be continued.

** 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.

Any patient using prohibited medications other than for the management of an exacerbation of COPD between Visits 1 and 10 must be withdrawn from the study after consultation with the Medical Monitor. Theophylline is not permitted at any time during the study.

6.11.4 Treatment of COPD Exacerbations

Only if clinically indicated, inhaled/oral steroids or antibiotics may be administered for the short-term (<14 days) treatment of COPD exacerbations. Patients will be allowed to remain in the study for a maximum of three Level 2 or Level 3 exacerbations after randomization at Visit 3 (Section 8.1.2).

After three Level 2 or Level 3 exacerbations, patients may be withdrawn from the study following consultation with the SB Medical Monitor.

Patients who take any corticosteroids or antibiotics for the treatment of COPD exacerbations during the run-in phase are not eligible to be randomized to the double-blind phase.

Patients experiencing an exacerbation of COPD which requires **longer than a 2-week course** of inhaled/oral steroids or antibiotics during the double-blind period should be discussed with the SB Medical Monitor and consideration given to withdrawing the patient from the study. The reason for withdrawal (exacerbation of COPD) should be clearly documented in the CRF.

Refer to Section 8.1.2 for definitions of the level of COPD exacerbations.

6.11.5 Concomitant Medication

All concomitant medications taken during the study, *including* 'as needed' (prn) albuterol, 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 utilization data will be collected in association with COPD disease exacerbations which require healthcare professional or medical intervention. Medical care utilization includes hospitalization, 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 nebulizer or injection and oxygen). The medical care utilization 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

At entry to the study, patients will be asked about the days per month that they miss work due to COPD-exacerbations and COPD-related symptoms. They will also be asked if they are restricted in performing leisure activities or require paid

or unpaid assistance with daily activities due to COPD-related symptoms. This data will be collected at each visit and recorded in the CRF.

7.3 Health Status Analyses

Short-Form 36 (Appendix E***)***

The MOS Short-Form 36 is a generic quality of life assessment tool which has been used extensively to evaluate the physical, mental and general health status of patients. [12,13] The SF-36 will be administered at Baseline (Visit 3) and at Week 24 (Visit 10). Any patient who withdraws from the study should complete the SF-36 at the time of withdrawal (Section 5.3.12). The SF-36 will be scored using the standard scoring methodology described in the SF-36 reference manual. [12]

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. [6,14,15] 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). [16]

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), at Week 12 (Visit 7) and at Week 24 (Visit 10). Any patient who withdraws from the study should complete the SGRQ at the time of withdrawal (Section 5.3.12).

Note: Since the SGRQ is a co-primary endpoint in this study, it is essential that the questionnaire is fully completed by the patients at each assessment. Any patient who is unable or unwilling to comply with this requirement, will not be randomized in the study.

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 fulfill 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 unfavorable 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. COPD exacerbations are categorized as Level 1, 2, or 3, based on the treatment received by the patient for the exacerbation. The levels of exacerbations will be rated as follows:

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

Level 2 Exacerbation: Acute worsening of COPD that requires additional treatment (e.g., a short course of oral steroids, antibiotics, etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

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

If more than three Level 2 or Level 3 COPD exacerbations occur during the double-blind phase, patients may need to be withdrawn from the study after consultation with the Medical Monitor. If a patient has an exacerbation of COPD that is longer than 2 weeks in duration during the double-blind period, the Investigator will contact the SB Medical Monitor regarding the patient's continuation in the study. If clinically indicated, short-term (<2 weeks) treatment of inhaled/oral corticosteroids or antibiotics can be prescribed for COPD exacerbations.

Patients who take any corticosteroids or antibiotics for the treatment of a COPD exacerbation during the run-in phase are not eligible to be randomized to the double-blind phase of the study.

Note: All exacerbations of COPD must be recorded in the COPD exacerbation section of the CRF. Any exacerbation of COPD, regardless of

level, that fulfills the SAE criteria must be recorded in the COPD SAE pages of the CRF.

8.1.3 Gastrointestinal Adverse Events

Adverse events related to the gastrointestinal tract will be closely monitored during this study. Patients will be instructed to call the Investigator to report any gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhea, 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. The patient will have a fecal occult blood test kit available at home in order to obtain a fecal sample prior to reporting to the clinic for evaluation of a gastrointestinal AE of concern. When the patient reports a gastrointestinal AE of concern, the Investigator will instruct the patient to use the FOB test kit dispensed for this purpose. The patient will be scheduled for a clinic visit within 24 hours and instructed to return the FOB test. The assessment at the clinic 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; an assessment of orthostatic changes in heart rate and blood pressure; and a review of the fecal occult blood test results. 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 fecal occult blood test. When the fecal occult blood test samples are analyzed, the Investigator will question the patient to determine if the results may have been affected by menstruation, bleeding hemorrhoids, blood in the urine, medications, vitamins, or foods. Whenever the patient cannot provide a fecal sample prior to or at the clinic visit, the Investigator should obtain a sample by digital rectal exam. Patients must be provided with replacement fecal occult blood test kits whenever the blank kits are used. If a fecal occult blood test is positive or if the patient reports melena during the randomized treatment phase of the study, the patient will be referred to a gastroenterologist for a **complete** colonoscopy as soon as possible within 10 to 14 days of the clinic visit. The colonoscopy should emphasizes visualization of the transverse colon with reporting of positive or negative findings, irrespective of other identified pathology or causes for gastrointestinal bleeding. Biopsies should be taken if appropriate. Results of the colonoscopy should be faxed to the Sponsor as soon as available. A blood sample will also be collected for pharmacokinetic (PK/PD) analysis of SB-207499 and SB-217493 plasma concentrations. 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 SB Medical Monitor.*

Assessments of fecal occult blood, complete blood count, and orthostatic changes in blood pressure will be completed until the gastrointestinal symptoms are resolved. Daily assessments will be performed by a qualified health care provider at the patient's home or by daily clinic visits. Any deterioration in the patients' condition since the previous assessment discovered by a health care provider will be reported to the Investigator by telephone immediately; all results will be forwarded to the Investigator by the end of the work day. 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 H.

Note: All gastrointestinal adverse events of clinical concern (bloody or black stools, abdominal discomfort; such as, pain or cramps, diarrhea 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 fulfills 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 SB within 24 hours (see Section 8.3.3)

A serious AE is any untoward medical occurrence which fulfills the definition for an AE (as defined in Section 8.1.1) AND in addition, is:

- Fatal
- Life threatening
- Disabling/incapacitating
- Results in hospitalization or prolongs a hospital stay
- A congenital abnormality

- Any important medical occurrence which the Investigator regards as serious based on appropriate medical judgment

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 judgment 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.

Hospitalization:

Hospitalization 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 hospitalization 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, hospitalizations 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 judgment should be exercised to ensure that other important medical events are promptly reported to SB. 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 randomized treatment will be documented on the Baseline Signs & Symptoms section within the CRF.

All AEs occurring after administration of the first dose of 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 changes in intensity/frequency then this should be recorded as a separate event (i.e. a new record started).

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 judgment. 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 judgment 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

SB 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 SB 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 SB 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 randomized 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 SB to fulfill 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 SmithKline Beecham

All serious AEs will be reported to SB **within 24 hours**. Facsimile transmission is always the preferred method of reporting (including non-working hours).

SB study contact : [redacted] MD
Glaxo Wellcome Inc, a GlaxoSmithKline Company
Facsimile number : [redacted]
Telephone number : [redacted]

Emergency 24 hour medical contact :
Telephone number : [redacted]

Investigators must not wait to receive all information before notifying SB 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 SB 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 SB 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 stabilized, the event is otherwise explained, or the patient is lost to follow-up.

All follow-up information must be forwarded to the SB contact (as specified in 8.3.3 above) **within 24 hours** of receipt.

To fulfill ethical and regulatory obligations, SB may request additional follow-up information on any serious AE and the Investigator is obligated to assist. When requested by SB, 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, diarrhea, 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 judgment 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 SB (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 SB. 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 SB 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 SB 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 SB 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 SB 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 SB medical contact as soon as possible thereafter.**

The Investigator must complete a Serious AE form and forward it to the SB 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 fulfill 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 SB must file it with the Investigator Brochure and must notify the Ethics Committee/IRB, if appropriate, according to local requirements.

9 Subject Completion and Withdrawal

9.1 Definitions

Patients who have completed the assessments scheduled for Week 24 (Visit 10) 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

Enrollment will continue until up to 830 patients have been randomized. The double-blind medication assigned to withdrawn patient(s) will not be re-used.

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** randomization, 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** randomization, the assessments and procedures of the visit and any additional early withdrawal assessments and procedures (Section 5.3.12) should be completed. Patients who withdraw from the study between visits will be asked to return within 24 hours of stopping study medication for early withdrawal assessments and procedures (Section 5.3.12).

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**

- **Termination of the study by SB**

- **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 SmithKline Beecham Pharmaceuticals will perform all statistical analyses.

10.1 Objectives

The primary objectives of this study are to demonstrate statistically and clinically significant differences between Ariflo and placebo in trough FEV_1 and the total score of the St. George's Respiratory Questionnaire (SGRQ) over 24 weeks.

10.2 Hypotheses

There are two primary hypotheses in this study. They are based on demonstrating the superiority of Ariflo to placebo with respect to **both** trough pre-bronchodilator FEV_1 and total score of the SGRQ. The hypotheses are based on a two-tailed test as follows:

$$H_0 : \mu_{ic} = \mu_{ip} \quad i = 1,2$$
$$H_a : \mu_{ic} \neq \mu_{ip} \quad \text{for all } i = 1,2$$

Where μ_{1c} is defined as the mean of the average change in FEV_1 over all double-blind visits and μ_{1p} Ariflo is defined similarly for placebo. μ_{2c} and μ_{2p} are defined as the corresponding means for the average change over all double-blind visits for the SGRQ total score.

10.3 Definition of Variables

10.3.1 Primary Efficacy Variable

The primary variables in this study are the change from baseline in trough pre-bronchodilator forced expiratory volume in 1 second (FEV_1) and the change from baseline in total score of the St. George's Respiratory Questionnaire (SGRQ). At each visit, the best FEV_1 from the three spirometry efforts performed by the patient will be used in the analysis. Baseline will be defined as the pre-bronchodilator FEV_1 evaluation performed at Visit 3. For total score of the SGRQ, baseline will be defined as the evaluation performed at Visit 3.

10.3.2 Secondary Efficacy Variables

There are four secondary endpoints in this study:

1. Change from baseline in Clinic FVC at trough. FVC provides complementary information to FEV_1 with respect to lung function.

2. Time to first COPD exacerbation.

3. Time to first level 2 or level 3 COPD exacerbation. These are exacerbations associated with some form of physician contact including ER visits and hospitalization.

4. Change from baseline in post-exercise breathlessness (modified Borg Scale).

10.3.3 Tertiary Efficacy Variables

- First and last dose effect for FEV_1, FVC, PEFR and FEF_{25-75}
- Post-bronchodilator effect for FEV_1, FVC, PEFR and FEF_{25-75}
- Clinic trough PEFR
- Clinic trough FEF_{25-75}
- Use of 'as-required' (prn) albuterol recorded in CRF according to the following categories:
  - Much less than usual
  - Less that usual
  - About the same as usual
  - More than usual
  - Much more than usual
- SGRQ subscales (symptoms, activities and impacts)
- Health status assessment: SF-36
- Health economic endpoints (impact on activities, healthcare utilization)
- Global Patient Assessment
- Global Investigator Assessment
- Exercise performance (distance walked) during the exercise tolerance test (6-minute walk with encouragement)
- Overall dyspnea (on a modified Borg scale) during usual activities
- Exertional (post-exercise) dyspnea (on a modified Borg scale)
- Post-exercise SaO_2
- SaO_2 at rest in patients with FEV_1 of <40% predicted for age, height and gender

- Arterial blood gases, PO_2 and PCO_2 in patients with FEV_1 of <40% living at high altitudes or having a resting SaO_2 <88%
- Cough assessment
- Sputum assessment

10.4 Comparisons of Interest

10.4.1 Primary Comparison of Interest

The primary comparisons will be based on two-tailed tests of hypothesis. A comparison will be done for the difference in change from baseline in pre-bronchodilator FEV_1 between the Ariflo group and the placebo treatment group (Ariflo – Placebo) averaged over all double-blind visits (protocol defined Visits 4, 5, 6, 7, 8, 9, 10) in the intent-to-treat population (see Section 10.7.1 for definition). The second primary comparison will be done for the difference in change from baseline in total score of the SGRQ between the Ariflo group and the placebo treatment group (Ariflo – Placebo) averaged over all double-blind visits (protocol defined Visits 7 and 10) in the intent-to-treat population. As both primary endpoints must demonstrate statistical significance, each of the primary comparisons will be performed at an alpha level of 0.05.

10.4.2 Secondary Comparisons of Interest

Secondary comparisons of interest will be the comparison between groups for FEV_1, SGRQ total score and all other secondary efficacy variables at Week 24 of the double-blind period and at endpoint. Endpoint will be defined as the last on-therapy evaluation in the double-blind period. Additional comparisons between treatment groups will be made for all efficacy variables at Weeks 4, 8, 12, 16, 20 and 24 of the double-blind period.

For COPD exacerbations the comparison of interest will be based on differences in the distribution of time to the first occurrence of the event.

10.5 Interim Analysis

No interim analysis is planned.

10.6 Target Sample Size

10.6.1 Sample Size Assumption

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. [18]

In order to obtain 550 completed patients, this study will randomize up to 830 patients in a ratio of 1:1 for SB 207499 to placebo. Power analyses performed for FEV_1 with the stated sample size indicate there will be greater than 90% power to detect a clinically relevant difference of 50 mL in FEV_1 assuming a standard deviation in the change from baseline at any given visit of 210 mL, a correlation between visits of 0.68 and a significance level of 0.05. A difference of 50 mL was chosen based on retrospective analysis of data from 039. These analyses demonstrated that the pre-specified choice of covariance structure led to an over-weighting of the early timepoints most likely resulting in an underestimation of the treatment effect.

10.6.2 Sample Size and Sensitivity

The power of the study 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)

Standard Deviation	Correlation	Statistical Power			
		Mean Difference (30mL)	Mean Difference (40mL)	Mean Difference (50mL)	Mean Difference (60mL)
190	0.60	59%	85%	96%	99%
190	0.65	57%	83%	95%	99%
190	0.75	54%	79%	93%	98%
190	0.80	52%	77%	90%	98%
210	0.60	51%	77%	92%	98%
210	0.65	49%	75%	91%	97%
210	0.75	47%	70%	87%	96%
210	0.80	45%	68%	84%	95%
230	0.60	44%	70%	87%	96%
230	0.65	42%	67%	85%	95%
230	0.75	40%	62%	81%	92%
230	0.80	38%	62%	77%	91%

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 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 (from protocol defined Visits 4, 5, 6, 7, 8, 9, 10) are available. An on-therapy assessment is defined as any evaluation performed within one day after the last dose of study medication in the 24-week double-blind period. The ITT population for the primary analysis of SGRQ total score 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 evaluation (from protocol defined Visits 7 or 10) are available. A similar definition will apply to all other continuous efficacy variables. For time-to-event endpoints (COPD exacerbations) the ITT population will be defined as all patients who received a dose of randomized study medication.

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 SGRQ.

Subpopulations of interest will be defined based on gender, COPD severity at study entry as defined by % of predicted FEV_1 and smoking history.

10.7.2 Statistical Methods

Efficacy Analysis

Descriptive statistics will be provided for all demographic and baseline characteristics.

All linear models to assess treatment effects for efficacy measures will be performed using SAS PROC MIXED®.

The primary assessment of treatment differences for the primary efficacy variables will be based on a repeated measures model with fixed effects for treatment, time and center. Baseline will also be included in the model as a covariate. Protocol-defined visits occurring at 2, 4, 8, 12, 16, 20 and 24 weeks of the double-blind period will be included in the analysis of FEV_1. Protocol-defined visits occurring at 12 and 24 weeks of the double-blind period will be included in the analysis of SGRQ total score. 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. Missing data will not be imputed for this analysis and treatment differences will be estimated using restricted maximum likelihood (REML). The impact of treatment-by-time interaction, treatment-by-center interaction, covariates (age, sex, disease severity), normality of the underlying data and covariance structure of the underlying data on the inference drawn from the above model will be explored. If evidence of a qualitative treatment-by-center interaction is found, exploratory analyses will be undertaken to further describe the interaction and results will be presented by center. 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. Interaction terms will be tested at a significance level of 0.10. The normality assumption will be explored through graphical examination of the residuals. Several analyses will be performed to describe the effects of dropouts on the estimation of treatment effect. Withdrawals will be characterized and

compared with the population of completed patients with respect to demographic and baseline characteristics. If there is evidence that withdrawals are not independent of response on the primary endpoints, a pattern mixture model [17] will be used to provide a weighted estimate of the treatment effect.

In addition to the repeated measures analysis, an ANOVA model with effects for treatment and center will be performed at each protocol defined double-blind visit as well as at endpoint.

All other continuous secondary efficacy variables will be analyzed using the repeated measures model described above and separately at each visit using the ANOVA model described above. Treatment-by-time and treatment-by-center interaction terms will not be assessed for secondary endpoints. The modified bonferroni procedure of Hochberg will be used to adjust the significance level in hypothesis testing for secondary endpoints. The adjustment will be made based on having two primary and four secondary endpoints. Effects on continuous tertiary endpoints will be described using the repeated measures ANOVA above but no formal hypothesis testing will be performed. First dose effects on pulmonary function parameters will be described at each timepoint using the ANOVA model described above.

Differences between groups in time to first COPD exacerbation will be assessed using the log-rank test. The exacerbation-free survival rate at 24 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, and percent-predicted FEV_1. If there are enough second exacerbations a multiple-event survival model will be used to compare the difference between two groups.

Time-to-first level 2/level 3 exacerbation will be analyzed similarly.

Use of 'as-required' (prn) albuterol recorded in CRF will also be analyzed. After collapsing patients into less than usual and more than usual groups, Fisher's Exact test will be used to describe the difference in treatment groups. Cough and sputum production will be analyzed similarly. The physicians and patients global evaluations will be collapsed into categories of improved ("very much", "much" or "minimally" improved) versus not improved ("no change", "very much worse",

"much worse" and "minimally worse"). The percentage of patients improved will be compared between groups using Fisher's exact test.

Safety Analysis

All subjects who receive at least one dose of double-blind, coded medication will be assessed for clinical safety and tolerability.

Clinical interpretation will be based upon a review of displays of laboratory values, vital signs, ECG parameters, and adverse experiences. Adverse experiences will be tabulated by relationship to study medication, severity, time of initial onset, and action taken. Summary statistics will be presented and statistical evaluation provided when appropriate.

If there is sufficient sample size, exploratory analyses may be performed to further characterize gastrointestinal adverse experiences.

Population Pharmacokinetic Analysis and PK/PD Analysis

SB-207499 and SB-217493 plasma concentration-time data will be reported/summarized in tabular and/or graphical form. Additionally, data from this study will be combined with data obtained in other relevant studies. The pooled SB-207499 plasma concentration-time data will be subjected to population pharmacokinetic (PK) analysis, using software such as NONMEM or other currently acceptable methods. Selection of specific pharmacokinetic parameters to be used for analysis will depend on the quality of the resultant data. Mean population parameters will be obtained, taking into account such variables as age, gender, weight and other concomitant medications. Inter-subject variability in these parameters will also be estimated, if the data permit. The result of this integrated population PK analysis will be reported separately from the clinical report of this study.

Steady state plasma concentrations of SB-207499 and the metabolite SB-217493 will be compared in patients with and without gastrointestinal adverse experiences that resulted in unscheduled clinic visits (and serious adverse experiences, if appropriate), using methods such as logistic regression analysis. In patients attending the clinic for these unscheduled visits, SB-207499 concentrations will be plotted relative to the previous dosing time, for graphical comparison with the expected plasma concentration profile. The metabolite:parent plasma concentration ratio in these samples will be compared graphically with the expected ratio.

Pharmacokinetic analyses will be performed by the Department of Pharmacokinetics, SmithKline Beecham Pharmaceuticals. All drug analysis and pharmacokinetic data will be stored in the Archives, Pharma-Bio (Holland) and SmithKline Beecham Pharmaceuticals, R&D, respectively.

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.

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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 fulfillment 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 recognized 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 minimize 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 judgment 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 judgment, 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 SB Medical Monitor and filed as an amendment/modification to this protocol.

Any amendment/modification to the protocol will be adhered to by the participating center (or all participating centers) 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

SB reserves the right to discontinue the clinical study at any time for medical or administrative reasons. When feasible, a 30-day written notification will be tendered.

IV. Case Report Form Instructions

Prior to screening the first potential participant, the Investigator will provide a list showing the signature and hand-written initials of all individuals authorized to make or change entries on CRFs. If the authorized individuals should change during the study, the Investigator is to inform SB.

CRFs (and patient diary cards, if applicable), will be supplied by SB 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 initialed, dated and justified by the authorized 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 randomized 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 SB 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 SB 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 SmithKline Beecham (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 SB-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 SB. 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.

SB agrees to retain a copy of the protocol, documentation, approvals and all other documents related to the study, including certificates that satisfactory audit and inspection procedures have been carried out.

VII. Audits

For the purpose of compliance with Good Clinical Practice and Regulatory Agency Guidelines, it may be necessary for SB or a Drug Regulatory Agency to conduct a site audit. This may occur at any time from start to after conclusion of the study.

When an Investigator signs the protocol, he agrees to allow the Drug Regulatory Agency and SB auditors to inspect his/her study records. Furthermore, if an

Investigator refuses an inspection, his data will not be accepted in support of a New Drug Registration and/or Application.

SB has a substantial investment in clinical studies. Having the highest quality data and studies are essential aspects of drug development. SB has a Regulatory Compliance staff who audit investigational sites. Regulatory Compliance assesses the quality of data with regard to accuracy, adequacy and consistency. In addition, Regulatory Compliance assures that SB sponsored-studies are 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 SB audits entail review of source documents supporting the adequacy and accuracy of CRFs, review of documentation required to be maintained, and checks on drug accountability. The SB audit, therefore, helps prepare an Investigator for a possible regulatory agency inspection, as well as assuring SB of the validity of the database across investigational sites.

The Inspector will be especially interested in the following items:

- Log of visits from the sponsor's representatives
- ERC/IRB 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/IRB and the sponsor
- Record retention

SB will gladly assist Investigators prepare for an inspection.

VIII. Confidentiality And Publication

You agree that all information communicated to you by SB is the exclusive property of SB 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 SB. You shall communicate the results of the work promptly to SB.

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 SB Medical Monitor prior to submission. SB will undertake to comment on such documents within four weeks.

All rights and interests world-wide in any inventions, know-how or other intellectual or industrial property rights which arise during the course of and/or as a result of the clinical study which is the subject of this Protocol or which otherwise arise from the information or materials supplied under this Agreement, shall be assigned to, vest in and remain the property of SmithKline Beecham plc.

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 Consent (Written or Oral Witnessed as appropriate)

INVESTIGATOR:

CLINICAL STUDY TITLE:	A randomized, 24-week, double-blind, placebo-controlled, parallel group study to evaluate the efficacy, safety and tolerability of Ariflo™ (15 mg BID) in patients with Chronic Obstructive Pulmonary Disease (COPD)
PROTOCOL NO:	SB 207499/156
SPONSOR:	SmithKline Beecham Pharmaceuticals ("The Company")
DATA CONTROLLER:	SmithKline Beecham Pharmaceuticals, Inc.

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 SmithKline Beecham Pharmaceuticals (SB) to investigate the safety and effectiveness of Ariflo. Ariflo 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.

Ariflo 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 Ariflo, 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 29 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 Ariflo
Treatment Group 2: Placebo (inactive tablets)

Although in every way they look like the active Ariflo 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 albuterol inhalers to take home with you. Albuterol 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.

Up to 830 patients at about 140 centers in North America will take part in this study.

You will be expected to visit the doctor's office at least 11 times at approximately the same time of day (10:00 a.m. ± 2 hours). 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 and 10 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. At two of these visits (Visit 3 and Visit 10), you will need to remain at your doctor's office or the clinic for at least 4 and a half hours since you will have 6 pulmonary ("breathing" or "blowing") function tests done. 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 fecal matter (stools) using test kits provided between Visits 1 and 3, between Visits 9 and 10, 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 hemorrhoids 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 10 mL (2 teaspoons) of blood will be taken through a needle from a vein for laboratory tests at 8 (and possibly 9) 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 3 visits. Urine samples for laboratory tests will be obtained at 8 and (possibly 9 visits). In addition, blood will be drawn to measure the amount of Ariflo in your blood. One sample of blood will be drawn at visit 3. Two samples will be drawn at Visit 5 and Visit 7. At Visit 5, you will need to stay at your doctor's office or the clinic, or you may be asked to return to the office or clinic for one blood sample that will be taken at any one time immediately after or up to 3 hours after you took your study medication. At Visit 7, you will need to stay at your doctor's office or the clinic, or you may be asked to return to the office or clinic for one blood sample that will be taken at any one time from 3 to 10 hours after you took your study medication. One sample will be drawn at Visit 10.

If you have severe COPD, blood will be taken through a needle from an artery in your wrist at 2 visits.

If you have an adverse event that your doctor considers serious, you may have blood taken to measure the amount of Ariflo in your blood.

You will walk for 6 minutes on a level surface at 9 visits to look at how well your lungs work when you exercise. After walking, your heart rate will be measured and the amount of oxygen in your bloodstream will be measured through your skin with a device clipped on your ear or finger. You will also be asked how short of breath you feel after exercising.

You will be asked to use a diary to write down if you feel different in any way since starting the study medication. The information in the diaries is very important.

The sponsor of the study or their representative may contact your doctor(s) and hospital(s) to obtain copies of your medical bills for 8 months following the date of your enrollment in this study. The information will be used to determine if taking Ariflo results in changes in the medical costs associated with your condition. This information is useful to determine whether Ariflo reduces the cost of medical care associated with your condition.

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 Ariflo.

In animal studies, the administration of Ariflo 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 Ariflo.

In previous research with Ariflo, more than 4000 people have participated in Ariflo 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 diarrhea, vomiting, and abdominal pain have also been noted in humans taking Ariflo.

In the interest of your safety, SB is researching these gastrointestinal complaints. If you experience black or bloody stools, abdominal discomfort, such as pain or cramps, diarrhea, or vomiting that cause you concern or interfere with daily activities (including eating or sleeping), you will be asked to contact your Investigator and you will visit the clinic within 24 hours. You will be given fecal occult blood test kits to be used at home if you experience a gastrointestinal complaint(s) of concern, that is, gastrointestinal symptoms that interfere with your daily activities or your ability to sleep. You must return the fecal occult blood test to the clinic when you go there for the evaluation of the complaint.

At the clinic, your doctor will discuss the complaint with you, complete a physical examination of the abdomen, measure your blood pressure in the lying and sitting positions and review the results of the fecal occult blood test that you performed at home. If you were not able to supply a fecal sample for the test, the doctor will obtain a sample by a rectal exam. The study doctor will ask if you have been menstruating, had bleeding hemorrhoids, or had blood in the urine, and will also question you about the medications, vitamins, and foods you have been taking. Blood will be drawn and you will give a sample of urine.

If the fecal occult blood test (or digital rectal exam) 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. The colonoscopy should be performed as

soon as possible, within 10 to 14 days after the clinic visit. 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 Ariflo 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 Ariflo. The relationship between these side effects and Ariflo or the study plan is uncertain, because the side effects have been seen in study patients receiving placebo as well as in patients receiving Ariflo.

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.

During the walk for 6 minutes, there is a small risk of abnormal blood pressure (up or down), fainting, disorders of the heart beat (too fast or too slow), and heart attack.

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 Ariflo cannot be ruled out at this time.

In order to evaluate the potential risk of giving Ariflo to women of childbearing potential if pregnancy should occur while taking Ariflo, studies were completed in pregnant animals. Ariflo 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 Ariflo, 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 Ariflo 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 Ariflo 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 Ariflo 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 SmithKline Beecham 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 SmithKline Beecham (or an agent of SmithKline Beecham) with access limited to appropriate SmithKline Beecham staff or other authorized 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.

SmithKline Beecham 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 Institutional Review Board (IRB) which operates independently of the Sponsor and the Investigator (study doctor). IRBs are primarily concerned with protecting the safety and rights of people who volunteer to participate as investigational research subjects. If you have questions about your rights as a research subject, you may contact:

[redacted] Institutional Review Board (IRB)

[redacted]
[redacted]
Telephone: [redacted]
Collect calls will be accepted.

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 a total of $_____ if you complete the entire study. If you do not complete the entire study, you will receive $_____ for every scheduled study visit you complete. The Sponsor will reimburse you for any additional 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. The FDA may also terminate your participation.

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 cooperate 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: _____

Appendix D Predicted FEV_1 Equations

Predicted FEV_1 (liters):

Females

$FEV_1 = 0.0342H - 0.0255A - 1.578$

Males

$FEV_1 = 0.0414H - 0.0244A - 2.190$

where H = height in cm
A = age in years

Reference

Crapo RO, Morris AH & Gardiner RM. Reference Spirometric Values Using Techniques and Equipment that Meet ATS Recommendations. Am Rev Respir Dis 1981; 123: 659 - 664.

Appendix E The SF-36 Health Survey Questionnaire

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

Appendix F The St. George's Respiratory Questionnaire

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

Appendix G ATS Guidelines for the Diagnosis of COPD

The diagnosis of COPD, as defined by the American Thoracic Society, is described below:

History

- Smoking: age at initiation, quantity smoked per day, whether or not still smoking (if not, date of cessation)
- Environmental (chronological): may disclose important risk factors
- Cough (chronic, productive): frequency and duration, whether or not productive (especially on awakening), presence or absence of blood
- Wheezing
- Acute chest illnesses: frequency, productive cough, wheezing, dyspnea, fever
- Dyspnea

Physical Examination

- Chest:
  Airflow obstruction evidenced by:
  -Wheezing during auscultation on slow or forced breathing
  -Prolongation of forced expiratory time
  Severe emphysema indicated by:
  -Overdistention of lungs in stable state, low diaphragmatic position
  -Decreased intensity of breath and heart sounds
  Severe disease suggested by (characteristic, not diagnostic):
  -Pursed lip breathing
  -Use of accessory respiratory muscles
  -Indrawing of lower interspaces
- Other: unusual positions to relieve dyspnea at rest, digital clubbing (suggests possibility of lung cancer or bronchiectasis), mild dependent edema (may be seen in absence of right heart failure)

Laboratory

- Chest radiography: diagnostic only of severe emphysema but essential to exclude other lung diseases
- Spirometry (pre- and post-bronchodilator): essential to confirm presence and reversibility of airflow obstruction and to quantify maximum level of ventilatory function
- Lung volumes: measurement of more than forced vital capacity not necessary except in special instances (e.g., presence of giant bullae)
- Carbon monoxide diffusing capacity: not necessary except in special instances (e.g., dyspnea out of proportion to severity of airflow limitation)
- Arterial blood gases: not needed in Stage I airflow obstruction (FEV_1 ≥50% predicted) essential in stages II and III airflow obstruction (FEV_1 <50% predicted); in very severe airflow obstruction, major monitoring tool

Appendix H Gastrointestinal Adverse Event Monitoring

H1. 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, diarrhea, vomiting) which cause the patient concern or interfere with usual activity (including eating and sleeping) at any time during the study. These symptoms should be recorded on the patient's diary card. 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 SB 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 health care provider. Any deterioration in the patient's condition discovered at a follow-up assessment that is performed by a health care provider other than the Investigator must be reported to the Investigator by telephone immediately. All results of follow-up assessments performed by a health care 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 judgment 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 anemia or gastrointestinal bleeding, vomiting, unexplained weight loss, dysphagia, an abdominal mass or lymphadenopathy or peritoneal signs.

H2. Assessments of Gastrointestinal Adverse Events

H2.1 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, diarrhea, vomiting) which cause the patient concern or interfere with usual activity (including sleeping or eating). The assessment must include a history, physical examination, laboratory assessment, and pharmacokinetic assessment, as outlined below. Patients who have a positive fecal occult blood test or melena during the randomized treatment phase of the study must be referred to a gastroenterologist for a colonoscopy as soon as possible, within 10 to 14 days of the clinic visit. 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:

- Fecal occult blood (may use self sample kit or rectal examination)
- Complete blood count with differential
- Urinalysis
- Amylase
- Electrolytes
- Blood glucose
- Liver function tests

Pharmacokinetic assessment:

A blood sample will be collected for pharmacokinetic (PK/PD) analysis of SB-207499 and SB-217493 plasma concentrations as close to the time of onset of the gastrointestinal adverse event as possible, that is, as soon as possible following presentation to the clinic.

Follow-up and Notification

All gastrointestinal adverse events (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhea, vomiting) which cause the patient concern or interfere with usual activity (including eating and sleeping) will be reported to the SmithKline Beecham Medical Monitor within 24 hours of initial assessment. These adverse events will be monitored daily until resolution as specified in I2.2.

Additional Testing

Referral to a gastroenterologist is mandatory if the patient has a positive fecal occult blood test or melena during the randomized treatment phase of the study. The colonoscopy must be performed as soon as possible, within 10 to 14 days of the clinic visit. It must be **complete** with emphasis on visualization 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.

H2.2 Daily Follow-up Assessments

Patients who report gastrointestinal adverse events that cause them concern or interfere with usual activity will be assessed daily until the adverse event resolves. Patients can return to the clinic for these evaluations or the Investigator may designate a qualified health care provider to perform the follow-up assessments. These assessments will include an interim 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.
- Fecal occult blood test (self sample kit or rectal examination).

Additional Testing:

Referral to a gastroenterologist is mandatory if the patient has a positive fecal occult blood test or melena during the randomized treatment phase of the study. The colonoscopy must be performed as soon as possible, within 10 to 14 days of the clinic visit. It must be **complete** with emphasis on visualization 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.

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- Rectal/pelvic examination
- Ultrasound of abdomen
- CT of abdomen
- Stool for ova and parasites
- Other diagnostic tests as deemed necessary by the Investigator
- Consider withdrawal for patients with severe or persistent symptoms that may be drug related.
- Referral to gastroenterologist, surgeon, or other specialist

If additional tests are performed, reports should be faxed to the Sponsor as soon as available.

Confidential

SmithKline Beecham

Ariflo™

SB 207499

Statistical Analysis Plan

Protocol 156

A Randomized, 24-week Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy, Safety and Tolerability of Ariflo™ (15 mg BID) in Patients with Chronic Obstructive Pulmonary Disease (COPD)

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November 27, 2000

Endorsements

Title: Statistical Analysis Plan

Table of Contents

1 Introduction 7
2 Objectives 7
3 Hypothesis 7
3.1 Null Hypothesis 8
3.2 Alternative Hypothesis 8
4 Key Definitions and Data Handling Conventions 8
4.1 Key Derivations and Calculations 8
4.1.1 Randomized Patient 8
4.1.2 Relative Day 8
4.1.2.1 Relative Day of Scheduled Assessment 8
4.1.2.2 Relative Day of Events (Adverse Events, Exacerbations) 8
4.1.3 Study Medication Record 9
4.1.3.1 Date of First Dose in the Double-blind Period 9
4.1.3.2 Date of Last Dose in the Double-blind Period 9
4.1.3.3 Exposure to Double-blind Study Medication 9
4.1.4 Compliance 9
4.1.4.1 Number of Tablets Consumed 9
4.1.4.2 Number of Days Between Visits 9
4.1.4.3 Visit Level Compliance 9
4.1.4.4 Days of Available Compliance Data 9
4.1.4.5 Overall Compliance 10
4.1.5 Visit Dates 10
4.1.6 Prior, Concomitant and Post-therapy Medications 10
4.1.6.1 Prior Medications 10
4.1.6.2 Concomitant Medications 10
4.1.6.3 Post-therapy Medications 10
4.1.7 Pulmonary Function Tests (PFTs) 10
4.1.7.1 Baseline PFTs 10
4.1.7.2 Repeat PFTs 11
4.1.7.3 Endpoint PFTs 11
4.1.7.4 Rules for Choosing Specific PFT Values for Analysis 11
4.1.8 Saint George's Respiratory Questionnaire (SGRQ) 11
4.1.8.1 Baseline SGRQ 11
4.1.8.2 Endpoint SGRQ 12
4.1.8.3 Treatment of Missing Values on SGRQ 12
4.1.8.4 Multiple Responses on SGRQ 12
4.1.9 SF-36 12

4.1.9.1 Baseline for SF-36 12
4.1.9.2 Treatment of Missing Values for SF-36 12
4.1.9.3 Multiple Responses for SF-36 12
4.1.10 COPD Exacerbations and Health Care Resource Utilization 12
4.1.11 Pooling of Centers for Efficacy Analysis 13
4.1.12 Adverse Events 13
4.1.12.1 Run-in Adverse Event (Baseline Sign and Symptom) 13
4.1.12.2 On-therapy Adverse Event 13
4.1.12.3 Post-therapy Adverse Event 13
4.1.12.4 Adverse Event Leading to Withdrawal 14
4.1.12.5 Adverse Event with Missing Onset Date 14
4.1.13 Electrocardiographs (ECGs) 14
4.1.13.1 Baseline ECGs 14
4.1.13.2 On-therapy ECGs 14
4.1.13.3 Duplicate ECGs 14
4.1.13.4 Worst-case On-therapy ECGs 14
4.1.13.5 New-onset ECG Finding 14
4.1.14 Clinical Laboratories 15
4.1.14.1 Baseline Labs 15
4.1.14.2 On-therapy Labs 15
4.1.14.3 Duplicate Labs 15
4.1.14.4 Worst-case On-therapy Labs 15
4.1.15 Orthostatic Vital Signs 15
4.1.15.1 Calculation of Orthostatic Changes 15
4.1.15.2 Baseline Orthostatic Vital Sign Change 16
4.1.15.3 On-therapy Orthostatic Vital Sign Change 16
4.1.15.4 Duplicate Orthostatic Vital Sign Change 16
4.1.15.5 Worst-case On-therapy Orthostatic Vital Sign Change 16
4.1.16 Sitting Vital Signs 16
4.1.16.1 Baseline Vital Signs 16
4.1.16.2 On-therapy Vital Signs 16
4.1.16.3 Duplicate Vital Signs 16
4.1.16.4 Worst-case On-therapy Vital Signs 17
4.2 Values of Clinical Concern 17
4.3 Protocol Violations 20
4.3.1 Violations of Eligibility Criteria 20
4.3.2 Excluded Medication Protocol Violations 21
4.3.3 Visit Specific Protocol Violations 22
4.3.4 Conduct of Study Deviations 22

4.4 Biometrics QC of Output 23
5 Analysis Populations and Analysis Datasets 23
5.1 Intent-to-treat (ITT) Population 23
5.2 Per-protocol (PP) Population 23
5.3 Sub-populations of Interest 23
6 Comparisons of Interest 24
6.1 Primary Comparisons of Interest 24
6.2 Other Comparisons of Interest 24
7 Targeted Sample Size 25
7.1 Sample Size Sensitivity 25
7.2 Sample Size Re-estimation 26
8 Definition of Variables Assessments 27
8.1 Primary Efficacy Variables 27
8.2 Other Variables 27
8.2.1 Secondary Endpoint Variables 27
8.2.2 Additional Tertiary Variables 27
9 Statistical Methodology 28
9.1 Patient Disposition, Baseline Characteristics and Demography 28
9.2 Efficacy Analysis 29
9.2.1 Analysis of Primary Efficacy 29
9.2.1.1 Primary Analysis of FEV_1 and SGRQ 29
9.2.1.2 Sensitivity Analyses to Assess Impact on Primary Analysis 29
9.2.2 Multiplicity 31
9.2.3 Analysis of Secondary Efficacy 31
9.2.4 Pharmacoeconomic Analysis 32
9.2.5 Interim Analysis 32
9.2.6 Meta-Analysis 32
9.3 Safety Analysis 32
9.3.1 Adverse Experiences 32
9.3.2 Clinical Laboratories 33
9.3.3 Vital Signs 33
9.3.4 Electrocardiographs 33

List of Tables

Table 1 Laboratory Values of Interest and Potential Clinical Concern 17
Table 2 Vital Sign Values of Interest and Potential Clinical Concern 18
Table 3 Electrocardiographic Values of Interest and Potential Clinical Concern 20
Table 4 Sample Size Sensitivity (sample size = 275/arm).....26

1 Introduction

Study 156 is being conducted as a pivotal Phase 3 study to assess the efficacy and safety of Ariflo™ versus placebo in patients with COPD. This is a double-blind, placebo controlled, randomized, parallel group study requiring a maximum of 12 visits over a 29-week period. A 4-week single-blind placebo run-in period will be followed by 24 weeks of treatment with double-blind study medication. A follow-up visit will be conducted within 7 ± 3 days of the completion of the 24-week double-blind phase or withdrawal from the study. Patients eligible to enter the double-blind period must meet the Randomization Criterion as defined in the protocol. Qualifying patients will be randomized in a 1:1 ratio to receive either Ariflo™ 15 mg or matching placebo tablets twice daily.

2 Objectives

The primary objective of the study is to demonstrate the clinical efficacy of Ariflo™ (15 mg BID) versus placebo by assessment of forced expiratory volume in 1 second (FEV_1) at trough drug levels and the total score of the St. George's Respiratory Questionnaire (SGRQ) over 24 weeks in patients with COPD.

The secondary objectives of the study are to examine risk of exacerbations and to compare the clinical efficacy of Ariflo™ versus placebo on additional pulmonary function tests (clinic trough measurements) and other clinical evaluations (e.g. breathlessness).

The additional objective of the study is to further define the clinical safety and tolerability of Ariflo™ through the assessment of adverse events, vital signs, clinical laboratory tests, and electrocardiograms (ECGs).

3 Hypothesis

The primary hypothesis of this study is based on demonstrating the superiority of Ariflo™ to placebo with respect to both FEV_1 and SGRQ.

3.1 Null Hypothesis

The null hypothesis is based on a two-tailed test H_0: $\mu_{ic} = \mu_{ip}$ for all i=1,2 where μ_{1c} is defined as the mean of the average change in FEV_1 for Ariflo™ and μ_{2c} is the mean of the average change in SGRQ for Ariflo™ over all double-blind visits and μ_{1p} and μ_{2p} are defined similarly for placebo.

3.2 Alternative Hypothesis

The alternative hypothesis is H_α: $\mu_{ic} \neq \mu_{ip}$ for both i=1 and 2, where μ_{ic} and μ_{ip} are defined similarly as above.

4 Key Definitions and Data Handling Conventions

4.1 Key Derivations and Calculations

4.1.1 Randomized Patient

Any patient who is confirmed to receive at least one dose of double-blind study medication and has a randomization id number assigned.

4.1.2 Relative Day

4.1.2.1 Relative Day of Scheduled Assessment

(date of assessment) – (date of first dose of double-blind study medication) + 1

4.1.2.2 Relative Day of Events (Adverse Events, Exacerbations)

(onset date of event) – (date of first dose of double-blind study medication) + 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.

4.1.3 Study Medication Record

4.1.3.1 Date of First Dose in the Double-blind Period

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

4.1.3.2 Date of Last Dose in the Double-blind Period

The later of the date provided in the study medication record, the date and time of the in-clinic dose at Visit 10 and the date provided on the study conclusion page of the case report form (CRF).

4.1.3.3 Exposure to Double-blind Study Medication

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

Randomized patients for whom a date of first dose in the double-blind period is not available but are confirmed to have received a dose of double-blind study medication will have an assumed exposure of one day.

4.1.4 Compliance

4.1.4.1 Number of Tablets Consumed

n(tablets dispensed) – n(tablets returned) – n(tablets lost)

4.1.4.2 Number of Days Between Visits

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

4.1.4.3 Visit Level Compliance

$$\frac{100 * (\text{number of tablets consumed})}{2 * (\text{number of days between visits})}$$

4.1.4.4 Days of Available Compliance Data

The number of days for which compliance data is available during the double-blind period.

4.1.4.5 Overall Compliance

$$\frac{100 * \sum(\text{number of tablets consumed})}{2 * (\text{days of available compliance data})}$$

4.1.5 Visit Dates

The date for each visit will be defined as the date recorded at each visit denoted as the date and time the patient presented to the clinic. If this date is not available, the date that standard vital signs were recorded will be used.

4.1.6 Prior, Concomitant and Post-therapy Medications

4.1.6.1 Prior Medications

Any medication used prior to the Randomization Visit (Visit 3) including those which continued beyond the date of first dose of double-blind study medication.

4.1.6.2 Concomitant Medications

Any medication initiated on 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.

4.1.6.3 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.

4.1.7 Pulmonary Function Tests (PFTs)

4.1.7.1 Baseline PFTs

The evaluation performed at Visit 3. Pulmonary function tests occurring greater than ten minutes after the first dose of double-blind study medication are not considered for baseline.

4.1.7.2 Repeat PFTs

When pulmonary function tests are repeated for a particular visit, the later of the two assessments will be used in the analysis.

4.1.7.3 Endpoint PFTs

For each PFT, 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. On-therapy baseline assessments will not be considered for endpoint.

4.1.7.4 Rules for Choosing Specific PFT Values for Analysis

- **FEV_1** – The best FEV_1 value from technically acceptable loops will be used. Technically acceptable loops will be designated by the investigator and/or the vendor used to gather and process pulmonary function test data; only technically acceptable loops will be made available to Data Ops and Biometrics for analysis. The best FEV_1 value will be identified as the loop where the variable READING on the raw data is equal to "1".

- **FVC** – The maximum FVC value from technically acceptable loops will be used. Note, not necessarily the same loop from which FEV_1 is selected.

- **PEFR** – The maximum PEFR value from technically acceptable loops will be used. Note, not necessarily from the same loop from which either FEV_1 or FVC is selected.

- **FEF_{25-75}** – The FEF_{25-75} value used in the analysis will be selected from the technically acceptable loop with the maximum summed value of FEV_1 and FVC. If two technically acceptable loops have the same summed value of FEV_1 and FVC, the maximum FEF_{25-75} from these two loops will be selected. If FEF_{25-75} is not available from the technically acceptable loop with this maximum summed value of FEV_1 and FVC, the value of FEF_{25-75} will be treated as missing for this visit in the analysis.

4.1.8 Saint George's Respiratory Questionnaire (SGRQ)

4.1.8.1 Baseline SGRQ

The evaluation performed at Visit 3.

4.1.8.2 Endpoint SGRQ

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.

4.1.8.3 Treatment of Missing Values on SGRQ

Missing values in Part 1 of the questionnaire will be assigned a weight of 0 provided at least one of the items in Part 1 was answered. If none of the items was answered in Part 1 the entire section will be set to missing as will the total score. Missing values in Part 2 of the questionnaire will not be considered in the calculation of the denominator. If more than 10 items are missing in Part 2, the entire portion of the questionnaire is invalidated and set to missing.

4.1.8.4 Multiple Responses on SGRQ

If multiple responses are available for a particular item, the average **weight** for that item will used in the analysis.

4.1.9 SF-36

4.1.9.1 Baseline for SF-36

The evaluation performed at Visit 3.

4.1.9.2 Treatment of Missing Values for SF-36

For those items that are missing, the average across all completed items in the same scale will be imputed. If a respondent leaves more than 50% of the items blank within a scale, then no imputation will be performed.

4.1.9.3 Multiple Responses for SF-36

If multiple responses are available for a particular item, the average score for that item will be used in the analysis.

4.1.10 COPD Exacerbations and Health Care Resource Utilization

Only those exacerbations with an onset date on or after the first dose of double-blind study medication and no later than one day after the last 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 classified as on-therapy. A censored patient for an event will be defined as any patient for whom the event is not observed during the on-therapy period. For patients who are censored, the time to event is defined as the total number of days of exposure to double-blind study medication. An identical approach will be adopted for events associated with healthcare resource utilization.

4.1.11 Pooling of Centers for Efficacy Analysis

Centers with less than four randomized patients will be pooled according to geographic region as follows:

Region 1: centers in [redacted]
Region 2: centers in [redacted]

Region 3: centers in [redacted]
Region 4: centers in [redacted]

Region 5: all centers in Canada.

4.1.12 Adverse Events

4.1.12.1 Run-in Adverse Event (Baseline Sign and Symptom)

Any event with an onset date prior to the initial dose of double-blind study medication. For events occurring on the date of initial dose of randomized 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.

4.1.12.2 On-therapy Adverse Event

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 classified as on-therapy.

4.1.12.3 Post-therapy Adverse Event

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

4.1.12.4 Adverse Event Leading to Withdrawal

Any event where the "withdrawn" field is checked as "Yes".

4.1.12.5 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.

4.1.13 Electrocardiographs (ECGs)

4.1.13.1 Baseline ECGs

The last ECG evaluation prior to receiving the first dose of double-blind study medication. Visit 3 trough assessments occurring greater than fifteen minutes after first dose of double-blind study medication will not be considered for baseline.

4.1.13.2 On-therapy ECGs

Any ECG 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.

4.1.13.3 Duplicate ECGs

In cases where multiple ECGs are available for a given visit the later of the two assessments will be taken. If a later evaluation can not reasonably be determined based on date and/or time then the average of the two assessments will be taken.

4.1.13.4 Worst-case On-therapy ECGs

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.

4.1.13.5 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 trough assessments).

4.1.14 Clinical Laboratories

4.1.14.1 Baseline Labs

The last laboratory evaluation prior to receiving the first dose of double-blind study medication. The last evaluation will be determined as that laboratory evaluation performed closest to or on the date of the randomization visit. Laboratories collected in association with Gastro-intestinal Adverse Events (GI AEs) of concern on the date of the randomization visit or prior to the date of the randomization visit will not be considered for baseline.

4.1.14.2 On-therapy Labs

Any Clinical laboratory performed after the first dose of randomized study medication and no later than one day after the last dose of randomized study medication. Visit 3 labs associated with GI AEs of concern will also be considered on-therapy.

4.1.14.3 Duplicate Labs

In cases where multiple labs are available for a given on-therapy visit the later of the two assessments will be taken. If a later evaluation can not reasonably be determined based on date and/or time then the average of the two assessments will be taken.

4.1.14.4 Worst-case On-therapy Labs

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.

4.1.15 Orthostatic Vital Signs

4.1.15.1 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:

$$\text{Orthostatic Change} = \text{measurement}_{\text{dependent}} - \text{measurement}_{\text{supine}}$$

4.1.15.2 Baseline Orthostatic Vital Sign Change

The last evaluation prior to receiving the first dose of double-blind study medication. As date and time are not available for orthostatic vital signs, all orthostatic vital sign measurements collected on or prior to Visit 3 will be considered for baseline.

4.1.15.3 On-therapy Orthostatic Vital Sign Change

Any evaluation 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.

4.1.15.4 Duplicate Orthostatic Vital Sign Change

In cases where multiple evaluations are available for a given visit the later of the two assessments will be taken. If a later evaluation can not reasonably be determined based on date and/or time then the average of the two assessments will be taken.

4.1.15.5 Worst-case On-therapy Orthostatic Vital Sign Change

This is defined as the result with the highest concern level observed during the double-blind treatment period.

4.1.16 Sitting Vital Signs

4.1.16.1 Baseline Vital Signs

The last evaluation prior to receiving the first dose of double-blind study medication. Assessments at Visit 3 occurring greater than fifteen minutes after the first dose of double-blind study medication will not be considered for baseline.

4.1.16.2 On-therapy Vital Signs

Any evaluation 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.

4.1.16.3 Duplicate Vital Signs

In cases where multiple evaluations are available for a given visit the later of the two assessments will be taken. If a later evaluation can not reasonably be

determined based on date and/or time then the average of the two assessments will be taken.

4.1.16.4 Worst-case On-therapy Vital Signs

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.

4.2 Values of Clinical Concern

Table 1 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 10^3/mm^3	(3.0 x 10^3/mm^3 – 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 10^9/L	[100 x 10^9/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

Parameter	Low Value of Concern	Low	High	High Value of Concern
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
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 2 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 3 Electrocardiographic Values of Interest and Potential Clinical Concern

Parameter	Low Concern	Low	High	High Concern
QRS interval	not defined	not defined	100 – 199	≥ 200 msec
PR interval	not defined	not defined	200 – 249	≥ 250 msec
Atrial rate	< 50 bpm	50 – 59 bpm	100 – 120 bpm	> 120 bpm
Ventricular rate	< 50 bpm	50 – 59 bpm	100 – 120 bpm	> 120 bpm
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
Uncorrected QT change from baseline	not defined	not defined	not defined	increase > 500 msec

4.3 Protocol Violations

4.3.1 Violations of Eligibility Criteria

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

- Patients previously randomized in an Ariflo™ study
- Pre-albuterol/salbutamol FEV_1/FVC ratio > 0.7 at Visit 1
- Increase in FEV_1 of >15% and 200 ml following albuterol/salbutamol at Visit 1

- Post-albuterol/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-albuterol/salbutamol clinic FEV_1 between Visits 1 and 3

4.3.2 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/albuterol 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/albuterol 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

- 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)

4.3.3 Visit Specific Protocol Violations

For these violations, primary efficacy data collected at the visit the violation occurred at 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

4.3.4 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)

4.4 Biometrics QC of Output

All data marts, analysis datasets and output will be reviewed per the biometrics QC SOP (BIO.802) and DART procedures.

5 Analysis Populations and Analysis Datasets

5.1 Intent-to-treat (ITT) Population

The intent-to-treat population for the primary analysis of FEV_1 will include all patients who are randomized and for whom a baseline and at least one on-therapy FEV_1 assessment (from protocol defined visits 4, 5, 6, 7, 8, 9, 10) are available. An on-therapy assessment is defined as any evaluation performed within one day after the last dose of study medication in the 24-week double blind period. The ITT population for the primary analysis of SGRQ total score 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 evaluation (from protocol defined visits 7 or 10) are available. A similar definition will apply to all other continuous efficacy variables. For time-to-event endpoints (COPD exacerbations) the ITT population will be defined as all patients who received a dose of randomized study medication.

5.2 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. Data will be excluded as described in Section 4.3. Analyses for the per-protocol population will be restricted to FEV_1 and SGRQ.

5.3 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** – [Non-smoker throughout, Smoker throughout]
- **Center** – [Centers utilized in Ariflo™ study 039, Centers not utilized in Ariflo™ study 039]

Note: The smoking status sub-populations of interest do not capture patients with changes in smoking status during the study.

6 Comparisons of Interest

6.1 Primary Comparisons of Interest

The primary comparisons will be based on two-tailed tests of hypothesis. A comparison will be done for the difference in change from baseline in pre-bronchodilator FEV_1 between the Ariflo™ group and the placebo group (Ariflo™ – Placebo) averaged over all double-blind visits (protocol defined Visits 4, 5, 6, 7, 8, 9, 10) in the intent-to-treat population. The second primary comparison will be done for the difference in change from baseline in total score of the SGRQ between the Ariflo™ group and the placebo group (Ariflo™ – Placebo) averaged over all double-blind visits (protocol defined Visits 7 and 10) in the intent-to-treat population. Each of the primary comparisons will be performed at an alpha level of 0.05.

6.2 Other Comparisons of Interest

Other comparisons of interest will be the comparison between groups for pre-bronchodilator FEV_1, SGRQ total score and all other secondary efficacy variables at Week 24 of the double-blind period and at endpoint. Endpoint will be defined as the last on-therapy evaluation in the double-blind period. Additional comparisons between treatment groups will be made for all efficacy variables at Weeks 2, 4, 8, 12, 16, 20 and 24 of the double-blind period.

For COPD exacerbations the comparison of interest will be based on differences in the distribution of time to the first occurrence of the event.

An additional comparison of interest will be the comparison of post-bronchodilator FEV_1 at Week 24.

7 Targeted Sample Size

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 randomize a total of 740 patients in a ratio of 1:1 for Ariflo™ to placebo. Power analyses performed for FEV_1 with the stated sample size indicate 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, a correlation between visits of 0.68 and a significance level of 0.05. There will also be a power of greater than 90% to detect a difference of 4 units (empirically defined as the minimum clinically important difference) in SGRQ assuming a standard deviation of 12 units.

7.1 Sample Size Sensitivity

The power of the study 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.

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[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 4 Sample Size Sensitivity (sample size = 275/arm)

		Statistical Power			
Standard Deviation	Correlation	Mean Difference (30 mL)	Mean Difference (40 mL)	Mean Difference (50 mL)	Mean Difference (60 ml)
190	0.60	59%	85%	96%	99%
190	0.65	57%	83%	95%	99%
190	0.75	54%	79%	93%	98%
190	0.80	52%	77%	90%	98%
210	0.60	51%	77%	92%	98%
210	0.65	49%	75%	91%	97%
210	0.75	47%	70%	87%	96%
210	0.80	45%	68%	84%	95%
230	0.60	44%	70%	87%	96%
230	0.65	42%	67%	85%	95%
230	0.75	40%	62%	81%	92%
230	0.80	38%	62%	77%	91%

7.2 Sample Size Re-estimation

There is no planned sample size re-estimation for this study.

8 Definition of Variables Assessments

8.1 Primary Efficacy Variables

The primary variables in this study are the change from baseline in trough forced expiratory volume in one second (FEV_1) and the change from baseline in total score on the St. George's Respiratory Questionnaire (SGRQ).

8.2 Other Variables

8.2.1 Secondary Endpoint Variables

There are four secondary endpoints in this study:

- Change from baseline in Clinic FVC at trough. FVC provides complementary information to FEV_1 with respect to lung function.
- Time to first COPD exacerbation.
- Time to first level 2 or level 3 COPD exacerbation. These are exacerbations associated with some form of physician contact including ER visits and hospitalization.
- Post-exercise breathlessness.

8.2.2 Additional Tertiary Variables

The following tertiary variables are being collected:

- First dose effect for FEV_1, FVC, PEFR and FEF_{25-75}
- Clinic trough PEFR
- Clinic trough FEF_{25-75}
- Use of 'as-required' (PRN) albuterol recorded on the CRF according to the following categories:
  - → Much less than usual
  - → Less than usual
  - → About the same as usual
  - → More than usual
  - → Much more than usual
- SGRQ subscales (symptoms, activities, impacts)

- Quality of life assessment (SF-36)
- Health economic endpoints (impact on activities, health care utilization)
- Global patient assessment
- Global investigator assessment
- Exercise performance (distance walked) during the exercise tolerance test (a six minute walk with encouragement)
- Overall dyspnea (on a modified Borg scale) during usual activities
- Exertional (post-exercise) dyspnea (on a modified Borg scale)
- Post exercise SaO_2
- SaO_2 at rest in patients with FEV_1 of <40% predicted for age, height and gender
- Arterial blood gases, PO_2 and PCO_2 in patients with FEV_1 of <40%, living at high altitudes or having a resting SaO_2 <88%
- Cough assessment
- Sputum Assessment
- Post-bronchodilator assessments of FEV_1, FVC, FEF_{25-75} and PEFR

9 Statistical Methodology

9.1 Patient Disposition, Baseline Characteristics and Demography

The distribution of time to withdrawal will be estimated using the Kaplan-Meier product limit. Baseline and demographic characteristics will be summarized using frequencies and percents as well as descriptive statistics. No hypothesis testing will be 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 WHO dictionary. The number and percentage of patients will be summarized according to generic terms.

Patient compliance will be calculated as described in Section 4 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.

9.2 Efficacy Analysis

9.2.1 Analysis of Primary Efficacy

All linear models to assess treatment effects for efficacy measures will be performed using SAS procedure MIXED. Centers randomizing less than four patients will be appropriately combined based upon their geographical location as described in Section 4.

9.2.1.1 Primary Analysis of FEV_1 and SGRQ

The primary assessment of treatment differences for the primary efficacy variables will be based on a repeated measures model with fixed effects for treatment, time and center[2]. Baseline will also be included in the model as a covariate. Protocol-defined visits occurring at 2, 4, 8, 12, 16, 20 and 24 weeks of the double-blind period will be included in the analysis of FEV_1. Protocol-defined visits occurring at 12 and 24 weeks of the double-blind period will be included in the analysis of SGRQ total score. 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. Missing data will not be imputed for this analysis and treatment differences will be estimated using restricted maximum likelihood.

9.2.1.2 Sensitivity Analyses to Assess Impact on Primary Analysis

Sensitivity analyses will be performed to evaluate the impact of treatment-by-time interaction, treatment-by-center interaction, covariates (age, sex, disease severity), normality of the underlying data and covariance structure of the underlying data on the inference drawn from the above model will be explored.

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[2] JENNRICH RI AND SCHLUCTER. 1986. Unbalanced repeated measures models with structured covariance matrices. *Biometrics,* **42,** 805-820.

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.

Treatment by Center Interaction

If evidence of a qualitative treatment-by-center interaction is found, exploratory analyses will be undertaken to further describe the interaction. Results will be presented by center Data will also be presented separately for centers that participated in protocol 039 versus those that did not. Treatment-by-center interaction will be tested at a significance level of 0.10.

Normality of Underlying Data

The normality assumption 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. Previous studies suggest that neither FEV_1 nor SGRQ exhibit gross departures from the normality assumption. However, if evidence of gross departures from normality is observed data transformations will be considered.

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 the primary endpoints. 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 both treatment groups.

If evidence of informative censoring is observed then a pattern mixture model will be used to estimate the treatment effect[3].

9.2.2 Multiplicity

As both FEV_1 and SGRQ total score are required to be positive in this study no multiplicity adjustment will be performed based on having co-primary endpoints. The modified Bonferroni procedure of Hochberg[4] will be used to adjust for secondary endpoints. The procedure will use the p-values from the two primary and four secondary endpoints.

9.2.3 Analysis of Secondary Efficacy

In addition to the repeated measures analysis, an ANOVA model with effects for treatment and center will be performed at each double-blind visit as well as at endpoint.

All other continuous secondary efficacy variables will be analyzed using the repeated measures model described above and separately at each visit using the ANOVA model described above. Treatment-by-time and treatment-by-center interaction terms will not be assessed for secondary variables.

For tertiary variables no formal hypothesis testing will be done. Treatment effects and associated 95% confidence intervals will be presented based on the methodology described above. First dose effects on pulmonary function parameters will be analyzed at each time point using the ANOVA model described above.

Differences between groups in time to first COPD exacerbation will be assessed using the log-rank test. The exacerbation-free survival rate at 24 weeks, and associated 95% confidence intervals, will be estimated for each treatment group using the Kaplan-Meier product limit.

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[3] LITTLE R.J.A., 1994. A Class of Pattern-Mixture Models for Normal Incomplete Data, Biometrika 81, 471-483.

[4] HOCHBERG Y. 1988. A sharper Bonferroni procedure for multiple tests of significance. *Biometrika,* **75,** 800-802.

Additionally, a Cox Proportional Hazards Model will be used to assess covariates influencing time to first exacerbation. Covariates will include treatment, gender, age, and percent-predicted FEV_1. If there are enough second exacerbations a multiple-event survival model as described by Wei, Lin and Weissfeld[5] will be used to compare the difference between two groups.

Time-to-first level 2/level 3 COPD exacerbation will be analyzed similarly.

9.2.4 Pharmacoeconomic Analysis

Time to first utilization will be analyzed by utilization type and across all utilizations using the Cox Proportional hazards model and log-rank test as described above. To account for multiple utilizations a Poisson regression model will be used.

Indirect costs including number of hours of paid and unpaid assistance will be summarized during the run-in period and across the entire double-blind period using descriptive statistics.

9.2.5 Interim Analysis

There are no planned interim analyses for this study.

9.2.6 Meta-Analysis

There is no planned Meta-analysis for this study.

9.3 Safety Analysis

9.3.1 Adverse Experiences

All adverse experiences in the double-blind period will be presented for both treatment groups by severity level (mild, moderate and severe), time, exacerbation level and hospitalization. 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 Ariflo™ group. In addition, the cumulative incidence of nausea, abdominal pain, diarrhea and vomiting by time will be estimated using the Kaplan-Meier product

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[5] L.J.WEI, D.Y.LIN, AND L. WEISSFELD. 1989. Regression Analysis of Multivariate Incomplete Failure Time Data By Modeling Marginal Distributions. JASA, Vol 84 **408,** 1065-1073

limit. This methodology will also be used to assess cumulative incidence of GI AEs. No formal statistical hypothesis testing will be performed for adverse experiences.

9.3.2 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 as defined in Section 4. 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.

9.3.3 Vital Signs

Descriptive Statistics for vital signs by visit/week and treatment group will be provided. Transitions from baseline in heart rate, systolic blood pressure and diastolic blood pressure will be summarized. The number and percent of patients with a concern will be presented by baseline category. A summary over the entire double-blind period will be performed using the "worst-case" for each patient as defined in Section 4. Patients appearing with both low and high values will be presented in both categories. A summary will also be performed at endpoint for each patient. Endpoint will be defined as the last on-therapy evaluation.

Orthostatic vital signs will be summarized for all patients and separately for the population of patients with GI AEs of concern. The number and percent of patients with a concern will be presented by baseline category. A summary over the entire double-blind period will be performed using the "worst-case" for each patient as defined in Section 4. A summary will also be performed at endpoint for each patient. Endpoint will be defined as the last on-therapy evaluation.

9.3.4 Electrocardiographs

Descriptive Statistics will be provided for ECG parameters (atrial rate, ventricular rate, PR interval, QRS interval, uncorrected QT interval and corrected QT (QTc) interval) by visit/week and treatment group. Transitions from baseline in atrial rate, ventricular rate, PR interval, QRS interval, uncorrected QT interval and QTc

interval will be summarized. The number and percent of patients with a concern will be presented by baseline category. A summary over the entire double-blind period will be performed using the "worst-case" for each patient as defined in Section 4. Patients appearing with both low and high values will be presented in both categories. A summary will also be performed at endpoint for each patient. Endpoint will be defined as the last on-therapy evaluation. In addition new-onset ECG findings based on cardiologist interpretation of the tracings will be presented by SNOMED terminology.

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

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PROTOCOL 207499/156

BOOK 1 : SCREENING TO RANDOMIZATION

A RANDOMIZED, 24-WEEK, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY, SAFETY AND TOLERABILITY OF ARIFLO™ (15 MG BID) IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

GENERAL INSTRUCTIONS

- *Write clearly in capital letters using a ball point pen.*
- *Do not write in shaded areas*
- *Answer ALL questions on every page*
- *Enter "N/A" if information requested is not available*
- *Initial and date all changes, additions or deletions. Use a single pen stroke to remove an incorrect entry*
- *Enter the patient initials on all pages on which information has been entered and the patient number and center number where required*

DATE

Please use the following three-letter abbreviations for the months

January	JAN
February	FEB
March	MAR
April	APR
May	MAY
June	JUN
July	JUL
August	AUG
September	SEP
October	OCT
November	NOV
December	DEC

e.g. | 0 1 | J A N | 0 0 | *= 1st January 2000*

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

PATIENT INITIALS

Please use the following format:

e.g. [redacted]

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*

STUDY PROCEDURES CHART 207499/156

Visit	1	2	3	3a	4	5	6	7	8	9	10		
Time relative to baseline (weeks)	Screen -4	-2	Baseline 0	+1	+2	+4	+8	+12	+16	+20	End Double-blind +24	Early Withdrawal[1]	Final Safety Follow-up +25
Signed written informed consent	x												
Medical & surgical history	x												
Physical examination[2]	x		x								x	x	x[3]
Pulmonary history & symptoms	x												
Postero-anterior chest radiograph[4]	x												
Exacerbation assessment/resource use	x	x	x	x	x	x	x	x	x	x	x	x	x
Medication history	x												
Overall breathlessness (modified Borg)	x	x	x		x	x	x	x	x	x	x		
Resting 12-lead ECG	x		x	x	x	x	x	x	x	x	x	x	x[3]
Vital signs (BP, HR)	x[5]	x	x[5]	x	x	x	x	x	x	x	x[5]	x[5]	x
Exercise Tolerance (6-Minute walk)	x	x	x			x	x	x	x	x	x	x	
Post-exercise SaO2 & breathlessness	x	x	x			x	x	x	x	x	x	x	
CO Diffusing Capacity (DLCO)[6]	x												
Albuterol reversibility[7]	x												
Laboratory tests	x		x[8]	x	x	x	x	x	x[9]	x[9]	x[8]	x[8]	x[3,9]
Dispense single-blind medication	x	x											
Albuterol Use		x	x	x	x	x	x	x	x	x	x		
Concomitant medication/medical procedures		x	x	x	x	x	x	x	x	x	x	x	x
PFTs (in absence of albuterol)[10]		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	
Baseline signs and symptoms/AEs[11]		x	x	x	x	x	x	x	x	x	x	x	x
Health status assessment: SGRQ			x					x			x	x	
Quality of life assessment: SF-36			x								x	x	
Cough and sputum assessments			x					x			x	x	
Pharmacokinetic evaluations[12]			x			x		x			x		
Arterial blood gas/SaO2[13]			x								x		
Hourly PFTs for 4 hrs post first/last dose [14]			x								x		
Dispense double-blind medication			x	x	x	x	x	x	x	x			
Investigator/Patient global assessment											x	x	
Study conclusion record												x	x

1 Patients who stop taking study medication between clinic visits will attend the clinic within 24 hours for an early withdrawal visit.

2 To include a respiratory examination.

3 If abnormalities at previous visit for patients who complete Visit 10 or withdraw from the study.

4 Postero-anterior chest X-ray must be performed at Visit 1 unless the film from a chest X-ray within the 12 weeks prior to Visit 1 is available to the Investigator.

5 Including Orthostatic vital signs.

6 DLCO should be done between Visit 1 and Visit 3 if not performed during the previous 24 weeks or if the results are unavailable.

7 Before and 15 to 30 (± 5) minutes after administration of 180 mcg albuterol via a MDI with a spacer to determine % predicted FEV_1, FVC, FEF_{25-75}, PEFR, and FEV_1: FVC.

8 In addition to usual laboratory tests, three fecal occult blood tests will be performed between Visits 1 and 3, between Visits 9 and 10, and at early withdrawal; amylase will be measured at Visit 3.

9 Urinary beta-HCG tests will be performed in females of childbearing potential. No other laboratory samples will be collected at Visits 8 and 9.

10 Includes FEV_1, FVC, FEF_{25-75}, PEFR, and FEV_1:FVC measured by centralized spirometry by the same person at each visit.

11 A diary will be used to record if patients feel different since starting study medication.

12 Visit 3: 3 hours post-dose. Visit 5: trough and 0.5-3 hours post-dose. Visit 7: trough and 3-10 hours post-dose. Visit 10: trough only.

13 In patients with <40% of predicted FEV_1 at Visit 1 and resting SaO_2 <88% or if the patient lives at a high altitude.

14 Pulmonary function tests 30 (± 5) minutes after albuterol followed by 4-hour post-double-blind drug assessments at Visits 3 and 10.

VISIT 1 - SCREENING

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Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

MOD1

Please do not split modules

Module 1 : **Visit 1 Screening**

CRF Pages **1 - 18**

Unprocessed Forms : **Within this module the following occur which will generate attachments that need to be brought in-house.**

None

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Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	
207499/156		[redacted]			Visit 1 Screening

PRESENTATION TO CLINIC

Record time of presentation to clinic ☐☐ 24hr:min

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?

☐ NA → Patient is not using beta$_2$ agonist.

☐ 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?

☐ NA → Patient is not using anticholinergic.

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: ☐☐☐ Day Month Yr ☐☐ 24hr:min

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.

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:* ☐☐

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes

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Protocol		Patient Number	Patient Initials		Visit 1 Screening
207499/156		[redacted]			

CONSENT

Date of signed informed consent to participate in this study ☐☐ ☐☐ ☐☐ Day Month Yr

DEMOGRAPHY

Date of Birth ☐☐ ☐☐ ☐☐ Day Month Year

Gender [M] ☐ Male [F] ☐ Female

Race [1] ☐ White [2] ☐ Black [3] ☐ Oriental [4] ☐ Other → *specify:* _____

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Protocol		Patient Number	Patient Initials		Visit 1 Screening
207499/156		[redacted]			

SIGNIFICANT MEDICAL/SURGICAL HISTORY AND PHYSICAL EXAMINATION
(INCLUDING RESPIRATORY EXAMINATION)

Is the patient suffering from or has he/she ever suffered from any **significant** medical or surgical condition, including any significant medical conditions detected during the physical examination?

☐ No

☑ Yes → *If 'Yes' please list below one diagnosis per line.*

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	[1] Past	[2] Ongoing
CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)		☐	☑
For SB			
		☐	☐
For SB			
		☐	☐
For SB			
		☐	☐
For SB			
		☐	☐
For SB			
		☐	☐
For SB			
		☐	☐
For SB			
		☐	☐
For SB			
		☐	☐
For SB			

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Protocol		Patient Number	Patient Initials		Visit 1 Screening
207499/156		[redacted]			

SIGNIFICANT MEDICAL/SURGICAL HISTORY AND PHYSICAL EXAMINATION (cont)

Diagnosis	Year of first diagnosis	[1] Past	[2] Ongoing
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			

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®
Selected short-acting inhaled beta$_2$-agonists	All **except** Ventolin®
Long-acting inhaled beta$_2$-agonists	Serevent®
Oral beta$_2$-agonists	Proventil®, Ventolin®, Volmax®, Brethine®
Nebulized beta$_2$-agonists	albuterol, metaproterenol, Alupent®, Isuprel®, Proventil®, Tornalate®, Ventolin®
Nebulized anticholinergics	Atrovent®
Inhaled cromolyn sodium	Intal®
Inhaled nedocromil	Tilade®
Oral xanthines	Slo-Bid®, Theo-Dur®
Leukotriene modifiers	Accolate®, Zyflo®, Singulair®
Mucolytics*	Mucomyst®, Mucosal®
Long-term oxygen therapy (LTOT)**	N/A

* Mucolytic administration should not be started during the study. Stable doses taken prior to study start may continue.

** 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. bid, prn)	**Route***	**Medical Illness/ Diagnosis** (or symptom in absence of a diagnosis)	**Start Date** (be as precise as possible) Day Mth Yr	**End Date** (or if Continuing mark box) Day Mth Yr	
TRADE NAME HERE	***200mcg***	***bid***	***IH***	***COPD***	15 JUN 00		✓
For SB							
For SB							

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Protocol	Patient Number	Patient Initials	Visit 1 Screening
207499/156	[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.*

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. 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.*

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Protocol	Patient Number	Patient Initials	Visit 1 Screening
207499/156	[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. 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 SB							

** For Route, see general instructions for acceptable abbreviations.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 1 Screening
207499/156		[redacted]			

AVERAGE ALCOHOL INTAKE

Number of units per week [ ][ ]

Note : A unit of alcohol is defined as 8 oz. (250 mL, half a pint) of beer, 4 oz. (125 mL, a medium-sized glass) of wine or 1 oz. (24mL, a measure) of spirits.

CHEST X-RAY

Perform a postero-anterior (PA) chest X-ray (unless one has been performed in the previous 12 weeks 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.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 1 Screening
207499/156		[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 or antibiotics, that required treatment to be prescribed by a physician, or for which the patient was hospitalized?

   ☐ No

   ☐ Yes → *If 'Yes' please withdraw the patient and complete the Study Continuation / Withdrawal page at the back of this book.*

SmithKline Beecham
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Protocol		Patient Number	Patient Initials		Visit 1 Screening
207499/156		[redacted]			

HEALTHCARE RESOURCE UTILIZATION

1. COPD-related emergency department visits

   How many times did the patient go to the emergency room / Urgent Care Center for COPD treatment during the past year?

   [0] ☐ 0
   [1] ☐ 1
   [2] ☐ 2
   [3] ☐ 3 - 4
   [4] ☐ 5 or more

2. COPD-related hospitalization

   How many times was the patient admitted to the hospital for COPD treatment during the past year?

   [0] ☐ 0
   [1] ☐ 1
   [2] ☐ 2
   [3] ☐ 3 - 4
   [4] ☐ 5 or more

INDIRECT COST

Does the patient perform work for which they are paid?

☐ No

☐ Yes → *If 'Yes', on average, how many hours per **week** does the patient work?*

☐☐.☐ Hours

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Protocol		Patient Number	Patient Initials		Visit 1 Screening
207499/156		[redacted]			

OVERALL BREATHLESSNESS ASSESSMENT

Give the patient a copy of the following scale when assessing breathlessness.

Please ask the patient the following question and record the answer below.

"Generally speaking, how has your breathlessness been during the previous week when you carried out tasks that usually cause you to be short of breath (e.g. walking, carrying shopping, climbing stairs, etc)?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Overall breathlessness score ☐☐.☐

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Protocol		Patient Number	Patient Initials		Visit 1 Screening
207499/156		[redacted]			

INVESTIGATOR INSTRUCTIONS

The following procedures (Vital Signs, ECG, and Exercise Tolerance Test) must be performed greater than 4 hours after the patient's last albuterol administration.

VITAL SIGNS

Height	Weight (light clothes, no shoes)	After Sitting for 5 Minutes	
		Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
☐ cm ☐ in	☐ kg ☐ lb		
☐☐☐.☐	☐☐☐.☐	☐☐☐/☐☐☐	☐☐☐

Were any clinically significant abnormalities noted?

☐ No

☐ Yes → *Record on the Significant Medical/Surgical History and Physical Examination page*

VITAL SIGNS - ORTHOSTATIC CHANGE

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)
☐☐☐/☐☐☐	☐☐☐	☐☐☐/☐☐☐	☐☐☐

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 ≥10 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
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Protocol		Patient Number	Patient Initials		Visit 1 Screening
207499/156		[redacted]			

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant abnormalities noted at this examination?

☐ No

☐ Yes → *If 'Yes', enter details on the Significant Medical/Surgical History and Physical Examination page.*

EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted? The distance walked should be entered even if the patient did not walk for 6 minutes.

☐ No

☐ Yes → *If 'Yes', Distance walked* ☐☐☐ [M] Meters ☐

[YD] Yards ☐

Record any adverse experiences which occur during the exercise tolerance test in the Baseline Signs and Symptoms section.

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Protocol		Patient Number	Patient Initials		Visit 1 Screening
207499/156		[redacted]			

POST-EXERCISE ASSESSMENTS *(Immediately after the patient completes the exercise tolerance)*

Heart Rate ☐☐☐ beats/min

SaO_2 ☐☐☐ %

Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

"How short of breath do you feel right now?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Post-exercise breathlessness score ☐☐.☐

INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise test (rest for at least 10 minutes) before performing the pulmonary function tests.

CARBON MONOXIDE DIFFUSING CAPACITY (DLCO)

A carbon monoxide diffusing capacity test (DLCO) should be done if one has not been performed within the previous 24 weeks or the results are not available. DLCO assessments may be scheduled between Visits 1 and 3.

Date of DLCO test ☐☐/☐☐/☐☐ (Day Month Yr)

Mean DLCO ☐☐.☐☐

Units *(Mark appropriate)*

☐ $mL.min^{-1}.mmHg^{-1}$

☐ $mmol.min^{-1}.kPa^{-1}$

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Protocol		Patient Number	Patient Initials		Visit 1 Screening
207499/156		[redacted]			

PRE-ALBUTEROL 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 confirm that the pulmonary function tests were performed

[1] ☐ Not performed

[2] ☐ Performed

Is the patient's pre-albuterol 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-albuterol Pulmonary Function Tests.*

POST-ALBUTEROL PULMONARY FUNCTION TESTS

Provide the patient with an albuterol MDI and spacer. Administer 180 mcg (2 puffs) of albuterol via MDI with a spacer. Remind the patient to use this inhaler (with or without the spacer), rather than any albuterol inhaler they may have at home, for "as required" rescue-medication use during the study. ***Record the start date for this prn albuterol use in the Prior and Concomitant medication section.***

Record the time of albuterol inhalation ☐☐ 24hr:min

Wait 15 - 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 confirm that the pulmonary function tests were performed

[1] ☐ Not performed

[2] ☐ Performed

Does the patient have a $\leq$ 15% and/or $\leq$ 200 ml increase in FEV_1 after administration of albuterol?

☐ 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-albuterol 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

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 1 Screening
207499/156		[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)*

SmithKline Beecham
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Protocol		Patient Number	Patient Initials		Visit 1 Screening
207499/156		[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. Patients with a clinical diagnosis of COPD, as defined by American Thoracic Society Guidelines (see Appendix G of the protocol).	☐	☐
3. Patients with a cigarette smoking history of ≥10 pack years (1 pack year = 20 cigarettes smoked per day for 1 year or the equivalent). Both current smokers and ex-smokers are eligible.	☐	☐
4. Patients with a pre-albuterol FEV_1 to FVC ratio (FEV_1:FVC) ≤ 0.7 at Visit 1 (Screening).	☐	☐
5. Patients with fixed airway obstruction, defined by ≤ 15% **or** ≤ 200 ml (or both) increase in FEV_1 after the administration of albuterol 180 mcg via MDI with a spacer at Visit 1 (Screening).	☐	☐
6. Patients with a post-albuterol FEV_1 between ≥30% and ≤ 70% of predicted normal for height, age and gender at Visit 1. Patients will be assessed 15 to 30 (± 5) minutes after receiving albuterol 180 mcg via MDI with a spacer.	☐	☐
7. Patients who give their signed written informed consent to participate.	☐	☐

Do not admit the patient to this study if any "NO" box has been marked.

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 1 Screening
207499/156		[redacted]			

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. Patients with poorly controlled COPD, defined as the occurrence of any of the following in the 2 weeks prior to Visit 1: acute worsening of COPD that is managed by the patient at home by self-treatment with corticosteroids or antibiotics, that requires treatment prescribed by a physician, or for which the patient is hospitalized.	☐	☐
4. Patients with active tuberculosis, lung cancer, or clinically overt bronchiectasis.	☐	☐
5. Patients with clinically significant cardiovascular, neurological, renal, endocrine, or hematological abnormalities that are uncontrolled on permitted therapy.	☐	☐
6. Patients with clinically significant gastrointestinal or hepatic abnormalities.	☐	☐
7. Patients with clinically significant orthostatic changes in blood pressure or heart rate at Visit 1 (Protocol Section 5.4.2).	☐	☐
8. Patients with a history of hypersensitivity to PDE4 inhibitors.	☐	☐
9. Patients with a history (or suspected history) of alcohol misuse or any other recreational substance abuse.	☐	☐
10. Patients who require treatment with inhaled cromolyn sodium or nedocromil, inhaled long-acting $beta_2$-agonists, oral $beta_2$-agonists, nebulized $beta_2$-agonists, nebulized anticholinergics, xanthines, leukotriene modifiers or oral/inhaled corticosteroids beyond Visit 1. All COPD medications except anticholinergic medication or albuterol via MDI should be withdrawn prior to or at Visit 1 (Screening).	☐	☐
11. Patients receiving treatment with long term oxygen therapy (LTOT), patients who require supplemental oxygen more often than on an occasional (prn) basis, or patients who require nocturnal positive pressure for sleep apnea.	☐	☐
12. Patients who have participated in a Pulmonary Rehabilitation Program within 4 weeks prior to Visit 1 (Screening) or who will enter a Pulmonary Rehabilitation Program during the study.	☐	☐
13. Patients 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).	☐	☐
14. Patients who have previously participated in an Ariflo (SB 207499) study and who received randomized study medication.	☐	☐
15. Patients unable to comply with study procedures (including completion of the health status questionnaires).	☐	☐

Do not admit the patient to this study if any "YES" box has been marked.
Additional Exclusion Criteria will be evaluated at Visit 3.

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 1

- *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 a diary card and remind the patient to use the card to record if they feel differently since starting the study.*

    - *Issue the patient the fecal occult blood test kit. Instruct the patient to follow the Patient Instructions provided with the kit. 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 10am + / - 2 hours.*

    - ***Remind the patient:***

        i *__not__ to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit (eg if study medication is taken at 08:00, the visit must be 16:00 or later).*

        ii *to refrain from using albuterol or anticholinergic agents during the **4 hours** immediately preceding the 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 albuterol inhaler and spacer, and the diary card.*

        v *to continue to take the anticholinergic medication, if prescribed, at a constant dose.*

        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, diarrhea, 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	Patient Initials		Visit 1 Screening
207499/156		[redacted]			

STUDY MEDICATION LABEL

Register the patient with SB's Registration and Medication Ordering System (RAMOS) by calling 1-866-726-6760. Issue the patient 20 days supply of **single-blind study medication** (2 bottles). The first 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.

Attach the tear-off labels from the study medication bottles 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	Attach label here

Date and time visit dose was taken ___ ___ ___ (Day Month Yr) ___ ___ (24hr:min)

PATIENT ACTIVITY POSTCARD

Please complete the patient activity postcard for ***Visit 1 Screening*** located in the postcard section of this CRF. Detach the postcard and mail promptly. Postage has been prepaid.

VISIT 2, WEEK -2
SINGLE-BLIND RUN-IN

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Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

MOD2

Please do not split modules

Module 2 : Visit 2, Visit 3 (Pre-Randomization), Baseline Signs and Symptoms, Concomitant Medications, Medical Procedures, COPD Exacerbations, Resource Utilization

CRF Pages 19 - 63

Unprocessed Forms : Within this module the following occur which will generate attachments that need to be brought in-house.

None

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Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	Visit 2 Single-blind Run-in Week -2
207499/156		[redacted]			

PRESENTATION TO CLINIC

Record time of presentation to clinic ☐☐ 24hr:min

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?

☐ NA → Patient is not using beta$_2$ agonist.

☐ 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?

☐ NA → Patient is not using anticholinergic.

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: ☐☐☐ 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 : ☐☐

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes

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Protocol		Patient Number	Patient Initials		Visit 2 Single-blind Run-in Week -2
207499/156		[redacted]			

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes ⟶ If 'Yes' please record details below.

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

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

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

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of excerbation (maximum level)	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1
	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2
	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3

If a patient experienced a COPD exacerbation that was treated with corticosteroids or antibiotics, 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.

RESOURCE UTILIZATION

If the patient has received any COPD exacerbation-related medical care since the last visit, record details in the Resource Utilization section at the back of this module.

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials	Visit 2 Single-blind Run-in Week -2
207499/156	[redacted]		

INDIRECT COST

Does the patient work?

☐ No

☐ Yes → *If 'Yes'*, has the patient missed work due to COPD-related symptoms, excluding scheduled protocol visits, since the last visit?

☐ No

☐ Yes → *If 'Yes', please record lost work days below:*

Start Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence

How many days since your last visit have you been restricted in performing your leisure activities, due to your COPD-related symptoms? *(please enter number of days below, if not restricted, enter 0)*

☐☐ Days

Since your last visit, how many hours per week did you require paid or unpaid assistance by a relative, friend or professional with your daily activities such as dressing, bathing, cooking, etc., due to your COPD-related symptoms? *(please enter number of hours below, if no paid or unpaid assistance, enter 0 in each instance)*

☐☐☐ Hours per week of **paid** assistance

☐☐☐ Hours per week of **unpaid** assistance

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 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.

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Protocol		Patient Number	Patient Initials		Visit 2 Single-blind Run-in Week -2
207499/156		[redacted]			

"AS NEEDED" ALBUTEROL USE

Record the patient's evaluation of their 'as needed' albuterol use since the last visit.

[1] ☐ Much less than usual
[2] ☐ Less than usual
[3] ☐ About the same as usual
[4] ☐ More than usual
[5] ☐ Much more than usual

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.

FECAL OCCULT BLOOD TEST

The fecal 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.

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

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'.

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Protocol		Patient Number	Patient Initials		Visit 2 Single-blind Run-in Week -2
207499/156		[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. bid)

Date and time of last dose of study medication prior to the study visit Day Month Yr 24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
40					

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance ≥ 80% and ≤120%?

☐ No → *If 'No' please remind the patient of the importance of taking the medication according to the protocol.*

☐ Yes

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Protocol		Patient Number	Patient Initials		Visit 2 Single-blind Run-in Week -2
207499/156		[redacted]			

OVERALL BREATHLESSNESS ASSESSMENT

Give the patient a copy of the following scale when assessing breathlessness.

Please ask the patient the following question and record the answer below.

"Generally speaking, how has your breathlessness been during the previous week when you carried out tasks that usually cause you to be short of breath (e.g. walking, carrying shopping, climbing stairs, etc)?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Overall breathlessness score ☐☐.☐

PULMONARY REHABILITATION PROGRAM

Has the patient entered a Pulmonary Rehabilitation Program since the last visit?

☐ No

☐ Yes

INVESTIGATOR INSTRUCTIONS

The following procedures (Vital Signs and Exercise Tolerance Test) must be performed more than 4 hours after the patient's last albuterol administration.

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Protocol		Patient Number	Patient Initials		Visit 2 Single-blind Run-in Week -2
207499/156		[redacted]			

VITAL SIGNS

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 module.*

EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted? The distance walked should be entered even if the patient did not walk for 6 minutes.

☐ No

☐ Yes → *If 'Yes', Distance walked* ☐☐☐ Meters ☐

Yards ☐

Record any adverse experiences which occur during the exercise tolerance test in the Baseline Signs and Symptoms section.

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Protocol		Patient Number	Patient Initials		Visit 2 Single-blind Run-in Week -2
207499/156		[redacted]			

POST-EXERCISE ASSESSMENTS *(Immediately after the patient completes the exercise tolerance)*

Heart Rate ☐☐☐ beats/min

SaO_2 ☐☐☐ %

Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

"How short of breath do you feel right now?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Post-exercise breathlessness score ☐☐.☐

INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise tolerance test (rest for at least 10 minutes) before performing the pulmonary function tests.

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Protocol		Patient Number	Patient Initials		Visit 2 Single-blind Run-in Week -2
207499/156		[redacted]			

PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed at least 4 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 confirm that the pulmonary function tests were performed

[1] ☐ Not performed

[2] ☐ Performed

Has the patient's absolute value of FEV$_1$ increased or decreased by > 20% between Visits 1 and 2?

☐ No

☐ Yes → *If 'Yes please withdraw the patient and complete the Study Continuation/Withdrawal page at the back of this book.*

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 2

- *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 a new diary card and remind the patient to use the card to record if they feel differently since starting the study.*

    - *Ask the patient to return for the next visit in 14 +/- 3 days at 10:00 +/- 2 hours.*

    - ***Remind the patient:***

        i *__not__ to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).*

        ii *to refrain from using albuterol or anticholinergic agents during the **4 hours** immediately preceding the 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 albuterol inhaler and spacer, and the diary card.*

        v *to continue to take the anticholinergic medication, if prescribed, at a constant dose.*

        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, diarrhea, 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 fecal occult blood test(s) by the next visit if not already done.*

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Protocol	Patient Number	Patient Initials	Visit 2 Single-blind Run-in Week -2
207499/156	[redacted]		

STUDY MEDICATION LABEL

Issue the patient 20 days supply of **single-blind study medication** (2 bottles) and an albuterol MDI and spacer for 'as required' use if applicable (remind the patient to use this inhaler rather than any albuterol inhaler they may have at home). The first 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.

Attach the tear-off labels from the study medication bottles 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

Attach label here

Date and time visit dose was taken Day Month Yr 24hr:min

PATIENT ACTIVITY POSTCARD

Please complete the patient activity postcard for ***Visit 2 Single Blind Run-In*** located in the postcard section of this CRF. Detach the postcard and mail promptly. Postage has been prepaid.

VISIT 3, DAY 1
BASELINE
(PRE-RANDOMIZATION)

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Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	Visit 3 Baseline Pre-randomization Day1
207499/156		[redacted]			

PRESENTATION TO CLINIC

Record time of presentation to clinic ☐☐ 24hr:min

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?

☐ NA → Patient is not using beta$_2$ agonist.

☐ 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?

☐ NA → Patient is not using anticholinergic.

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: ☐☐☐ 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 : ☐☐

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes

ST. GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

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

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Protocol		Patient Number	Patient Initials		Visit 3
207499/156		[redacted]			

ST. GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE (PAGE 1 OF 5)

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Protocol		Patient Number	Patient Initials		Visit 3
207499/156		[redacted]			

SF - 36 (HEALTH STATUS QUESTIONNAIRE) (Page 1 of 5)

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Protocol	Patient Number	Patient Initials	Visit 3 Baseline Pre-randomization Day1
207499/156	[redacted]		

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes → *If 'Yes' please record details below.*

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

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

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

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of excerbation (maximum level)	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1
	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2
	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3

If a patient experienced a COPD exacerbation that was treated with corticosteroids or antibiotics, 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.

RESOURCE UTILIZATION

Please complete the COPD Resource Utilization section at the back of this module.

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Protocol		Patient Number	Patient Initials		Visit 3 Baseline Pre-randomization Day1
207499/156		[redacted]			

INDIRECT COST

Does the patient work?

☐ No

☐ Yes → *If 'Yes'*, has the patient missed work due to COPD-related symptoms, excluding scheduled protocol visits, since the last visit?

☐ No

☐ Yes → *If 'Yes', please record lost work days below:*

Start Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence

How many days since your last visit have you been restricted in performing your leisure activities, due to your COPD-related symptoms? *(please enter number of days below, if not restricted, enter 0)*

☐☐ Days

Since your last visit, how many hours per week did you require paid or unpaid assistance by a relative, friend or professional with your daily activities such as dressing, bathing, cooking, etc., due to your COPD-related symptoms? *(please enter number of hours below, if no paid or unpaid assistance, enter 0 in each instance)*

☐☐☐ Hours per week of **paid** assistance

☐☐☐ Hours per week of **unpaid** assistance

BASELINE SIGNS AND SYMPTOMS

Please complete the Baseline Signs and Symptoms 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 Baseline Signs and Symptoms section at the back of this module. The patient should refer to the notes in their diary when answering this question.

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Protocol		Patient Number	Patient Initials		Visit 3 Baseline Pre-randomization Day1
207499/156		[redacted]			

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.

"AS NEEDED" ALBUTEROL USE

Record the patient's evaluation of their 'as needed' albuterol use since the last visit.

[1] ☐ Much less than usual
[2] ☐ Less than usual
[3] ☐ About the same as usual
[4] ☐ More than usual
[5] ☐ Much more than usual

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.

FECAL OCCULT BLOOD TEST

If not completed previously, record results from the test(s) in the Fecal Occult Blood Test section in Visit 2.

Has the patient had a positive fecal 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 module.*

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Protocol		Patient Number	Patient Initials		Visit 3 Baseline Pre-randomization Day1
207499/156		[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. bid)

Date and time of last dose of study medication prior to the study visit Day Month Yr 24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
40					

Note: If this is a morning visit, patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance ≥ 80% and ≤120%?

☐ No → *If 'No' please withdraw the patient and complete the Study Continuation/Withdrawal page at the back of this book.*

☐ Yes

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Protocol		Patient Number	Patient Initials		Visit 3 Baseline Pre-randomization Day1
207499/156		[redacted]			

OVERALL BREATHLESSNESS ASSESSMENT

Give the patient a copy of the following scale when assessing breathlessness.

Please ask the patient the following question and record the answer below.

"Generally speaking, how short of breath have you been during the previous week when you carried out tasks that usually cause you to be short of breath (e.g. walking, carrying shopping, climbing stairs, etc)?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Overall breathlessness score ☐☐.☐

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Protocol		Patient Number	Patient Initials		Visit 3 Baseline Pre-randomization Day1
207499/156		[redacted]			

COUGH AND SPUTUM PRODUCTION ASSESSMENTS

*Please ask the patient the following questions and record the answers below (Mark **one** box per section only.)*

COUGH

How troubled have you been by cough today?

[0] ☐ No symptoms at all

[1] ☐ Some symptoms, but hardly noticeable

[2] ☐ Symptoms noticeable and a little uncomfortable

[3] ☐ Symptoms definitely noticeable and uncomfortable

[4] ☐ Symptoms very bad and extremely uncomfortable

SPUTUM PRODUCTION

How much sputum have you produced today?

[0] ☐ No sputum at all

[1] ☐ Some sputum, but not as much as usual

[2] ☐ As much as usual

[3] ☐ More than usual

[4] ☐ A lot more than usual

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 Exercise Tolerance Test) must be performed greater than 4 hours after the patient's last albuterol administration.

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Protocol	Patient Number	Patient Initials	Visit 3 Baseline Pre-randomization Day1
207499/156	[redacted]		

VITAL SIGNS

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 module.*

VITAL SIGNS - ORTHOSTATIC CHANGE

1st Measurement: After 5 Minutes Supine

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
___ / ___	___

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
___ / ___	___

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 ≥ 10 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'.*

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Protocol		Patient Number	Patient Initials		Visit 3 Baseline Pre-randomization Day1
207499/156		[redacted]			

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant changes noted at this examination compared to Screening?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Baseline Signs and Symptoms section at the back of this module.*

RESTING SaO_2

Measure Resting SaO_2 by pulse oximetry for all patients with an FEV_1 < 40% of predicted for age, height and gender at Visit 1.

[1] ☐ Measurement not required (patient's FEV_1 at Visit 1 ≥ 40% of predicted)

[2] ☐ Measurement required but not performed

[3] ☐ Measurement taken, *please record value below:*

Resting SaO_2 ☐☐☐ %

EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted? The distance walked should be entered even if the patient did not walk for 6 minutes.

☐ No

☐ Yes → *If 'Yes', Distance walked* ☐☐☐ Meters [M] ☐

Yards [YD] ☐

Record any adverse experiences which occur during the exercise tolerance test in the Baseline Signs and Symptoms section at the back of this module.

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Protocol		Patient Number	Patient Initials		Visit 3 Baseline Pre-randomization Day1
207499/156		[redacted]			

POST-EXERCISE ASSESSMENTS *(Immediately after the patient completes the exercise tolerance test)*

Heart Rate ☐☐☐ beats/min

SaO_2 ☐☐☐ %

Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

"How short of breath do you feel right now?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Post-exercise breathlessness score ☐☐.☐

SmithKline Beecham
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Protocol	Patient Number	Patient Initials	Visit 3 Baseline Pre-randomization Day1
207499/156	[redacted]		

INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise tolerance test (rest for at least 10 minutes) before performing the pulmonary function tests.

PULMONARY FUNCTION TESTS - PRE-ALBUTEROL

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 randomized, additional pulmonary function tests will be performed after a dose of study albuterol is given in the clinic (Book 2) AND prior to the first dose of randomized 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 confirm that the pulmonary function tests were performed

[1] ☐ Not performed

[2] ☐ Performed

RANDOMIZATION CRITERION

Has the patient's absolute value of FEV$_1$ increased or decreased by > 20% between Visits 1 and 3?

☐ Yes → *If 'Yes' please withdraw the patient and complete the Study Continuation/Withdrawal page at the back of this book.*

☐ No

ADDITIONAL EXCLUSION CRITERIA

Complete the following exclusion criteria.	**Yes**	**No**
1. The patient has had a positive fecal occult blood test result between Visit 1 and 3.	☐	☐
2. The patient has a clinically significant orthostatic change in blood pressure or heart rate at Visit 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.

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 is 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 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 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

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Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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)

If no baseline events prior to randomization into study please mark this box ☐

Baseline Event *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***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 randomization	[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 Concomitant Medication and/or Medical Procedures section if appropriate*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific event?	☐ Yes ☐ No	☐ Yes ☐ No

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials
207499/156	[redacted]	

BASELINE SIGNS AND SYMPTOMS (or events, or diagnoses) - Continued

*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)

If no baseline events prior to randomization into study please mark this box ☐

Baseline Event *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***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 randomization	[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 Concomitant Medication and/or Medical Procedures section if appropriate*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific event?	☐ Yes ☐ No	☐ Yes ☐ No

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials
207499/156	[redacted]	

BASELINE SIGNS AND SYMPTOMS (or events, or diagnoses) - Continued

*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)

If no baseline events prior to randomization into study please mark this box ☐

Baseline Event *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***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 randomization	[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 Concomitant Medication and/or Medical Procedures section if appropriate*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific event?	☐ Yes ☐ No	☐ Yes ☐ No

CONCOMITANT MEDICATION
excluding treatment for COPD Exacerbations
(These are recorded in the COPD Exacerbations section)

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 (albuterol) 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 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 Route, see General Instructions for acceptable abbreviations.*

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 (albuterol) 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 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 Route, see General Instructions for acceptable abbreviations.*

MEDICAL PROCEDURES
excluding treatment for COPD Exacerbations
(These are recorded in the COPD Exacerbations section)

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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			
For SB			

COPD EXACERBATION SECTION

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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***

If no COPD Exacerbations prior to randomization please mark this box. ☐

Baseline Event	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***If patient died, STOP: go to SAE COPD Exacerbation pages.***	[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) *See definitions page for Baseline Signs & Symptoms form.*	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Relationship to study procedures performed prior to randomization	[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 on the COPD Medications or Procedures page*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific event prior to randomization?	☐ Yes ☐ No	☐ Yes ☐ No

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

DETAILS OF COPD EXACERBATIONS - CONTINUED

*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***

If no COPD Exacerbations prior to randomization please mark this box. ☐

Baseline Event	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***If patient died, STOP: go to SAE COPD Exacerbation pages.***	[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) *See definitions page for Baseline Signs & Symptoms form.*	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Relationship to study procedures performed prior to randomization	[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 on the COPD Medications or Procedures page*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific event prior to randomization?	☐ Yes ☐ No	☐ Yes ☐ No

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 minimize 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	Center Number	Patient Number	Patient Initials
207499/156		[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 hospitalization (excluding elective surgery or routine clinical procedures)
[5] ☐ hospitalization 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 _____

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 randomization code broken at investigational site? ☐ No ☐ Yes

Randomization 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 _____

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible) Day Mth Yr	End Date (or if Continuing mark box) Day Mth Yr	
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							

** For Route, see General Instructions for acceptable abbreviations.*

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			

RESOURCE UTILIZATION

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

RESOURCE UTILIZATION

Has the patient utilized any COPD Exacerbation-related medical care between Visits 1 and 3?

☐ No

☐ Yes → *If 'Yes', please record details below*

Has the patient had any **Physician Visits** (COPD care excluding scheduled protocol visits) between Visits 1 and 3?

☐ No

☐ Yes → *If 'Yes', please record details below*

Date of Visit Day Mth Yr	Reason for Visit

Has the patient had any **Emergency Room (ER)/Urgent Care Visits/Procedures (i.e., lung surgery)** between Visits 1 and 3?

☐ No

☐ Yes → *If 'Yes', please record details below*

Date of Visit Day Mth Yr	Reason for Visit	Patient Admitted from ER? Yes	No
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

RESOURCE UTILIZATION - (cont)

Has the patient had any **Hospitalizations** between Visits 1 and 3?

☐ No

☐ Yes → *If 'Yes', please record details below* ***(also record details of any hospitalization in the Serious Adverse Experience - COPD Exacerbation section)***

Name of Hospital & City	Date of Admission Day Mth Yr	Date of Discharge Day Mth Yr	Reason for Admission

Has the patient had any **Intensive Care Unit (ICU) stays** ***(did the patient stay in the ICU during any of the above hospitalizations?)*** between Visits 1 and 3?

☐ 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

STUDY CONTINUATION / WITHDRAWAL

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

CONC1

Please do not split modules

Module: Study Continuation / Withdrawal

CRF Pages: 64

Unprocessed Forms: Within this module, the following occur which will generate attachments that need to be brought in-house.

None

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

STUDY CONTINUATION/WITHDRAWAL

Is the patient continuing into the double-blind treatment phase of the study?

☐ Yes → *If 'Yes' please sign in the appropriate space below and continue immediately to Book 2.*

☐ No → *If 'No' please mark the **PRIMARY** cause of withdrawal and sign the box below.*

[1] ☐ Baseline sign/symptom (complete BS&S form)

[10] ☐ Does not meet inclusion/exclusion criteria

[3] ☐ Protocol deviation (including non-compliance)

[4] ☐ Lost to follow-up

[5] ☐ Other - specify: _____

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

PATIENT ACTIVITY POSTCARD

Please complete the patient activity postcard for ***Visit 3 Pre-randomization***, located in the postcard section of this CRF. Detach the postcard and mail promptly. Postage has been prepaid.

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	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

SAE1

Please do not split modules

Module: Serious Adverse Experiences

CRF Pages: 65 - 66

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	SB Receipt Date (Day Month Year)
207499/156		[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 hospitalization (excluding elective surgery or routine clinical procedures)
[5] ☐ hospitalization 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 section
☐ Yes ☐ No

Was patient withdrawn due to this specific SAE ?
☐ Yes ☐ No

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 randomization code broken at investigational site? ☐ No ☐ Yes

Randomization 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 _____

SmithKline Beecham
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Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

FORMD1

Please do not split modules

Module: Form D

CRF Pages: 67

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

FORM D

Certified Cause of Death _____

Date of Death Day Month Yr → *Please complete Serious Adverse Experience section.*

Was a post-mortem examination carried out?

☐ No

☐ Yes → *If 'Yes' please summarize findings (include diagnosis):*

_____

_____

_____

_____

Reporting Physician's Signature _____ Date Day Month Yr

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Protocol	Center Number	Patient Number	Patient Initials		OPTIONAL Repeat Lab
207499/156		[redacted]			

RPLAB1

Please do not split modules

Module: Repeat Lab

CRF Pages: 68

Unprocessed Forms: Within this module, the following tests / procedures occur which may generate attachments.

None

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Protocol	Center Number	Patient Number	Patient Initials		OPTIONAL Repeat Lab
207499/156		[redacted]			

REPEAT 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.*

REPEAT 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.*

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Protocol	Center Number	Patient Number	Patient Initials	Investigator
207499/156		[redacted]		

CRF TRACKING/REVIEW FORM

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 - 18	☐	☐	
MOD2	V2, V3, BSS, CM, MP, COPD, RU	19 - 63	☐	☐	
CONC1	Continuation/Withdrawal	64	☐	☐	
SAE1	Serious Adverse Experiences	65 - 66	☐	☐	
FORMD1	Form D	67	☐	☐	
RPLAB1	Repeat Labs	68	☐	☐	

If multiple modules are submitted together, please ensure they are sorted according to the order above

Site Monitor's Comments (e.g. protocol violations or deviations)

Site Monitor's Signature _____ Date Submitted ☐☐ Day ☐☐ Month ☐☐ Yr

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

CONFIDENTIAL

SmithKline Beecham
Pharmaceuticals

PROTOCOL 207499/156

BOOK 2 : RANDOMIZATION TO VISIT 7

A RANDOMIZED, 24-WEEK, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY, SAFETY AND TOLERABILITY OF ARIFLO™ (15 MG BID) IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

Attach pharmacokinetic sampling group identification label here

GENERAL INSTRUCTIONS

- *Write clearly in capital letters using a black ball point pen and press firmly so that all copies are legible*
- *Do not write in shaded areas*
- *Answer ALL questions on every page*
- *Enter "N/A" if information requested is not available*
- *Initial and date all changes, additions or deletions. Use a single pen stroke to remove an incorrect entry*
- *Enter the patient initials on all pages on which information has been entered and the patient number and center number where required*

Do not enter additional data/information after the set of CRF pages has been split/separated

The cover flap or plastic writing board should be used to divide each set of pages before writing on them with a ball point pen

DATE

Please use the following three-letter abbreviations for the months

January	JAN
February	FEB
March	MAR
April	APR
May	MAY
June	JUN
July	JUL
August	AUG
September	SEP
October	OCT
November	NOV
December	DEC

e.g. | 0 1 | J A N | 0 0 | = *1st January 2000*

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

PATIENT INITIALS

Please use the following format:

e.g. [redacted]

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*

STUDY PROCEDURES CHART 207499/156

Visit	1	2	3	3a	4	5	6	7	8	9	10		
Time relative to baseline (weeks)	Screen -4	-2	Baseline 0	+1	+2	+4	+8	+12	+16	+20	End Double-blind +24	Early Withdrawal[1]	Final Safety Follow-up +25
Signed written informed consent	x												
Medical & surgical history	x												
Physical examination[2]	x		x								x	x	x[3]
Pulmonary history & symptoms	x												
Postero-anterior chest radiograph[4]	x												
Exacerbation assessment/resource use	x	x	x	x	x	x	x	x	x	x	x	x	x
Medication history	x												
Overall breathlessness (modified Borg)	x	x	x		x	x	x	x	x	x	x		
Resting 12-lead ECG	x		x	x	x	x	x	x	x	x	x	x	x[3]
Vital signs (BP, HR)	x[5]	x	x[5]	x	x	x	x	x	x	x	x[5]	x[5]	x
Exercise Tolerance (6-Minute walk)	x	x	x			x	x	x	x	x	x	x	
Post-exercise SaO2 & breathlessness	x	x	x			x	x	x	x	x	x	x	
CO Diffusing Capacity (DLCO)[6]	x												
Albuterol reversibility[7]	x												
Laboratory tests	x		x[8]	x	x	x	x	x	x[9]	x[9]	x[8]	x[8]	x[3,9]
Dispense single-blind medication	x	x											
Albuterol Use		x	x	x	x	x	x	x	x	x	x		
Concomitant medication/medical procedures		x	x	x	x	x	x	x	x	x	x	x	x
PFTs (in absence of albuterol)[10]		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	
Baseline signs and symptoms/AEs[11]		x	x	x	x	x	x	x	x	x	x	x	x
Health status assessment: SGRQ			x					x			x	x	
Quality of life assessment: SF-36			x								x	x	
Cough and sputum assessments			x					x			x	x	
Pharmacokinetic evaluations[12]			x			x		x			x		
Arterial blood gas/SaO2[13]			x								x		
Hourly PFTs for 4 hrs post first/last dose [14]			x								x		
Dispense double-blind medication			x	x	x	x	x	x	x	x			
Investigator/Patient global assessment											x	x	
Study conclusion record												x	x

1 Patients who stop taking study medication between clinic visits will attend the clinic within 24 hours for an early withdrawal visit.

2 To include a respiratory examination.

3 If abnormalities at previous visit for patients who complete Visit 10 or withdraw from the study.

4 Postero-anterior chest X-ray must be performed at Visit 1 unless the film from a chest X-ray within the 12 weeks prior to Visit 1 is available to the Investigator.

5 Including Orthostatic vital signs.

6 DLCO should be done between Visit 1 and Visit 3 if not performed during the previous 24 weeks or if the results are unavailable.

7 Before and 15 to 30 (± 5) minutes after administration of 180 mcg albuterol via a MDI with a spacer to determine % predicted FEV_1, FVC, FEF_{25-75}, PEFR, and FEV_1: FVC.

8 In addition to usual laboratory tests, three fecal occult blood tests will be performed between Visits 1 and 3, between Visits 9 and 10, and at early withdrawal; amylase will be measured at Visit 3.

9 Urinary beta-HCG tests will be performed in females of childbearing potential. No other laboratory samples will be collected at Visits 8 and 9.

10 Includes FEV_1, FVC, FEF_{25-75}, PEFR, and FEV_1:FVC measured by centralized spirometry by the same person at each visit.

11 A diary will be used to record if patients feel different since starting study medication.

12 Visit 3: 3 hours post-dose. Visit 5: trough and 0.5-3 hours post-dose. Visit 7: trough and 3-10 hours post-dose. Visit 10: trough only.

13 In patients with <40% of predicted FEV_1 at Visit 1 and resting SaO_2 <88% or if the patient lives at a high altitude.

14 Pulmonary function tests 30 (± 5) minutes after albuterol followed by 4-hour post-double-blind drug assessments at Visits 3 and 10.

VISIT 3, DAY 1
POST-RANDOMIZATION

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Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

MOD3

Please do not split modules

Module 3 : **Visit 3 (Post-Randomization), Visit 3A, Visit 4, Visit 5, Adverse Experiences, Concomitant Medication, Medical Procedures, COPD Exacerbations, Resource Utilization**

CRF Pages **69 - 126**

Unprocessed Forms : **Within this module the following occur which will generate attachments that need to be brought in-house.**

None

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Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	Visit 3 Post-randomization Day 1
207499/156		[redacted]			

LABORATORY TESTS

Please take blood samples for hematology, 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. If the pregnancy test is positive, please withdraw the patient from the study, complete the Serious Adverse Experiences form and forward it to SB within 24 hours. Complete the Visit for Early Withdrawal between Scheduled Visits and the Study Continuation/ Withdrawal section at the back of this book.

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 (If a re-test is necessary, please use the Repeat Lab page at the end of this book)*

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Protocol		Patient Number	Patient Initials		Visit 3 Post-randomization Day 1
207499/156		[redacted]			

ARTERIAL BLOOD GASES

If a resting SaO2 test was required at this visit AND the patient's resting SaO2 < 88% OR the patient lives at a high altitude, please take an arterial blood gas sample for analysis if feasible. The patient should be rested (5 to 10 minute rest) after pulmonary function tests.

☐ Not required

☐ Sample required but not taken

PO_2 (mmHg)	PCO_2 (mmHg)	HCO_3- (mEq/L)	pH	SaO_2 %
☐☐☐	☐☐	☐☐	☐.☐☐	☐☐☐

POST-ALBUTEROL PULMONARY FUNCTION TESTS

Issue the patient an albuterol inhaler for 'as-required' use and retrieve their old inhaler.
Administer 180mcg (2 puffs) of albuterol via MDI with a spacer.

Record the time of albuterol inhalation ☐☐ 24hr:min

Wait 30 minutes *(+/-5 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 manuals)****. For each set of three FEV_1 measurements, one FEV_1 must be within 10% of the highest.*

Please confirm that the pulmonary function tests were performed

[1] ☐ Not Performed

[2] ☐ Performed

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Protocol		Patient Number	Patient Initials		Visit 3 Post-randomization Day 1
207499/156		[redacted]			

PATIENT RANDOMIZATION

Following completion of all preceding assessments contact RAMOS (1-866-726-6760) to obtain the container and randomization numbers assigned to the patient.

Please enter the 5-digit Randomization 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

Enter 6-digit Code as it appears on the study medication label ☐☐☐☐☐☐

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

The patient should remain in the clinic for the next 4 hours, during which time the patient will be observed and will undergo hourly pulmonary function testing (to be recorded on the following pages).

PHARMACOKINETIC EVALUATION

Assign the patient to the 'Early' or 'Late' group for pharmacokinetic sampling.

[1] ☐ Early

[2] ☐ Late

Select the appropriate label ('early' or 'late') from those supplied and affix it to the cover of this book.

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Protocol		Patient Number	Patient Initials		Visit 3 Post-randomization Day 1
207499/156		[redacted]			

POST-DOSE PULMONARY FUNCTION TESTS

Pulmonary function tests will be completed every hour in the 4-hour period following administration of the first dose of study medication.

Ask the patient to avoid using additional albuterol or anticholinergic medication and to refrain from smoking if at all possible.

If the patient uses their albuterol or anticholinergic medication during this period, the tests should be abandoned.

Time post-dose	Completed? Yes	No
1 Hour	☐	☐
2 Hours	☐	☐
Perform ECG and Pharmacokinetic Evaluation		
3 Hours	☐	☐
4 Hours	☐	☐

ADVERSE EXPERIENCES

Record any adverse experiences which occur during the pulmonary function tests in the Adverse Experience section at the back of this module.

12 LEAD ELECTROCARDIOGRAM - 3 HOURS POST DOSE

The ECG should be performed before the 3-hour post-dose pulmonary function test and after the patient has been semi-supine for 5 minutes.

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant changes noted at this examination compared to Baseline?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of this module.*

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Protocol		Patient Number	Patient Initials		Visit 3 Post-randomization Day 1
207499/156		[redacted]			

PHARMACOKINETIC EVALUATIONS - 3 HOURS POST DOSE

Collect a blood sample (5mL) 3 hours post dose (after the ECG and before the 3-hour post-dose pulmonary function test) for pharmacokinetic evaluation.

Was a pharmacokinetic sample taken?

☐ No

☐ Yes → *If 'Yes'*, 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)

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 3

- *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 a diary card and remind the patient to use the card to record if they feel differently since starting the study.*

    - *Ask the patient to return for Visit 3A in 7 +/- 2 days and for Visit 4 in 14 +/- 3 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. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).*

        iii *to refrain from using albuterol or anticholinergic agents during the **4 hours** immediately preceding the 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 albuterol inhaler and spacer, and the diary card.*

        vi *to continue to take the anticholinergic medication, if prescribed, at a constant dose.*

        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, diarrhea, 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.*

VISIT 3A, WEEK 1

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Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	
207499/156		[redacted]			Visit 3A Week 1

PRESENTATION TO CLINIC

Record time of presentation to clinic ☐☐ 24hr:min

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?

☐ NA → Patient is not using beta$_2$ agonist.

☐ 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?

☐ NA → Patient is not using anticholinergic.

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: ☐☐☐ 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 : ☐☐

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes

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Protocol	Patient Number	Patient Initials	Visit 3A Week 1
207499/156	[redacted]		

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes → *If 'Yes' please record details below. If the patient has had more than three Level 2 or 3 exacerbations since the start of double-blind medication, patient may be withdrawn after consultation with the Medical Monitor. If withdrawing, complete the assessments scheduled at this visit and the Assessments for Patients Withdrawing at Visit 3A. The SGRQ and SF-36 should be completed before any additional assessments.*

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

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

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

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of excerbation (maximum level)	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1
	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2
	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations, including an increase in usual COPD medications, must be recorded in the COPD Medications or Procedures pages.

RESOURCE UTILIZATION

If the patient has received any COPD exacerbation-related medical care since the last visit, record details in the Resource Utilization section at the back of this module.

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Protocol		Patient Number	Patient Initials		Visit 3A Week 1
207499/156		[redacted]			

INDIRECT COST

Does the patient work?

☐ No

☐ Yes → *If 'Yes'*, has the patient missed work due to COPD-related symptoms, excluding scheduled protocol visits, since the last visit?

☐ No

☐ Yes → *If 'Yes', please record lost work days below:*

Start Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence

How many days since your last visit have you been restricted in performing your leisure activities, due to your COPD-related symptoms? *(please enter number of days below, if not restricted, enter 0)*

☐☐ Days

Since your last visit, how many hours per week did you require paid or unpaid assistance by a relative, friend or professional with your daily activities such as dressing, bathing, cooking, etc., due to your COPD-related symptoms? *(please enter number of hours below, if no paid or unpaid assistance, enter 0 in each instance)*

☐☐☐ Hours per week of **paid** assistance

☐☐☐ Hours per week of **unpaid** assistance

ADVERSE EXPERIENCES

If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

CONCOMITANT MEDICATION

If there has been any change in the patient's concomitant medication excluding treatment for COPD exacerbations (this is recorded in the COPD Exacerbations section) since the last visit, please record details in the Concomitant Medication section at the back of this module.

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Protocol		Patient Number	Patient Initials		Visit 3A Week 1
207499/156		[redacted]			

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.

"AS NEEDED" ALBUTEROL USE

Record the patient's evaluation of their 'as needed' albuterol use since the last visit.

[1] ☐ Much less than usual
[2] ☐ Less than usual
[3] ☐ About the same as usual
[4] ☐ More than usual
[5] ☐ Much more than usual

SmithKline Beecham Pharmaceuticals

Protocol	Patient Number	Patient Initials	Visit 3A Week 1
207499/156	[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. bid)

Date and time of last dose of study medication prior to the study visit Day Month Yr 24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
20					

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance ≥ 80% and ≤120%?

☐ No → *If 'No' please remind the patient of the importance of taking the medication according to the protocol.*

☐ Yes

PULMONARY REHABILITATION PROGRAM

Has the patient entered a Pulmonary Rehabilitation Program since the last visit?

☐ No

☐ Yes

SmithKline Beecham
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Protocol		Patient Number	Patient Initials		Visit 3A Week 1
207499/156		[redacted]			

INVESTIGATOR INSTRUCTIONS

The following procedures (Vital Signs and ECG) must be performed greater than 4 hours after the patient's last albuterol administration.

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
☐☐☐/☐☐☐	☐☐☐

Are there any **clinically significant worsenings** since Baseline?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes.

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant changes noted at this examination compared to Baseline?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of this module.*

SmithKline Beecham
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Protocol	Patient Number	Patient Initials	Visit 3A Week 1
207499/156	[redacted]		

LABORATORY TESTS

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 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.

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes', please record the findings and/or diagnosis in the Adverse Experiences section (If a re-test is necessary, please use the Repeat Lab page at the end of this book)*

STUDY MEDICATION LABEL

Issue the patient a 10 day supply of study medication (20 tablets).

Attach the tear-off label from the study medication bottle dispensed at this visit in the space below. Record the start date in the Study Medication Record section in the next visit.

Attach label here

Enter 6-digit Code as it appears on the study medication label ☐☐☐☐☐☐

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

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 3A

- *If the patient **is not continuing** in the study, please complete the assessments for Visit 3A and Assessments for Patients Withdrawing at Visit 3A.*
- *If the patient **is continuing** in the study, please:*
  - *Issue the patient a diary card and remind the patient to use the card to record if they feel differently since starting the study.*
  - *Ask the patient to return to the clinic for Visit 4 as previously scheduled.*
  - ***Remind the patient:***

    i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after breakfast.*

    ii ***not** to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).*

    iii *to refrain from using albuterol or anticholinergic agents during the **4 hours** immediately preceding the 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 albuterol inhaler and spacer, and the diary card.*

    vi *to continue to take the anticholinergic medication, if prescribed, at a constant dose.*

    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, diarrhea, 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.*

PATIENT ACTIVITY POSTCARD

Please complete the patient activity postcard for ***Visit 3A*** located in the postcard section of this CRF. Detach the postcard and mail promptly. Postage has been prepaid.

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Withdrawal at Visit 3A Week 1
207499/156		[redacted]			

ASSESSMENTS FOR PATIENTS WITHDRAWING AT VISIT 3A

Complete the assessments below only for patients who are withdrawing from the study.

ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

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

COUGH AND SPUTUM PRODUCTION ASSESSMENTS

*Please ask the patient the following questions and record the answers below (Mark **one** box per section only.)*

COUGH

How troubled have you been by cough today?

[0] ☐ No symptoms at all

[1] ☐ Some symptoms, but hardly noticeable

[2] ☐ Symptoms noticeable and a little uncomfortable

[3] ☐ Symptoms definitely noticeable and uncomfortable

[4] ☐ Symptoms very bad and extremely uncomfortable

SPUTUM PRODUCTION

How much sputum have you produced today?

[0] ☐ No sputum at all

[1] ☐ Some sputum, but not as much as usual

[2] ☐ As much as usual

[3] ☐ More than usual

[4] ☐ A lot more than usual

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Withdrawal at Visit 3A Week 1
207499/156		[redacted]			

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a **clinically significant worsening** in the patient's physical condition since the previous examination?

☐ No

☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of this module.*

EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted? The distance walked should be entered even if the patient did not walk for 6 minutes.

☐ No

☐ Yes → *If 'Yes', Distance walked* ☐☐☐ Meters ☐

Yards ☐

Record any adverse experiences which occur during the exercise tolerance test in the Adverse Experience section at the back of this module.

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Withdrawal at Visit 3A Week 1
207499/156		[redacted]			

POST-EXERCISE ASSESSMENTS *(Immediately after the patient completes the exercise tolerance)*

Heart Rate ☐☐☐ beats/min

SaO_2 ☐☐☐ %

Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

"How short of breath do you feel right now?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Post-exercise breathlessness score ☐☐.☐

INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise test (rest for at least 10 minutes) before performing the pulmonary function tests.

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Withdrawal at Visit 3A Week 1
207499/156		[redacted]			

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 confirm that the pulmonary function tests were performed

[1] ☐ Not performed

[2] ☐ Performed

FECAL OCCULT BLOOD TEST

Issue the patient the fecal occult blood test kit. Instruct the patient to follow the Patient Instructions provided with the kit. Samples should be collected as specified on three consecutive bowel movements or three bowel movements closely spaced in time and returned to the clinic as soon as possible.

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

Are these findings clinically significant?

☐ No

☐ Yes → *If 'Yes' please record the details in the Adverse Experience section at the back of this module.*

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials	Withdrawal at Visit 3A Week 1
207499/156	[redacted]		

VITAL SIGNS - ORTHOSTATIC CHANGE

1st Measurement: After 5 Minutes Supine

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
___ / ___	___

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
___ / ___	___

Are there any **clincially significant worsenings** since Baseline?

☐ No

☐ Yes → *If 'Yes' please record details in the Adverse Experience section at the back of this module.*

INVESTIGATOR GLOBAL ASSESSMENT

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	Patient Initials		Withdrawal at Visit 3A Week 1
207499/156		[redacted]			

PATIENT GLOBAL ASSESSMENT

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

INVESTIGATOR INSTRUCTIONS

Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return for the Safety Follow-Up Visit in 7 +/- 3 days.

VISIT 4, WEEK 2

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	Visit 4 Week 2
207499/156		[redacted]			

PRESENTATION TO CLINIC

Record time of presentation to clinic ☐☐ 24hr:min

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?

☐ NA → Patient is not using beta$_2$ agonist.

☐ 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?

☐ NA → Patient is not using anticholinergic.

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: ☐☐☐ 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 : ☐☐

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials	Visit 4 Week 2
207499/156	[redacted]		

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes → *If 'Yes' please record details below. If the patient has had more than three Level 2 or 3 exacerbations since the start of double-blind medication, patient may be withdrawn after consultation with the Medical Monitor. If withdrawing, complete the assessments scheduled at this visit and the Assessments for Patients Withdrawing at Visit 4. The SGRQ and SF-36 should be completed before any additional assessments.*

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

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

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

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of excerbation (maximum level)	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1
	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2
	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations, including an increase in usual COPD medications, must be recorded in the COPD Medications or Procedures pages.

RESOURCE UTILIZATION

If the patient has received any COPD exacerbation-related medical care since the last visit, record details in the Resource Utilization section at the back of this module.

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials	Visit 4 Week 2
207499/156	[redacted]		

INDIRECT COST

Does the patient work?

☐ No

☐ Yes → *If 'Yes'*, has the patient missed work due to COPD-related symptoms, excluding scheduled protocol visits, since the last visit?

☐ No

☐ Yes → *If 'Yes', please record lost work days below:*

Start Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence

How many days since your last visit have you been restricted in performing your leisure activities, due to your COPD-related symptoms? *(please enter number of days below, if not restricted, enter 0)*

☐☐ Days

Since your last visit, how many hours per week did you require paid or unpaid assistance by a relative, friend or professional with your daily activities such as dressing, bathing, cooking, etc., due to your COPD-related symptoms? *(please enter number of hours below, if no paid or unpaid assistance, enter 0 in each instance)*

☐☐☐ Hours per week of **paid** assistance

☐☐☐ Hours per week of **unpaid** assistance

ADVERSE EXPERIENCES

If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

CONCOMITANT MEDICATION

If there has been any change in the patient's concomitant medication excluding treatment for COPD exacerbations (this is recorded in the COPD Exacerbations section) since the last visit, please record details in the Concomitant Medication section at the back of this module.

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 4 Week 2
207499/156		[redacted]			

"AS NEEDED" ALBUTEROL USE

Record the patient's evaluation of their 'as needed' albuterol use since the last visit.

[1] ☐ Much less than usual
[2] ☐ Less than usual
[3] ☐ About the same as usual
[4] ☐ More than usual
[5] ☐ Much more than usual

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	Patient Initials		Visit 4 Week 2
207499/156		[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. bid)

Date and time of last dose of study medication prior to the study visit Day Month Yr 24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
20					

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance < 80% or >120%?

☐ No

☐ Yes → *If 'Yes' please check the percent compliance at the previous visit. If compliance was <80% or >120% at the last visit, please contact the Medical Monitor to discuss patient withdrawal. If the patient is to be withdrawn from the study, complete the assessments scheduled at this visit and the Assessments for Patients Withdrawing at Visit 4. The SGRQ and SF-36 should be completed before any additional assessments.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 4 Week 2
207499/156		[redacted]			

OVERALL BREATHLESSNESS ASSESSMENT

Give the patient a copy of the following scale when assessing breathlessness.

Please ask the patient the following question and record the answer below.

"Generally speaking, how has your breathlessness been during the previous week when you carried out tasks that usually cause you to be short of breath (e.g. walking, carrying shopping, climbing stairs, etc)?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Overall breathlessness score ☐☐.☐

PULMONARY REHABILITATION PROGRAM

Has the patient entered a Pulmonary Rehabilitation Program since the last visit?

☐ No

☐ Yes

INVESTIGATOR INSTRUCTIONS

The following procedures (Vital Signs and ECG) must be performed greater than 4 hours after the patient's last albuterol administration.

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials	Visit 4 Week 2
207499/156	[redacted]		

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
☐☐☐/☐☐☐	☐☐☐

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes.

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant changes noted at this examination compared to the last visit?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of this module.*

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 confirm that the pulmonary function tests were performed

[1] ☐ Not Performed

[2] ☐ Performed

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials	Visit 4 Week 2
207499/156	[redacted]		

LABORATORY TESTS

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 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.

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes', please record the findings and/or diagnosis in the Adverse Experiences section (If a re-test is necessary, please use the Repeat Lab page at the end of this book)*

STUDY MEDICATION LABEL

Issue the patient a 20 day supply of study medication (2 bottles, 20 tablets per bottle). Attach the tear-off label from each of the study medication bottles 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

Attach study medication label here

Enter 6-digit Code as it appears on the study medication label ☐☐☐☐☐☐

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

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 4

- *If the patient **is not continuing** in the study, please complete the assessments for Visit 4 and the Assessments for Patients Withdrawing at Visit 4.*
- *If the patient **is continuing** in the study, please:*
    - *Issue the patient a diary card and and remind the patient to use the card to record if they feel differently since starting the study.*
    - *Ask the patient to return for the next visit in 14 +/- 3 days at 10:00 (+/-2 hours). Visit 5 must be performed in the morning.*
    - ***Remind the patient:***
        - i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after breakfast.*
        - ii ***not** to take the morning dose of study medication at home on the day of the next clinic visit.*
        - iii *to refrain from using albuterol or anticholinergic agents during the **4 hours** immediately preceding the 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 albuterol inhaler and spacer, and the diary card.*
        - vi *to continue to take the anticholinergic medication, if prescribed, at a constant dose.*
        - 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, diarrhea, 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.*

PHARMACOKINETIC EVALUATION REMINDER

Check the label on the front cover of this book to find out which sampling group (Early or Late) the patient was assigned to at Randomization (switching between groups is not permitted). Remind the patient that they will be having 2 blood samples drawn at the following visit and that the samples will be taken up to 2 hours post-dose for those in the Early group and up to 3 hours post-dose for those in the Late group.

PATIENT ACTIVITY POSTCARD

Please complete the patient activity postcard for ***Visit 4*** located in the postcard section of this CRF. Detach the postcard and mail promptly. Postage has been prepaid.

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Withdrawal at Visit 4 Week 2
207499/156		[redacted]			

ASSESSMENTS FOR PATIENTS WITHDRAWING AT VISIT 4

Complete the assessments below only for patients who are withdrawing from the study.

ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

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

INVESTIGATOR GLOBAL ASSESSMENT

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

PATIENT GLOBAL ASSESSMENT

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

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Protocol		Patient Number	Patient Initials		Withdrawal at Visit 4 Week 2
207499/156		[redacted]			

COUGH AND SPUTUM PRODUCTION ASSESSMENTS

*Please ask the patient the following questions and record the answers below (Mark **one** box per section only.)*

COUGH

How troubled have you been by cough today?

[0] ☐ No symptoms at all

[1] ☐ Some symptoms, but hardly noticeable

[2] ☐ Symptoms noticeable and a little uncomfortable

[3] ☐ Symptoms definitely noticeable and uncomfortable

[4] ☐ Symptoms very bad and extremely uncomfortable

SPUTUM PRODUCTION

How much sputum have you produced today?

[0] ☐ No sputum at all

[1] ☐ Some sputum, but not as much as usual

[2] ☐ As much as usual

[3] ☐ More than usual

[4] ☐ A lot more than usual

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a **clinically significant worsening** in the patient's physical condition since the previous examination?

☐ No

☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of this module.*

SmithKline Beecham
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Protocol		Patient Number	Patient Initials		Withdrawal at Visit 4 Week 2
207499/156		[redacted]			

FECAL OCCULT BLOOD TEST

Issue the patient the fecal occult blood test kit. Instruct the patient to follow the Patient Instructions provided with the kit. Samples should be collected as specified on three consecutive bowel movements or three bowel movements closely spaced in time and returned to the clinic as soon as possible.

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

Are these findings clinically significant?

☐ No

☐ Yes → *If 'Yes' please record the details in the Adverse Experience section at the back of this module.*

VITAL SIGNS - ORTHOSTATIC CHANGE

1st Measurement: After 5 Minutes Supine

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
☐☐☐/☐☐☐	☐☐☐

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
☐☐☐/☐☐☐	☐☐☐

Are there any **clincially significant worsenings** since Baseline?

☐ No

☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of this module.*

INVESTIGATOR INSTRUCTIONS

Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return for the Safety Follow-Up Visit in 7 +/- 3 days.

VISIT 5, WEEK 4

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	
207499/156		[redacted]			Visit 5 Week 4

PRESENTATION TO CLINIC

Record time of presentation to clinic ☐☐ 24hr:min

Visit 5 must be performed in the morning at 10:00 (± 2 hours).

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?

☐ NA → Patient is not using beta$_2$ agonist.

☐ 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?

☐ NA → Patient is not using anticholinergic.

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: ☐☐☐ 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 : ☐☐

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 5 Week 4
207499/156		[redacted]			

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes → *If 'Yes' please record details below. If the patient has had more than three Level 2 or 3 exacerbations since the start of double-blind medication, patient maybe withdrawn after consultation with the Medical Monitor. If withdrawing, complete the assessments scheduled at this visit (except for the post-dose pharmacokinetic blood sample) and the Assessments for Patients Withdrawing at Visit 5. The SGRQ and SF-36 should be completed before any additional assessments.*

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

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

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

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of excerbation (maximum level)	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1
	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2
	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations, including an increase in usual COPD medications, must be recorded in the COPD Medications or Procedures pages.

RESOURCE UTILIZATION

Please complete the Resource Utilization section at the back of this module. If the patient has received any COPD exacerbation-related medical care since the last visit, record details in the Resource Utilization section at the back of this module.

SmithKline Beecham Pharmaceuticals

Protocol	Patient Number	Patient Initials	Visit 5 Week 4
207499/156	[redacted]		

INDIRECT COST

Does the patient work?

☐ No

☐ Yes → *If 'Yes'*, has the patient missed work due to COPD-related symptoms, excluding scheduled protocol visits, since the last visit?

☐ No

☐ Yes → *If 'Yes', please record lost work days below:*

Start Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence

How many days since your last visit have you been restricted in performing your leisure activities, due to your COPD-related symptoms? *(please enter number of days below, if not restricted, enter 0)*

☐☐ Days

Since your last visit, how many hours per week did you require paid or unpaid assistance by a relative, friend or professional with your daily activities such as dressing, bathing, cooking, etc., due to your COPD-related symptoms? *(please enter number of hours below, if no paid or unpaid assistance, enter 0 in each instance)*

☐☐☐ Hours per week of **paid** assistance

☐☐☐ Hours per week of **unpaid** assistance

ADVERSE EXPERIENCES

Please complete the Adverse Experience section at the back of this module. If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 5 Week 4
207499/156		[redacted]			

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.

"AS NEEDED" ALBUTEROL USE

Record the patient's evaluation of their 'as needed' albuterol use since the last visit.

[1] ☐ Much less than usual
[2] ☐ Less than usual
[3] ☐ About the same as usual
[4] ☐ More than usual
[5] ☐ Much more than usual

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	Patient Initials		Visit 5 Week 4
207499/156		[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. bid)

Date and time of last dose of study medication prior to the study visit ____ Day Month Yr ____ 24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
40					

Note: Patients should not have taken the morning dose of study medication prior to this visit.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance < 80% or > 120%?

☐ No

☐ Yes → *If 'Yes' please check the percent compliance at the previous visit. If compliance was <80% or >120% at the last visit, please contact the Medical Monitor to discuss patient withdrawal. If the patient is to be withdrawn, complete the assessments scheduled at this visit (except for the post-dose pharmacokinetics blood sample) and the Assessments for Patients Withdrawing at Visit 5. The SGRQ and SF-36 should be completed before any additional assessments.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 5 Week 4
207499/156		[redacted]			

OVERALL BREATHLESSNESS ASSESSMENT

Give the patient a copy of the following scale when assessing breathlessness.

Please ask the patient the following question and record the answer below.

"Generally speaking, how has your breathlessness been during the previous week when you carried out tasks that usually cause you to be short of breath (e.g. walking, carrying shopping, climbing stairs, etc)?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Overall breathlessness score ☐☐.☐

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 Exercise Tolerance Test) must be performed greater than 4 hours after the patient's last albuterol administration.

SmithKline Beecham Pharmaceuticals

Protocol	Patient Number	Patient Initials	Visit 5 Week 4
207499/156	[redacted]		

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
☐☐☐ / ☐☐☐	☐☐☐

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes.

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant changes noted at this examination compared to the last visit?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of this module.*

EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted? The distance walked should be entered even if the patient did not walk for 6 minutes.

☐ No

☐ Yes → *If 'Yes', Distance walked* ☐☐☐ [M] Meters ☐

[YD] Yards ☐

Record any adverse experiences which occur during the exercise tolerance test in the Adverse Experience section at the back of this module.

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Protocol		Patient Number	Patient Initials		Visit 5 Week 4
207499/156		[redacted]			

POST-EXERCISE ASSESSMENTS *(Immediately after the patient completes the exercise tolerance)*

Heart Rate ☐☐☐ beats/min

SaO_2 ☐☐☐ %

Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

"How short of breath do you feel right now?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Post-exercise breathlessness score ☐☐.☐

INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise test (rest for at least 10 minutes) before performing the pulmonary function tests.

SmithKline Beecham Pharmaceuticals

Protocol	Patient Number	Patient Initials	Visit 5 Week 4
207499/156	[redacted]		

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 confirm that the pulmonary function tests were performed

[1] ☐ Not Performed

[2] ☐ Performed

LABORATORY TESTS

Please take blood samples for hematology, 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. If the pregnancy test is positive, please withdraw the patient from the study, complete the Serious Adverse Experiences form and forward it to SB within 24 hours. Complete the Visit for Early Withdrawal Between Scheduled Visits and the Study Continuation/ Withdrawal section at the back of this book.

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes', please record the findings and/or diagnosis in the Adverse Experiences section (If a re-test is necessary, please use the Repeat Lab page at the end of this book)*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 5 Week 4
207499/156		[redacted]			

PHARMACOKINETIC EVALUATIONS - PRE-DOSE BLOOD SAMPLE

Record the date and time of the previous two doses of study medication.

Study Medication Taken	Date Day Mth Yr	Time 24hr:min	Did the patient take this dose with food ?	
Yesterday's Morning Dose			☐ Yes	☐ No
Yesterday's Evening Dose			☐ Yes	☐ No

Collect a pre-dose blood sample (5mL) for pharmacokinetic evaluation.

Was a pharmacokinetic sample taken?

☐ No

☐ Yes → *If 'Yes',* 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)

Did the patient accidentally take this morning's dose prior to attending the clinic?

☐ No

☐ Yes → *If 'Yes', check that the Study Medication Record for this visit is recorded correctly.*

SmithKline Beecham
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Protocol	Patient Number	Patient Initials	Visit 5 Week 4
207499/156	[redacted]		

STUDY MEDICATION LABEL

Issue the patient a 35 day supply of study medication (1 bottle, 70 tablets). Attach the tear-off label from the study medication bottle dispensed at this visit in the space below. Record the start date in the Study Medication Record section in the next visit section. Issue the patient an albuterol inhaler and retrieve their old inhaler for 'as-required' use.

Attach study medication label here

Enter 6-digit Code as it appears on the study medication label ☐☐☐☐☐☐

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)

Reminder: The patient's evening dose of study medication must not be taken until the post-dose pharmacokinetic sample has been taken.

PHARMACOKINETIC EVALUATIONS - POST-DOSE BLOOD SAMPLE

A blood sample is to be collected for pharmacokinetic evaluation, but not immediately. Please read the instructions below carefully before proceeding and refer to the label on the front cover of this book for which group (Early or Late) the patient was assigned to. 'Early' sample is to be collected between 0.5 and 2 hours post dose at this visit. 'Late' sample is to be collected between 1.5 and 3 hours post dose at this visit. ***Note: it is very important that samples from different patients are obtained over a broad range of times within each of these pre-defined sampling "windows" to prevent data-bunching at the extremes of each window (e.g. do not routinely collect samples at 0.5 hours in every "Early" group patient, instead collect samples at random times between 0.5 and 2 hours in different patients in this group. The same applies for the other sampling window).***

Collect a blood sample (5mL) for pharmacokinetic evaluation.

Was a pharmacokinetic sample taken?

☐ No

☐ Yes → *If 'Yes'*, 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)

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 5

- *If the patient **is not continuing** in the study, please complete the assessments for Visit 5 (except the post-dose pharmacokinetics blood sample) and the Assessments for Patients Withdrawing at Visit 5.*
- *If the patient **is continuing** in the study, please:*
  - *Issue the patient a diary card and and remind the patient to use the card to record if they feel differently since starting the study.*
  - *Ask the patient to return for the next visit in 28 +/- 6 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 breakfast.*

    ii ***not** to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).*

    iii *to refrain from using albuterol or anticholinergic agents during the **4 hours** immediately preceding the 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 albuterol inhaler and spacer, and the diary card.*

    vi *to continue to take the anticholinergic medication, if prescribed, at a constant dose.*

    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, diarrhea, 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.*

PATIENT ACTIVITY POSTCARD

Please complete the patient activity postcard for ***Visit 5*** located in the postcard section of this CRF. Detach the postcard and mail promptly. Postage has been prepaid.

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Withdrawal at Visit 5 Week 4
207499/156		[redacted]			

ASSESSMENTS FOR PATIENTS WITHDRAWING AT VISIT 5

Complete the assessments below only for patients who are withdrawing from the study.

ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

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

INVESTIGATOR GLOBAL ASSESSMENT

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

PATIENT GLOBAL ASSESSMENT

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

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Pharmaceuticals

Protocol	Patient Number	Patient Initials	Withdrawal at Visit 5 Week 4
207499/156	[redacted]		

COUGH AND SPUTUM PRODUCTION ASSESSMENTS

*Please ask the patient the following questions and record the answers below (Mark **one** box per section only.)*

COUGH

How troubled have you been by cough today?

[0] ☐ No symptoms at all

[1] ☐ Some symptoms, but hardly noticeable

[2] ☐ Symptoms noticeable and a little uncomfortable

[3] ☐ Symptoms definitely noticeable and uncomfortable

[4] ☐ Symptoms very bad and extremely uncomfortable

SPUTUM PRODUCTION

How much sputum have you produced today?

[0] ☐ No sputum at all

[1] ☐ Some sputum, but not as much as usual

[2] ☐ As much as usual

[3] ☐ More than usual

[4] ☐ A lot more than usual

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a **clinically significant worsening** in the patient's physical condition since the previous examination?

☐ No

☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of this module.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Withdrawal at Visit 5 Week 4
207499/156		[redacted]			

FECAL OCCULT BLOOD TEST

Issue the patient the fecal occult blood test kit. Instruct the patient to follow the Patient Instructions provided with the kit. Samples should be collected as specified on three consecutive bowel movements or three bowel movements closely spaced in time and returned to the clinic as soon as possible.

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

Are these findings clinically significant?

☐ No

☐ Yes → *If 'Yes' please record the details in the Adverse Experience section at the back of this module.*

VITAL SIGNS - ORTHOSTATIC CHANGE

1st Measurement: After 5 Minutes Supine

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
☐☐☐ / ☐☐☐	☐☐☐

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
☐☐☐ / ☐☐☐	☐☐☐

Are there any **clincially significant worsenings** since Baseline?

☐ No

☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of this module.*

INVESTIGATOR INSTRUCTIONS

Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return for the Safety Follow-Up Visit in 7 +/- 3 days.

ADVERSE EXPERIENCES (Non-serious)

DEFINITIONS

INTENSITY (Maximum)

MILD	*Adverse experience which is easily tolerated*
MODERATE	*Adverse experience sufficiently discomforting to interfere with daily activities*
SEVERE	*Adverse experience which prevents normal everyday activities*

RELATIONSHIP TO INVESTIGATIONAL DRUG

NOT RELATED	*The adverse experience is definitely not related to the test drug*
UNLIKELY	*There are other more likely causes and the drug is not suspected as a cause*
SUSPECTED (REASONABLE POSSIBILITY)	*A direct cause and effect relationship between the drug and the adverse experience has not been demonstrated but there is a reasonable possibility that the experience was caused by the drug*
PROBABLE	*There probably is a direct cause and effect relationship between the adverse experience and the study drug*

SERIOUS ADVERSE EXPERIENCE (SAE)

An SAE is any 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	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

ADVERSE EXPERIENCES (Non-serious)

*Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Have you felt different in any way since starting the treatment or since the 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).

If no adverse experiences occured since Randomization, please mark this box. ☐

Adverse Experience *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***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) *See definitions page for Adverse Experience*	[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 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	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

ADVERSE EXPERIENCES (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

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the Serious Adverse Experience (SAE) section (See opposite for definitions of an SAE).

If no adverse experiences occured since Randomization, please mark this box. ☐

Adverse Experience *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***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) *See definitions page for Adverse Experience*	[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 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	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

ADVERSE EXPERIENCES (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

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the Serious Adverse Experience (SAE) section (See opposite for definitions of an SAE).

If no adverse experiences occured since Randomization, please mark this box. ☐

Adverse Experience *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***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) *See definitions page for Adverse Experience*	[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 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)

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

CONCOMITANT MEDICATION

Record any changes in concomitant medication taken since Randomization. (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 (albuterol) use, using the date the study inhaler was returned.

☐ No concomitant medication changes since Randomization

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 Route, see General Instructions for acceptable abbreviations.*

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 (albuterol) 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 Route, see General Instructions for acceptable abbreviations.*

MEDICAL PROCEDURES
excluding treatment for COPD Exacerbations
(These are recorded in the COPD Exacerbations section)

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 Randomization?

☐ 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			

COPD EXACERBATION SECTION

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 Randomization should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages***

If no COPD Exacerbations since randomization, please mark this box. ☐

Adverse Experience	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***If patient died, STOP: go to SAE COPD Exacerbation pages.***	[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) *See definitions page for Adverse Experience*	[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 COPD Medication and/or Medical Procedures section*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

DETAILS OF COPD EXACERBATIONS - CONTINUED

*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 Randomization should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages***

If no COPD Exacerbations since randomization, please mark this box. ☐

Adverse Experience	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***If patient died, STOP: go to SAE COPD Exacerbation pages.***	[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) *See definitions page for Adverse Experience*	[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 COPD Medication and/or Medical Procedures section*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No

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	Center Number	Patient Number	Patient Initials	SB Receipt Date (Day Month Year)
207499/156		[redacted]		

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation

Person Reporting SAE _____
(Please print clearly)

AEGIS Number _____

Serious Adverse Experience
(Please print clearly)

→ *Specify reason(s) for considering this a serious AE. Mark all that apply.*

For SmithKline Beecham

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

[1] ☐ fatal
[2] ☐ life threatening
[3] ☐ disabling/incapacitating
[4] ☐ results in hospitalization (excluding elective surgery or routine clinical procedures)
[5] ☐ hospitalization 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 COPD Medication and Medical Procedures section ←
☐ Yes ☐ No

Was patient withdrawn due to this specific SAE ?
☐ Yes ☐ No

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation (cont)

Relevant Laboratory Data
Please provide relevant abnormal laboratory data below

Test	Date	Value	Units	Normal Range
	Day Month Yr			
	Day Month Yr			
	Day Month Yr			
	Day Month Yr			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomization code broken at investigational site? ☐ No ☐ Yes

Randomization 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 _____

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

SERIOUS ADVERSE EXPERIENCE - COPD EXACERBATION (Cont.) PHARMACOKINETIC EVALUATION

If the patient presents to the clinic within 24 hours of the onset of a serious adverse experience (SAE) COPD Exacerbation or with an ongoing SAE COPD Exacerbation, please collect a blood sample (5mL) for pharmacokinetic evaluation.

Was a pharmacokinetic sample taken?

☐ No

☐ Yes → *If 'Yes',* 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 taken prior to the onset of the serious adverse experience - COPD exacerbation

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 serious adverse experience - COPD exacerbation?

☐ No

☐ Yes → *If 'Yes',* record date and time of last dose of study medication taken prior to collection of the pharmacokinetic sample.

Day Month Yr 24hr:min

Was this dose taken with food?

☐ No

☐ Yes

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

MEDICATION FOR COPD EXACERBATIONS

Has the patient taken any medication for COPD exacerbations since Randomization?

☐ No

☐ Yes → *If 'Yes', please record details below*

Drug Name (Trade Name Preferred)	Unit Dose (eg 500mg)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible) Day Mth Yr	End Date (or if Continuing mark box) Day Mth Yr	
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							

** For Route, see General Instructions for acceptable abbreviations.*

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

MEDICAL PROCEDURES FOR COPD EXACERBATIONS

Have any non-medication, therapeutic, diagnostic or surgical procedures been performed for COPD exacerbations since Randomization?

☐ 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		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			

RESOURCE UTILIZATION

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

RESOURCE UTILIZATION

Has the patient utilized any COPD Exacerbation-related medical care since Randomization?

☐ No

☐ Yes → *If 'Yes', please record details below*

Has the patient had any **Physician Visits** (COPD care excluding scheduled protocol visits) since Randomization?

☐ No

☐ Yes → *If 'Yes', please record details below*

Date of Visit Day Mth Yr	Reason for Visit

Has the patient had any **Emergency Room (ER)/Urgent Care Visits/Procedures (i.e., lung surgery)** since Randomization?

☐ No

☐ Yes → *If 'Yes', please record details below*

Date of Visit Day Mth Yr	Reason for Visit	Patient Admitted from ER? Yes	No
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐

SmithKline Beecham
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Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

RESOURCE UTILIZATION - (cont)

Has the patient had any **Hospitalizations** since Randomization?

☐ No

☐ Yes → *If 'Yes', please record details below* ***(also record details of any hospitalization in the Serious Adverse Experience - COPD Exacerbation section)***

Name of Hospital & City	Date of Admission Day Mth Yr	Date of Discharge Day Mth Yr	Reason for Admission

Has the patient had any **Intensive Care Unit (ICU) stays** ***(did the patient stay in the ICU during any of the above hospitalizations?)*** since Randomization?

☐ 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

VISIT 6, WEEK 8

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

MOD4

Please do not split modules

Module 4 : **Visit 6, Visit 7, Adverse Experiences, Concomitant Medication, Medical Procedures, COPD Exacerbations, Resource Utilization**

CRF Pages **127 - 173**

Unprocessed Forms : **Within this module the following occur which will generate attachments that need to be brought in-house.**

None

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Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	Visit 6 Week 8
207499/156		[redacted]			

PRESENTATION TO CLINIC

Record time of presentation to clinic ☐☐ 24hr:min

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?

☐ NA → Patient is not using beta$_2$ agonist.

☐ 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?

☐ NA → Patient is not using anticholinergic.

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: ☐☐☐ 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 : ☐☐

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes

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Pharmaceuticals

Protocol	Patient Number	Patient Initials	Visit 6 Week 8
207499/156	[redacted]		

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes → *If 'Yes' please record details below. If the patient has had more than three Level 2 or 3 exacerbations since the start of double-blind medication, patient may be withdrawn after consultation with the Medical Monitor. If withdrawing, complete the assessments scheduled at this visit and the Assessments for Patients Withdrawing at Visit 6. The SGRQ and SF-36 should be completed before any additional assessments.*

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

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

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

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of excerbation (maximum level)	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1
	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2
	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations, including an increase in usual COPD medications, must be recorded in the COPD Medications or Procedures pages.

RESOURCE UTILIZATION

If the patient has received any COPD exacerbation-related medical care since the last visit, record details in the Resource Utilization section at the back of this module.

SmithKline Beecham
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Protocol	Patient Number	Patient Initials	Visit 6 Week 8
207499/156	[redacted]		

INDIRECT COST

Does the patient work?

☐ No

☐ Yes → *If 'Yes', has the patient missed work due to COPD-related symptoms, excluding scheduled protocol visits, since the last visit?*

☐ No

☐ Yes → *If 'Yes', please record lost work days below:*

Start Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence

How many days since your last visit have you been restricted in performing your leisure activities, due to your COPD-related symptoms? *(please enter number of days below, if not restricted, enter 0)*

☐☐ Days

Since your last visit, how many hours per week did you require paid or unpaid assistance by a relative, friend or professional with your daily activities such as dressing, bathing, cooking, etc., due to your COPD-related symptoms? *(please enter number of hours below, if no paid or unpaid assistance, enter 0 in each instance)*

☐☐☐ Hours per week of **paid** assistance

☐☐☐ Hours per week of **unpaid** assistance

ADVERSE EXPERIENCES

If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

CONCOMITANT MEDICATION

If there has been any change in the patient's concomitant medication excluding treatment for COPD exacerbations (this is recorded in the COPD Exacerbations section) since the last visit, please record details in the Concomitant Medication section at the back of this module.

SmithKline Beecham
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Protocol	Patient Number	Patient Initials	Visit 6 Week 8
207499/156	[redacted]		

"AS NEEDED" ALBUTEROL USE

Record the patient's evaluation of their 'as needed' albuterol use since the last visit.

[1] ☐ Much less than usual
[2] ☐ Less than usual
[3] ☐ About the same as usual
[4] ☐ More than usual
[5] ☐ Much more than usual

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	Patient Initials	Visit 6 Week 8
207499/156	[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. bid)

Date and time of last dose of study medication prior to the study visit ____ Day Month Yr ____ 24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
70					

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance < 80% or >120%?

☐ No

☐ Yes → *If 'Yes' please check the percent compliance at the previous visit. If compliance was <80% or >120% at the last visit, please contact the Medical Monitor to discuss patient withdrawal. If the patient is to be withdrawn, complete the assessments scheduled at this visit and the Assessments for Patients Withdrawing at Visit 6. The SGRQ and SF-36 should be completed before any additional assessments.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 6 Week 8
207499/156		[redacted]			

OVERALL BREATHLESSNESS ASSESSMENT

Give the patient a copy of the following scale when assessing breathlessness.

Please ask the patient the following question and record the answer below.

"Generally speaking, how has your breathlessness been during the previous week when you carried out tasks that usually cause you to be short of breath (e.g. walking, carrying shopping, climbing stairs, etc)?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Overall breathlessness score ☐☐.☐

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 Exercise Tolerance Test) must be performed greater than 4 hours after the patient's last albuterol administration.

SmithKline Beecham
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Protocol	Patient Number	Patient Initials	Visit 6 Week 8
207499/156	[redacted]		

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
☐☐☐/☐☐☐	☐☐☐

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes.

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant changes noted at this examination compared to the last visit?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of this module.*

EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted? The distance walked should be entered even if the patient did not walk for 6 minutes.

☐ No

☐ Yes → *If 'Yes', Distance walked* ☐☐☐ [M] Meters ☐

[YD] Yards ☐

Record any adverse experiences which occur during the exercise tolerance test in the Adverse Experience section at the back of this module.

SmithKline Beecham
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Protocol		Patient Number	Patient Initials		Visit 6 Week 8
207499/156		[redacted]			

POST-EXERCISE ASSESSMENTS *(Immediately after the patient completes the exercise tolerance)*

Heart Rate ☐☐☐ beats/min

SaO_2 ☐☐☐ %

Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

"How short of breath do you feel right now?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Post-exercise breathlessness score ☐☐.☐

INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise test (rest for at least 10 minutes) before performing the pulmonary function tests.

SmithKline Beecham
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Protocol		Patient Number	Patient Initials		Visit 6 Week 8
207499/156		[redacted]			

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 confirm that the pulmonary function tests were performed

[1] ☐ Not Performed

[2] ☐ Performed

LABORATORY TESTS

Please take blood samples for hematology, 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. If the pregnancy test is positive, please withdraw the patient from the study, complete the Serious Adverse Experiences form and forward it to SB within 24 hours. Complete the Visit for Early Withdrawal between Scheduled Visits and the Study Continuation/ Withdrawal section at the back of this book.

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes', please record the findings and/or diagnosis in the Adverse Experiences section (If a re-test is necessary, please use the Repeat Lab page at the end of this book)*

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials	Visit 6 Week 8
207499/156	[redacted]		

STUDY MEDICATION LABEL

Issue the patient a 35 day supply of study medication (1 bottle, 70 tablets). Attach the tear-off label from the study medication bottle dispensed at this visit in the space below. Record the start date in the Study Medication Record section in the next visit section. Issue the patient an albuterol inhaler and retrieve their old inhaler for 'as-required' use.

Attach study medication label here

Enter 6-digit Code as it appears on the study medication label | | | | | | |

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

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 6

- *If the patient **is not continuing** in the study, please complete the assessments for Visit 6 and the Assessments for Patients Withdrawing at Visit 6.*
- *If the patient **is continuing** in the study, please:*
  - *Issue the patient a diary card and and remind the patient to use the card to record if they feel differently since starting the study.*
  - *Ask the patient to return for the next visit in 28 +/- 6 days at 10:00 (+/- 2 hours). Visit 7 must be performed in the morning.*
  - ***Remind the patient:***
    - i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after breakfast.*
    - ii ***not** to take the morning dose of study medication at home on the day of the next clinic visit.*
    - iii *to refrain from using albuterol or anticholinergic agents during the **4 hours** immediately preceding the 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 albuterol inhaler and spacer, and the diary card.*
    - vi *to continue to take the anticholinergic medication, if prescribed, at a constant dose.*
    - 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, diarrhea, 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.*

PHARMACOKINETIC EVALUATION REMINDER

Check the label on the front cover of this book to find out which sampling group (Early or Late) the patient was assigned to at Randomization (switching between groups is not permitted). Remind the patient that they will be having 2 blood samples drawn at the following visit and that the samples will be taken up to 6 hours post-dose for those in the Early group and up to 10 hours post-dose for those in the Late group. If the patient expresses unwillingness to stay in the clinic for so long at Visit 7, then the patient has the option of going home and coming back the same day.

PATIENT ACTIVITY POSTCARD

Please complete the patient activity postcard for ***Visit 6*** located in the postcard section of this CRF. Detach the postcard and mail promptly. Postage has been prepaid.

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Withdrawal at Visit 6 Week 8
207499/156		[redacted]			

ASSESSMENTS FOR PATIENTS WITHDRAWING AT VISIT 6

Complete the assessments below only for patients who are withdrawing from the study.

ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

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

INVESTIGATOR GLOBAL ASSESSMENT

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

PATIENT GLOBAL ASSESSMENT

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SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials	Withdrawal at Visit 6 Week 8
207499/156	[redacted]		

COUGH AND SPUTUM PRODUCTION ASSESSMENTS

*Please ask the patient the following questions and record the answers below (Mark **one** box per section only.)*

COUGH

How troubled have you been by cough today?

[0] ☐ No symptoms at all

[1] ☐ Some symptoms, but hardly noticeable

[2] ☐ Symptoms noticeable and a little uncomfortable

[3] ☐ Symptoms definitely noticeable and uncomfortable

[4] ☐ Symptoms very bad and extremely uncomfortable

SPUTUM PRODUCTION

How much sputum have you produced today?

[0] ☐ No sputum at all

[1] ☐ Some sputum, but not as much as usual

[2] ☐ As much as usual

[3] ☐ More than usual

[4] ☐ A lot more than usual

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a **clinically significant worsening** in the patient's physical condition since the previous examination?

☐ No

☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of this module.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Withdrawal at Visit 6 Week 8
207499/156		[redacted]			

FECAL OCCULT BLOOD TEST

Issue the patient the fecal occult blood test kit. Instruct the patient to follow the Patient Instructions provided with the kit. Samples should be collected as specified on three consecutive bowel movements or three bowel movements closely spaced in time and returned to the clinic as soon as possible.

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

Are these findings clinically significant?

☐ No

☐ Yes → *If 'Yes' please record the details in the Adverse Experience section at the back of this module.*

VITAL SIGNS - ORTHOSTATIC CHANGE

1st Measurement: After 5 Minutes Supine

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
☐☐☐/☐☐☐	☐☐☐

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
☐☐☐/☐☐☐	☐☐☐

Are there any **clincially significant worsenings** since Baseline?

☐ No

☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of this module.*

INVESTIGATOR INSTRUCTIONS

Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return for the Safety Follow-Up Visit in 7 +/- 3 days.

VISIT 7, WEEK 12

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	
207499/156		[redacted]			Visit 7 Week 12

PRESENTATION TO CLINIC

Record time of presentation to clinic ☐☐ 24hr:min

Visit 7 must be performed in the morning at 10:00 (± 2 hours).

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?

☐ NA → Patient is not using beta$_2$ agonist.

☐ 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?

☐ NA → Patient is not using anticholinergic.

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: ☐☐☐☐ 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 : ☐☐

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes

ST. GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE

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

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 7 Week 12
207499/156		[redacted]			

ST. GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE (PAGE 1 OF 5)

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St. George's Hospital Respiratory Questionnaire. Reproduced and used with permission from PW Jones. US version adapted and modified with permission by Judith Barr, Sc.D., Northeastern Univ., Boston, MA.

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Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 7 Week 12
207499/156		[redacted]			

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes → *If 'Yes' please record details below. If the patient has had more than three Level 2 or 3 exacerbations since the start of double-blind medication, patient may be withdrawn after consultation with the Medical Monitor. If withdrawing, complete the assessments scheduled at this visit (except for the post-dose pharmacokinetic blood sample) and the Assessments for Patients Withdrawing at Visit 7. The SGRQ and SF-36 should be completed before any additional assessments.*

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

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

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

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of excerbation (maximum level)	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1
	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2
	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations, including an increase in usual COPD medications, must be recorded in the COPD Medications or Procedures pages.

RESOURCE UTILIZATION

Please complete the Resource Utilization section at the back of this module. If the patient has received any COPD exacerbation related medical care since the previous visit, please complete the COPD Resource Utilization section at the back of this module.

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials	Visit 7 Week 12
207499/156	[redacted]		

INDIRECT COST

Does the patient work?

☐ No

☐ Yes → *If 'Yes'*, has the patient missed work due to COPD-related symptoms, excluding scheduled protocol visits, since the last visit?

☐ No

☐ Yes → *If 'Yes', please record lost work days below:*

Start Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence

How many days since your last visit have you been restricted in performing your leisure activities, due to your COPD-related symptoms? *(please enter number of days below, if not restricted, enter 0)*

☐☐ Days

Since your last visit, how many hours per week did you require paid or unpaid assistance by a relative, friend or professional with your daily activities such as dressing, bathing, cooking, etc., due to your COPD-related symptoms? *(please enter number of hours below, if no paid or unpaid assistance, enter 0 in each instance)*

☐☐☐ Hours per week of **paid** assistance

☐☐☐ Hours per week of **unpaid** assistance

ADVERSE EXPERIENCES

Please complete the Adverse Experience section at the back of this module. If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

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Protocol		Patient Number	Patient Initials		Visit 7 Week 12
207499/156		[redacted]			

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.

"AS NEEDED" ALBUTEROL USE

Record the patient's evaluation of their 'as needed' albuterol use since the last visit.

[1] ☐ Much less than usual
[2] ☐ Less than usual
[3] ☐ About the same as usual
[4] ☐ More than usual
[5] ☐ Much more than usual

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	Patient Initials	Visit 7 Week 12
207499/156	[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. bid)

Date and time of last dose of study medication prior to the study visit ____ ____ ____ (Day Month Yr) ____ ____ (24hr:min)

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
70					

Note: Patients should not have taken the morning dose of study medication prior to this visit.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance < 80% or >120%?

☐ No

☐ Yes → *If 'Yes' please check the percent compliance at the previous visit. If compliance was <80% or >120% at the last visit, please contact the Medical Monitor to discuss patient withdrawal. If the patient is to be withdrawn, complete the assessments scheduled at this visit (except for the post-dose pharmacokinetics blood sample) and the Assessments for Patients Withdrawing at Visit 7. The SF-36 should be completed before any additional assessments.*

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Protocol		Patient Number	Patient Initials		Visit 7 Week 12
207499/156		[redacted]			

OVERALL BREATHLESSNESS ASSESSMENT

Give the patient a copy of the following scale when assessing breathlessness.

Please ask the patient the following question and record the answer below.

"Generally speaking, how has your breathlessness been during the previous week when you carried out tasks that usually cause you to be short of breath (e.g. walking, carrying shopping, climbing stairs, etc)?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Overall breathlessness score ☐☐.☐

PULMONARY REHABILITATION PROGRAM

Has the patient entered a Pulmonary Rehabilitation Program since the last visit?

☐ No

☐ Yes

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 7 Week 12
207499/156		[redacted]			

COUGH AND SPUTUM PRODUCTION ASSESSMENTS

*Please ask the patient the following questions and record the answers below (Mark **one** box per section only.)*

COUGH

How troubled have you been by cough today?

[0] ☐ No symptoms at all

[1] ☐ Some symptoms, but hardly noticeable

[2] ☐ Symptoms noticeable and a little uncomfortable

[3] ☐ Symptoms definitely noticeable and uncomfortable

[4] ☐ Symptoms very bad and extremely uncomfortable

SPUTUM PRODUCTION

How much sputum have you produced today?

[0] ☐ No sputum at all

[1] ☐ Some sputum, but not as much as usual

[2] ☐ As much as usual

[3] ☐ More than usual

[4] ☐ A lot more than usual

INVESTIGATOR INSTRUCTIONS

The following procedures (Vital Signs, ECG, and Exercise Tolerance Test) must be performed greater than 4 hours after the patient's last albuterol administration.

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
☐☐☐ / ☐☐☐	☐☐☐

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 7 Week 12
207499/156		[redacted]			

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes.

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant changes noted at this examination compared to the last visit?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of this module.*

EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted? The distance walked should be entered even if the patient did not walk for 6 minutes.

☐ No

☐ Yes → *If 'Yes', Distance walked* ☐☐☐ [M] Meters ☐

[YD] Yards ☐

Record any adverse experiences which occur during the exercise tolerance test in the Adverse Experience section at the back of this module.

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Protocol		Patient Number	Patient Initials		Visit 7 Week 12
207499/156		[redacted]			

POST-EXERCISE ASSESSMENTS *(Immediately after the patient completes the exercise tolerance)*

Heart Rate ☐☐☐ beats/min

SaO_2 ☐☐☐ %

Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

"How short of breath do you feel right now?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Post-exercise breathlessness score ☐☐.☐

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Protocol	Patient Number	Patient Initials	Visit 7 Week 12
207499/156	[redacted]		

INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise tolerance test (rest for at least 10 minutes) before performing the pulmonary function tests.

PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed 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 confirm that the pulmonary function tests were performed

[1] ☐ Not Performed

[2] ☐ Performed

LABORATORY TESTS

Please take blood samples for hematology, 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. If the pregnancy test is positive, please withdraw the patient from the study, complete the Serious Adverse Experiences form and forward it to SB within 24 hours. Complete the Visit for Early Withdrawal Between Scheduled Visits and the Study Continuation/ Withdrawal section at the back of this book.

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes', please record the findings and/or diagnosis in the Adverse Experiences section (If a re-test is necessary, please use the Repeat Lab page at the end of this book)*

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Protocol		Patient Number	Patient Initials		Visit 7 Week 12
207499/156		[redacted]			

PHARMACOKINETIC EVALUATIONS - PRE-DOSE BLOOD SAMPLE

Record the date and time of the previous two doses of study medication.

Study Medication Taken	Date Day Mth Yr	Time 24hr:min	Did the patient take this dose with food ?	
Yesterday's Morning Dose			☐ Yes	☐ No
Yesterday's Evening Dose			☐ Yes	☐ No

Collect a pre-dose blood sample (5mL) for pharmacokinetic evaluation.

Was a pharmacokinetic sample taken?

☐ No

☐ Yes → *If 'Yes',* 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)

Did the patient accidentally take this morning's dose prior to attending the clinic?

☐ No

☐ Yes → *If 'Yes', check that the Study Medication Record for this visit is recorded correctly.*

SmithKline Beecham
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Protocol	Patient Number	Patient Initials	Visit 7 Week 12
207499/156	[redacted]		

STUDY MEDICATION LABEL

Issue the patient a 35 day supply of study medication (1 bottle, 70 tablets). Attach the tear-off label from the study medication bottle dispensed at this visit in the space below. Record the start date in the Study Medication Record section in the next visit section. Issue the patient an albuterol inhaler and retrieve their old inhaler for 'as-required' use.

Attach study medication label here

Enter 6-digit Code as it appears on the study medication label ☐☐☐☐☐☐

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)

Reminder: The patient's evening dose of study medication must not be taken until the post-dose pharmacokinetic sample has been taken.

PHARMACOKINETIC EVALUATIONS - POST-DOSE BLOOD SAMPLE

A blood sample is to be collected for pharmacokinetic evaluation, but not immediately. Please read the instructions below carefully before proceeding and refer to the label on the front cover of this book for which group (Early or Late) the patient was assigned to. 'Early' sample is to be collected between 3 and 6 hours post dose at this visit. 'Late' sample is to be collected between 5 and 10 hours post dose at this visit. ***Note: it is very important that samples from different patients are obtained over a broad range of times within each of these pre-defined sampling "windows" to prevent data-bunching at the extremes of each window (e.g. do not routinely collect samples at 3 hours in every "Early" group patient, instead collect samples at random times between 3 and 6 hours in different patients in this group. The same applies for the other sampling window).***

Collect a blood sample (5mL) for pharmacokinetic evaluation.

Was a pharmacokinetic sample taken?

☐ No

☐ Yes → *If 'Yes'*, 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)

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 7

- *If the patient **is not continuing** in the study, please complete the assessments for Visit 7 (except the post-dose pharmacokinetics blood sample) and the Assessments for Patients Withdrawing at Visit 7.*
- *If the patient **is continuing** in the study, please:*
  - *Issue the patient a diary card and and remind the patient to use the card to record if they feel differently since starting the study.*
  - *Ask the patient to return for the next visit in 28 +/- 6 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. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).*
    - iii *to refrain from using albuterol or anticholinergic agents during the **4 hours** immediately preceding the 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 albuterol inhaler and spacer, and the diary card.*
    - vi *to continue to take the anticholinergic medication, if prescribed, at a constant dose.*
    - 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, diarrhea, 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.*

PATIENT ACTIVITY POSTCARD

Please complete the patient activity postcard for ***Visit 7*** located in the postcard section of this CRF. Detach the postcard and mail promptly. Postage has been prepaid.

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials	Withdrawal at Visit 7 Week 12
207499/156	[redacted]		

ASSESSMENTS FOR PATIENTS WITHDRAWING AT VISIT 7

Complete the assessments below only for patients who are withdrawing from the study.

SF-36 QUESTIONNAIRE

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

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a **clinically significant worsening** in the patient's physical condition since the previous examination?

☐ No

☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of this module.*

INVESTIGATOR GLOBAL ASSESSMENT

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

PATIENT GLOBAL ASSESSMENT

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

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Protocol		Patient Number	Patient Initials		Withdrawal at Visit 7 Week 12
207499/156		[redacted]			

FECAL OCCULT BLOOD TEST

Issue the patient the fecal occult blood test kit. Instruct the patient to follow the Patient Instructions provided with the kit. Samples should be collected as specified on three consecutive bowel movements or three bowel movements closely spaced in time and returned to the clinic as soon as possible.

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

Are these findings clinically significant?

☐ No

☐ Yes → *If 'Yes' please record the details in the Adverse Experience section at the back of this module.*

VITAL SIGNS - ORTHOSTATIC CHANGE

1st Measurement: After 5 Minutes Supine

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
☐☐☐/☐☐☐	☐☐☐

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
☐☐☐/☐☐☐	☐☐☐

Are there any **clincially significant worsenings** since Baseline?

☐ No

☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of this module.*

INVESTIGATOR INSTRUCTIONS

Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return for the Safety Follow-Up Visit in 7 +/- 3 days.

ADVERSE EXPERIENCES (Non-serious)

DEFINITIONS

INTENSITY (Maximum)

MILD	*Adverse experience which is easily tolerated*
MODERATE	*Adverse experience sufficiently discomforting to interfere with daily activities*
SEVERE	*Adverse experience which prevents normal everyday activities*

RELATIONSHIP TO INVESTIGATIONAL DRUG

NOT RELATED	*The adverse experience is definitely not related to the test drug*
UNLIKELY	*There are other more likely causes and the drug is not suspected as a cause*
SUSPECTED (REASONABLE POSSIBILITY)	*A direct cause and effect relationship between the drug and the adverse experience has not been demonstrated but there is a reasonable possibility that the experience was caused by the drug*
PROBABLE	*There probably is a direct cause and effect relationship between the adverse experience and the study drug*

SERIOUS ADVERSE EXPERIENCE (SAE)

An SAE is any 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	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

ADVERSE EXPERIENCES (Non-serious)

*Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Have you felt different in any way since starting the treatment or since the 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).

If no adverse experiences occured since the previous module (i.e., since Visit 5), please mark this box. ☐

Adverse Experience *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***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) *See definitions page for Adverse Experience*	[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 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	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

ADVERSE EXPERIENCES (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

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the Serious Adverse Experience (SAE) section (See opposite for definitions of an SAE).

If no adverse experiences occured since the previous module (i.e., since Visit 5), please mark this box. ☐

Adverse Experience *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***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) *See definitions page for Adverse Experience*	[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 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	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

ADVERSE EXPERIENCES (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

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the Serious Adverse Experience (SAE) section (See opposite for definitions of an SAE).

If no adverse experiences occured since the previous module (i.e., since Visit 5), please mark this box. ☐

Adverse Experience *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***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) *See definitions page for Adverse Experience*	[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 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)

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

CONCOMITANT MEDICATION

Record any changes in concomitant medication taken since the previous module (i.e., since Visit 5). (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 (albuterol) use, using the date the study inhaler was returned.

☐ No concomitant medication changes since the previous module (i.e., since Visit 5)

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 Route, see General Instructions for acceptable abbreviations.*

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 (albuterol) 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 Route, see General Instructions for acceptable abbreviations.

MEDICAL PROCEDURES
excluding treatment for COPD Exacerbations
(These are recorded in the COPD Exacerbations section)

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 (i.e., since Visit 5)?

☐ 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			

COPD EXACERBATION SECTION

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 Visit 5 should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages***

If no COPD Exacerbations since previous module (i.e., since Visit 5), please mark this box. ☐

Adverse Experience	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***If patient died, STOP: go to SAE COPD Exacerbation pages.***	[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) *See definitions page for Adverse Experience*	[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 COPD Medication 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	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

DETAILS OF COPD EXACERBATIONS - CONTINUED

*An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy.*
All exacerbations of COPD since the previous module (i.e., since Visit 5) should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). ***COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages***

If no COPD Exacerbations since previous module (i.e., since Visit 5), please mark this box. ☐

Adverse Experience	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***If patient died, STOP: go to SAE COPD Exacerbation pages.***	[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) *See definitions page for Adverse Experience*	[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 COPD Medication and/or Medical Procedures section if appropriate*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No

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	Center Number	Patient Number	Patient Initials	SB Receipt Date Day Month Year
207499/156		[redacted]		

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation

Person Reporting SAE _____
(Please print clearly)

AEGIS Number

Serious Adverse Experience *(Please print clearly)*: **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

Specify reason(s) for considering this a serious AE. Mark all that apply.

- [1] ☐ fatal
- [2] ☐ life threatening
- [3] ☐ disabling/incapacitating
- [4] ☐ results in hospitalization (excluding elective surgery or routine clinical procedures)
- [5] ☐ hospitalization 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 COPD Medication and/or Medical Procedures section*: ☐ Yes ☐ No

Was patient withdrawn due to this specific SAE ?: ☐ Yes ☐ No

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation (cont)

Relevant Laboratory Data
Please provide relevant abnormal laboratory data below

Test	Date	Value	Units	Normal Range
	Day Month Yr			
	Day Month Yr			
	Day Month Yr			
	Day Month Yr			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomization code broken at investigational site? ☐ No ☐ Yes

Randomization 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 _____

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

SERIOUS ADVERSE EXPERIENCE - COPD EXACERBATION (Cont.) PHARMACOKINETIC EVALUATION

If the patient presents to the clinic within 24 hours of the onset of a serious adverse experience (SAE) COPD Exacerbation or with an ongoing SAE COPD Exacerbation, please collect a blood sample (5mL) for pharmacokinetic evaluation.

Was a pharmacokinetic sample taken?

☐ No

☐ Yes → *If 'Yes',* 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 taken prior to the onset of the serious adverse experience - COPD exacerbation

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 serious adverse experience - COPD exacerbation?

☐ No

☐ Yes → *If 'Yes',* record date and time of last dose of study medication taken prior to collection of the pharmacokinetic sample.

Day Month Yr 24hr:min

Was this dose taken with food?

☐ No

☐ Yes

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

MEDICATION FOR COPD EXACERBATIONS

Has the patient taken any medication for COPD exacerbations since the previous module (i.e., since Visit 5)?

☐ No

☐ Yes → *If 'Yes', please record details below*

Drug Name (Trade Name Preferred)	Unit Dose (eg 500mg)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible) Day Mth Yr	End Date (or if Continuing mark box) Day Mth Yr	
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							

** For Route, see General Instructions for acceptable abbreviations.*

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

MEDICAL PROCEDURES FOR COPD EXACERBATIONS

Have any non-medication, therapeutic, diagnostic or surgical procedures been performed for COPD exacerbations since the previous module (i.e., since Visit 5)?

☐ 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		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			

RESOURCE UTILIZATION

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

RESOURCE UTILIZATION

Has the patient utilized any COPD Exacerbation-related medical care since the previous module (i.e., since Visit 5)?

☐ No

☐ Yes → *If 'Yes', please record details below*

Has the patient had any **Physician Visits** (COPD care excluding scheduled protocol visits) since the previous module (i.e., since Visit 5)?

☐ No

☐ Yes → *If 'Yes', please record details below*

Date of Visit Day Mth Yr	Reason for Visit

Has the patient had any **Emergency Room (ER)/Urgent Care Visits/Procedures (i.e., lung surgery)** since the previous module (i.e., since Visit 5)?

☐ No

☐ Yes → *If 'Yes', please record details below*

Date of Visit Day Mth Yr	Reason for Visit	Patient Admitted from ER? Yes	No
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

RESOURCE UTILIZATION - (cont)

Has the patient had any **Hospitalizations** since the previous module (i.e., since Visit 5)?

☐ No

☐ Yes → *If 'Yes', please record details below* ***(also record details of any hospitalization in the Serious Adverse Experience - COPD Exacerbation section)***

Name of Hospital & City	Date of Admission Day Mth Yr	Date of Discharge Day Mth Yr	Reason for Admission

Has the patient had any **Intensive Care Unit (ICU) stays** ***(did the patient stay in the ICU during any of the above hospitalizations?)*** since the previous module (i.e., since Visit 5)?

☐ 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

EARLY WITHDRAWAL BETWEEN SCHEDULED VISITS

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

EW1

Please do not split modules

Module: **Early Withdrawal between scheduled visits**

CRF Pages **174 - 184**

Unprocessed Forms : **Within this module the following occur which will generate attachments that need to be brought in-house.**

SGRQ Quality of Life Assessment
SF-36

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

Complete these assessments ONLY for patients who withdraw from the study between scheduled clinic visits. These assessments should be completed within 24 hours of stopping study medication.

PRESENTATION TO CLINIC

Record time of presentation to clinic ☐☐ 24hr:min

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?

☐ NA → Patient is not using beta$_2$ agonist.

☐ 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?

☐ NA → Patient is not using anticholinergic.

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: ☐☐☐ (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 : ☐☐

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

ST. GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

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

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes ⟶ *If 'Yes' please record details below.*

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

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

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

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of excerbation (maximum level)	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1
	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2
	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of the module that contains the visit (or visit interval) at which the patient withdrew, 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.

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Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

RESOURCE UTILIZATION

If the patient has received any COPD exacerbation related medical care since the previous visit, record details in the Resource Utilization section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.

INDIRECT COST

Does the patient work?

☐ No

☐ Yes → *If 'Yes'*, has the patient missed work due to COPD-related symptoms, excluding scheduled protocol visits, since the last visit?

☐ No

☐ Yes → *If 'Yes', please record lost work days below:*

Start Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence

How many days since your last visit have you been restricted in performing your leisure activities, due to your COPD-related symptoms? *(please enter number of days below, if not restricted, enter 0)*

☐☐ Days

Since your last visit, how many hours per week did you require paid or unpaid assistance by a relative, friend or professional with your daily activities such as dressing, bathing, cooking, etc., due to your COPD-related symptoms? *(please enter number of hours below, if no paid or unpaid assistance, enter 0 in each instance)*

☐☐☐ Hours per week of **paid** assistance

☐☐☐ Hours per week of **unpaid** assistance

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

ADVERSE EXPERIENCES

If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of the module which contains the visit (or visit interval) at which the patient withdrew. 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 the module which contains the visit (or visit interval) at which the patient withdrew.

"AS NEEDED" ALBUTEROL USE

Record the patient's evaluation of their 'as needed' albuterol use since the last visit.

[1] ☐ Much less than usual
[2] ☐ Less than usual
[3] ☐ About the same as usual
[4] ☐ More than usual
[5] ☐ Much more than usual

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 the module which contains the visit (or visit interval) at which the patient withdrew.

INVESTIGATOR GLOBAL ASSESSMENT

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

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Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

PATIENT GLOBAL ASSESSMENT

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

COUGH AND SPUTUM PRODUCTION ASSESSMENTS

*Please ask the patient the following questions and record the answers below (Mark **one** box per section only.)*

COUGH

How troubled have you been by cough today?

[0] ☐ No symptoms at all

[1] ☐ Some symptoms, but hardly noticeable

[2] ☐ Symptoms noticeable and a little uncomfortable

[3] ☐ Symptoms definitely noticeable and uncomfortable

[4] ☐ Symptoms very bad and extremely uncomfortable

SPUTUM PRODUCTION

How much sputum have you produced today?

[0] ☐ No sputum at all

[1] ☐ Some sputum, but not as much as usual

[2] ☐ As much as usual

[3] ☐ More than usual

[4] ☐ A lot more than usual

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a **clinically significant worsening** in the patient's physical condition since the previous examination?

☐ No

☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of this module.*

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Pharmaceuticals

Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

FECAL OCCULT BLOOD TEST

Issue the patient the fecal occult blood test kit. Instruct the patient to follow the Patient Instructions provided with the kit. Samples should be collected as specified on three consecutive bowel movements or three bowel movements closely spaced in time and returned to the clinic as soon as possible.

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

Are these findings clinically significant?

☐ No

☐ Yes → *If 'Yes' please record the details in the Adverse Experience section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.*

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Pharmaceuticals

Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[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. bid)

Date and time of last dose of study medication prior to the study visit ☐☐ ☐☐ ☐☐ Day Month Yr ☐☐☐☐ 24hr:min

Did the patient take their last dose with food?

☐ No

☐ Yes

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance

Note: If this is a morning visit, patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance ≥ 80% and ≤120%?

☐ No

☐ Yes

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[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 and ECG) must be performed greater than 4 hours after the patient's last albuterol administration.

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
☐☐☐ / ☐☐☐	☐☐☐

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.*

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials	Early Withdrawal between Scheduled Visits
207499/156	[redacted]		

VITAL SIGNS - ORTHOSTATIC CHANGE

1st Measurement: After 5 Minutes Supine

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
☐☐☐ / ☐☐☐	☐☐☐

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
☐☐☐ / ☐☐☐	☐☐☐

Are there any clinically significant worsenings since Baseline?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes.

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant changes noted at this examination compared to the last visit?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.*

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Pharmaceuticals

Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted? The distance walked should be entered even if the patient did not walk for 6 minutes.

☐ No

☐ Yes → *If 'Yes', Distance walked* ☐☐☐ [M] Meters ☐

[YD] Yards ☐

Record any adverse experiences which occur during the exercise tolerance test in the Adverse Experience section at the back of the module which contains the visit (or visit interval) at which the patient withdrew).

POST-EXERCISE ASSESSMENTS *(Immediately after the patient completes the exercise tolerance)*

Heart Rate ☐☐☐ beats/min

SaO_2 ☐☐☐ %

Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

"How short of breath do you feel right now?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Post-exercise breathlessness score ☐☐.☐

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials	Early Withdrawal between Scheduled Visits
207499/156	[redacted]		

INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise test (rest for at least 10 minutes) before performing the pulmonary function tests.

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 confirm that the pulmonary function tests were performed

[1] ☐ Not performed

[2] ☐ Performed

LABORATORY TESTS

Please take blood samples for hematology, 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. If the pregnancy test is positive, please complete the Serious Adverse Experiences form and forward it to SB within 24 hours.

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes', please record the findings and/or diagnosis in the Adverse Experiences section (If a re-test is necessary, please use the Repeat Lab page at the end of this book)*

INSTRUCTION TO THE INVESTIGATOR

Please complete the Study Continuation / Withdrawal page at the end of Book 2.
Ask the patient to return for the Safety Follow-Up Visit in 7 +/- 3 days.

PATIENT ACTIVITY POSTCARD

Please complete the patient activity postcard for ***Early Withdrawal Between Scheduled Visits*** located in the postcard section of this CRF. Detach the postcard and mail promptly. Postage has been prepaid.

SAFETY FOLLOW-UP

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

SFU1

Please do not split modules

Module: Safety Follow-Up

CRF Pages 185 - 190

Unprocessed Forms : Within this module the following occur which will generate attachments that need to be brought in-house.

None

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	
207499/156		[redacted]			Safety Follow-Up

INVESTIGATOR INSTRUCTIONS

Complete these assessments only for those patients who have withdrawn from the study. These assessments should be completed within 7 +/- 3 days after discontinuation of study medication.

PRESENTATION TO CLINIC

Record time of presentation to clinic ☐☐ 24hr:min

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?

☐ NA → Patient is not using $beta_2$ agonist.

☐ 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?

☐ NA → Patient is not using anticholinergic.

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: ☐☐☐ 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 : ☐☐

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Safety Follow-Up
207499/156		[redacted]			

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes ⟶ *If 'Yes' please record details below.*

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

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

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

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of excerbation (maximum level)	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1
	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2
	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of the module which contains the visit (or the visit interval) at which the patient withdrew, 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 UTILIZATION

If the patient has received any COPD exacerbation related medical care since the previous visit, record details in the Resource Utilization section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Safety Follow-Up
207499/156		[redacted]			

INDIRECT COST

Does the patient work?

☐ No

☐ Yes → *If 'Yes'*, has the patient missed work due to COPD-related symptoms, excluding scheduled protocol visits, since the last visit?

☐ No

☐ Yes → *If 'Yes', please record lost work days below:*

Start Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence

How many days since your last visit have you been restricted in performing your leisure activities, due to your COPD-related symptoms? *(please enter number of days below, if not restricted, enter 0)*

☐☐ Days

Since your last visit, how many hours per week did you require paid or unpaid assistance by a relative, friend or professional with your daily activities such as dressing, bathing, cooking, etc., due to your COPD-related symptoms? *(please enter number of hours below, if no paid or unpaid assistance, enter 0 in each instance)*

☐☐☐ Hours per week of **paid** assistance

☐☐☐ Hours per week of **unpaid** assistance

ADVERSE EXPERIENCES

If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Safety Follow-Up
207499/156		[redacted]			

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 the module which contains the visit (or visit interval) at which the patient withdrew. ***At the patient's final study visit, record the end date for prn study rescue medication (albuterol) use, using the date the study inhaler was returned.***

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 the module which contains the visit (or visit interval) at which the patient withdrew.

PULMONARY REHABILITATION PROGRAM

Has the patient entered a Pulmonary Rehabilitation Program since the last visit?

☐ No

☐ Yes

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
☐☐☐/☐☐☐	☐☐☐

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Safety Follow-Up
207499/156		[redacted]			

12 LEAD ELECTROCARDIOGRAM

If any abnormalities were observed at the last visit, please perform a 12-lead ECG. The ECG should be performed after the patient has been semi-supine for 5 minutes.

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant changes noted at this examination compared to the last visit?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.*

LABORATORY TESTS

If abnormal laboratory results were reported at the previous visit, 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 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.

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes', please record the findings and/or diagnosis in the Adverse Experiences section at the back of the module which contains the visit (or visit interval) at which the patient withdrew. (If a re-test is necessary, please use the Repeat Lab page at the end of this book)*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Safety Follow-Up
207499/156		[redacted]			

PREGNANCY TEST

Is the patient a female of child-bearing potential?

☐ No

☐ Yes → *If 'Yes' please perform a urine pregnancy test locally.*

Urine Sample Date ☐☐ ☐☐☐ ☐☐
Day Month Yr

Is the patient pregnant?

☐ No

☐ Yes → *If the pregnancy test is positive, complete the Serious Adverse Experiences form and forward it to SB within 24 hours.*

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

If any abnormalities were noted at the last visit, please perform a physical examination (including respiratory examination).

Were any clinically significant changes noted at this examination compared to the last visit?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.*

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 confirm that the pulmonary function tests were performed

[1] ☐ Not performed

[2] ☐ Performed

PATIENT ACTIVITY POSTCARD

Please complete the patient activity postcard for ***Safety Follow-Up Visit*** located in the postcard section of this CRF. Detach the postcard and mail promptly. Postage has been prepaid.

STUDY CONTINUATION / WITHDRAWAL

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

CONC2

Please do not split modules

Module: **Study Continuation / Withdrawal**

CRF Pages **191**

Unprocessed Forms : **Within this module the following occur which will generate attachments that need to be brought in-house.**

None

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

STUDY CONTINUATION/WITHDRAWAL

Is the patient continuing in the study?

☐ Yes → *If 'Yes' please continue in Book 3.*

☐ No → *If 'No' please mark the **PRIMARY** cause of withdrawal and record the date of final visit and date of final dose.*

[1] ☐ Adverse experience (complete AE form)

[2] ☐ Insufficient therapeutic effect

[3] ☐ Protocol deviation (including non-compliance)

[4] ☐ Lost to follow-up

[7] ☐ Other - specify: _____

Date of Final Visit ☐☐ ☐☐ ☐☐ Day Month Yr

Date of Final Dose ☐☐ ☐☐ ☐☐ Day Month Yr

INVESTIGATOR SIGNATURE

I certify that I have reviewed the data on this case report form, 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	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

SAE2

Please do not split modules

Module: Serious Adverse Experiences, Pharmacokinetic Evaluation for Serious Adverse Experiences

CRF Pages 192 - 194

Unprocessed Forms : Within this module the following occur which will generate attachments that need to be brought in-house.

None

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	SB Receipt Date (Day Month Year)
207499/156		[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 hospitalization (excluding elective surgery or routine clinical procedures)
[5] hospitalization 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 section*
Yes No

Was patient withdrawn due to this specific SAE ?
Yes No

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 randomization code broken at investigational site? ☐ No ☐ Yes

Randomization 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 _____

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Protocol		Patient Number	Patient Initials		
207499/156		[redacted]			

SERIOUS ADVERSE EXPERIENCE (Cont.) PHARMACOKINETIC EVALUATION

If the patient presents to the clinic within 24 hours of the onset of a serious adverse experience (SAE) or with an ongoing SAE, please collect a blood sample (5mL) for pharmacokinetic evaluation.

Was a pharmacokinetic sample taken?

☐ No

☐ Yes → *If 'Yes',* 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 taken prior to the onset of the serious adverse experience

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 serious adverse experience?

☐ No

☐ Yes → *If 'Yes',* record date and time of last dose of study medication taken prior to collection of the pharmacokinetic sample.

Day Month Yr 24hr:min

Was this dose taken with food?

☐ No

☐ Yes

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Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

FORMD2

Please do not split modules

Module: Form D

CRF Pages: 195

SmithKline Beecham
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Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

FORM D

Certified Cause of Death _____

Date of Death Day Month Yr → *Please complete Serious Adverse Experience section.*

Was a post-mortem examination carried out?

☐ No

☐ Yes → *If 'Yes' please summarize findings (include diagnosis):*

_____

_____

_____

_____

Reporting Physician's Signature _____ Date Day Month Yr

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Protocol	Center Number	Patient Number	Patient Initials		OPTIONAL Repeat Lab
207499/156		[redacted]			

RPLAB2

Please do not split modules

Module: Repeat Lab

CRF Pages: 196

Unprocessed Forms: Within this module, the following tests / procedures occur which may generate attachments.

None

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Protocol	Center Number	Patient Number	Patient Initials		OPTIONAL Repeat Lab
207499/156		[redacted]			

REPEAT 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, complete the Early Withdrawal between Scheduled Visits 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.*

REPEAT 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, complete the Early Withdrawal between Scheduled Visits 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.*

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Protocol	Center Number	Patient Number	Patient Initials	Investigator
207499/156		[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	
MOD3	Vst 3-5, AE, CM, MP, COPD, RU	69 - 126	☐	☐	
MOD4	V6, V7 , AE, CM, MP, COPD, RU	127 - 173	☐	☐	
EW1	Early Withdrawal	174 - 184	☐	☐	
SFU1	Safety Follow-Up	185 - 190	☐	☐	
CONC2	Continuation/Withdrawal	191	☐	☐	
SAE2	Serious Adverse Experiences	192 - 194	☐	☐	
FORMD2	Form D	195	☐	☐	
RPLAB2	Repeat Lab	196	☐	☐	

If multiple modules are submitted together, please ensure they are sorted according to the order above

Site Monitor's Comments (e.g. protocol violations or deviations)

Site Monitor's Signature _____ Date Submitted ☐☐ ☐☐ ☐☐
Day Month Yr

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

CONFIDENTIAL

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PROTOCOL 207499/156

BOOK 3 : VISIT 8 TO STUDY CONCLUSION

A RANDOMIZED, 24-WEEK, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY, SAFETY AND TOLERABILITY OF ARIFLO™ (15 MG BID) IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

GENERAL INSTRUCTIONS

- *Write clearly in capital letters using a black ball point pen and press firmly so that all copies are legible*
- *Do not write in shaded areas*
- *Answer ALL questions on every page*
- *Enter "N/A" if information requested is not available*
- *Initial and date all changes, additions or deletions. Use a single pen stroke to remove an incorrect entry*
- *Enter the patient initials on all pages on which information has been entered and the patient number and center number where required*

Do not enter additional data/information after the set of CRF pages has been split/separated

The cover flap or plastic writing board should be used to divide each set of pages before writing on them with a ball point pen

DATE

Please use the following three-letter abbreviations for the months

January	JAN
February	FEB
March	MAR
April	APR
May	MAY
June	JUN
July	JUL
August	AUG
September	SEP
October	OCT
November	NOV
December	DEC

e.g. | 0 1 | J A N | 0 0 | = *1st January 2000*

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

PATIENT INITIALS

Please use the following format:

e.g. [redacted]

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*

STUDY PROCEDURES CHART 207499/156

Visit	1	2	3	3a	4	5	6	7	8	9	10		
	Screen		Baseline								End Double-blind	Early Withdrawal[1]	Final Safety Follow-up
Time relative to baseline (weeks)	-4	-2	0	+1	+2	+4	+8	+12	+16	+20	+24		+25
Signed written informed consent	x												
Medical & surgical history	x												
Physical examination[2]	x		x								x	x	x[3]
Pulmonary history & symptoms	x												
Postero-anterior chest radiograph[4]	x												
Exacerbation assessment/resource use	x	x	x	x	x	x	x	x	x	x	x	x	x
Medication history	x												
Overall breathlessness (modified Borg)	x	x	x		x	x	x	x	x	x	x		
Resting 12-lead ECG	x		x	x	x	x	x	x	x	x	x	x	x[3]
Vital signs (BP, HR)	x[5]	x	x[5]	x	x	x	x	x	x	x	x[5]	x[5]	x
Exercise Tolerance (6-Minute walk)	x	x	x			x	x	x	x	x	x	x	
Post-exercise SaO2 & breathlessness	x	x	x			x	x	x	x	x	x	x	
CO Diffusing Capacity (DLCO)[6]	x												
Albuterol reversibility[7]	x												
Laboratory tests	x		x[8]	x	x	x	x	x	x[9]	x[9]	x[8]	x[8]	x[3,9]
Dispense single-blind medication	x	x											
Albuterol Use		x	x	x	x	x	x	x	x	x	x		
Concomitant medication/medical procedures		x	x	x	x	x	x	x	x	x	x	x	x
PFTs (in absence of albuterol)[10]		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	
Baseline signs and symptoms/AEs[11]		x	x	x	x	x	x	x	x	x	x	x	x
Health status assessment: SGRQ			x					x			x	x	
Quality of life assessment: SF-36			x								x	x	
Cough and sputum assessments			x					x			x	x	
Pharmacokinetic evaluations[12]			x			x		x			x		
Arterial blood gas/SaO2[13]			x								x		
Hourly PFTs for 4 hrs post first/last dose [14]			x								x		
Dispense double-blind medication			x	x	x	x	x	x	x	x			
Investigator/Patient global assessment											x	x	
Study conclusion record												x	x

1 Patients who stop taking study medication between clinic visits will attend the clinic within 24 hours for an early withdrawal visit.

2 To include a respiratory examination.

3 If abnormalities at previous visit for patients who complete Visit 10 or withdraw from the study.

4 Postero-anterior chest X-ray must be performed at Visit 1 unless the film from a chest X-ray within the 12 weeks prior to Visit 1 is available to the Investigator.

5 Including Orthostatic vital signs.

6 DLCO should be done between Visit 1 and Visit 3 if not performed during the previous 24 weeks or if the results are unavailable.

7 Before and 15 to 30 (± 5) minutes after administration of 180 mcg albuterol via a MDI with a spacer to determine % predicted FEV_1, FVC, FEF_{25-75}, PEFR, and FEV_1: FVC.

8 In addition to usual laboratory tests, three fecal occult blood tests will be performed between Visits 1 and 3, between Visits 9 and 10, and at early withdrawal; amylase will be measured at Visit 3.

9 Urinary beta-HCG tests will be performed in females of childbearing potential. No other laboratory samples will be collected at Visits 8 and 9.

10 Includes FEV_1, FVC, FEF_{25-75}, PEFR, and FEV_1:FVC measured by centralized spirometry by the same person at each visit.

11 A diary will be used to record if patients feel different since starting study medication.

12 Visit 3: 3 hours post-dose. Visit 5: trough and 0.5-3 hours post-dose. Visit 7: trough and 3-10 hours post-dose. Visit 10: trough only.

13 In patients with <40% of predicted FEV_1 at Visit 1 and resting SaO_2 <88% or if the patient lives at a high altitude.

14 Pulmonary function tests 30 (± 5) minutes after albuterol followed by 4-hour post-double-blind drug assessments at Visits 3 and 10.

VISIT 8, WEEK 16

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Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

MOD5

Please do not split modules

Module 5 : Visit 8, Visit 9, Adverse Experiences, Concomitant Medications, Medical Procedures, COPD Exacerbations, Resource Utilization

CRF Pages 197 - 240

Unprocessed Forms : Within this module the following occur which will generate attachments that need to be brought in-house.

None

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Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	
207499/156		[redacted]			Visit 8 Week 16

PRESENTATION TO CLINIC

Record time of presentation to clinic ☐☐ 24hr:min

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?

☐ NA → Patient is not using beta$_2$ agonist.

☐ 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?

☐ NA → Patient is not using anticholinergic.

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: ☐☐☐ 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 : ☐☐

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes

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Protocol		Patient Number	Patient Initials		Visit 8 Week 16
207499/156		[redacted]			

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes → *If 'Yes' please record details below. If the patient has had more than three Level 2 or 3 exacerbations since the start of double-blind medication, patient may be withdrawn after consultation with the Medical Monitor. If withdrawing, complete the assessments scheduled at this visit and the Assessments for Patients Withdrawing at Visit 8. The SGRQ and SF-36 should be completed before any additional assessments.*

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

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

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

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of excerbation (maximum level)	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1
	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2
	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations, including an increase in usual COPD medications, must be recorded in the COPD Medications or Procedures pages.

RESOURCE UTILIZATION

If the patient has received any COPD exacerbation-related medical care since the last visit, record details in the Resource Utilization section at the back of this module.

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Protocol	Patient Number	Patient Initials	Visit 8 Week 16
207499/156	[redacted]		

INDIRECT COST

Does the patient work?

☐ No

☐ Yes → *If 'Yes'*, has the patient missed work due to COPD-related symptoms, excluding scheduled protocol visits, since the last visit?

☐ No

☐ Yes → *If 'Yes', please record lost work days below:*

Start Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence

How many days since your last visit have you been restricted in performing your leisure activities, due to your COPD-related symptoms? *(please enter number of days below, if not restricted, enter 0)*

☐☐ Days

Since your last visit, how many hours per week did you require paid or unpaid assistance by a relative, friend or professional with your daily activities such as dressing, bathing, cooking, etc., due to your COPD-related symptoms? *(please enter number of hours below, if no paid or unpaid assistance, enter 0 in each instance)*

☐☐☐ Hours per week of **paid** assistance

☐☐☐ Hours per week of **unpaid** assistance

ADVERSE EXPERIENCES

If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

CONCOMITANT MEDICATION

If there has been any change in the patient's concomitant medication excluding treatment for COPD exacerbations (this is recorded in the COPD Exacerbations section) since the last visit, please record details in the Concomitant Medication section at the back of this module.

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Protocol		Patient Number	Patient Initials		Visit 8 Week 16
207499/156		[redacted]			

"AS NEEDED" ALBUTEROL USE

Record the patient's evaluation of their 'as needed' albuterol use since the last visit.

[1] ☐ Much less than usual
[2] ☐ Less than usual
[3] ☐ About the same as usual
[4] ☐ More than usual
[5] ☐ Much more than usual

MEDICAL PROCEDURES

If there have been any non-medication, therapeutic, diagnostic or surgical procedures excluding those for COPD exacerbations (these are recorded in the COPD Exacerbations section) performed since the last visit, please record details in the Medical Procedures section at the back of this module.

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Protocol	Patient Number	Patient Initials	Visit 8 Week 16
207499/156	[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. bid)

Date and time of last dose of study medication prior to the study visit ☐☐☐☐☐☐ Day Month Yr ☐☐☐☐ 24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
70	☐☐	☐☐	☐☐	☐☐	☐☐☐

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance < 80% or > 120%?

☐ No

☐ Yes → *If 'Yes' please check the percent compliance at the previous visit. If compliance was <80% or >120% at the last visit, please contact the Medical Monitor to discuss patient withdrawal. If the patient is to be withdrawn, complete the assessments scheduled at this visit and the Assessments for Patients Withdrawing at Visit 8. The SGRQ and SF-36 should be completed before any additional assessments.*

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Protocol		Patient Number	Patient Initials		Visit 8 Week 16
207499/156		[redacted]			

OVERALL BREATHLESSNESS ASSESSMENT

Give the patient a copy of the following scale when assessing breathlessness.

Please ask the patient the following question and record the answer below.

"Generally speaking, how has your breathlessness been during the previous week when you carried out tasks that usually cause you to be short of breath (e.g. walking, carrying shopping, climbing stairs, etc)?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Overall breathlessness score ☐☐.☐

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 Exercise Tolerance Test) must be performed greater than 4 hours after the patient's last albuterol administration.

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Protocol	Patient Number	Patient Initials	Visit 8 Week 16
207499/156	[redacted]		

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
☐☐☐/☐☐☐	☐☐☐

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes.

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant changes noted at this examination compared to the last visit?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of this module.*

EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted? The distance walked should be entered even if the patient did not walk for 6 minutes.

☐ No

☐ Yes → *If 'Yes', Distance walked* ☐☐☐ Meters ☐

Yards ☐

Record any adverse experiences which occur during the exercise tolerance test in the Adverse Experience section at the back of this module.

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Protocol		Patient Number	Patient Initials		Visit 8 Week 16
207499/156		[redacted]			

POST-EXERCISE ASSESSMENTS *(Immediately after the patient completes the exercise tolerance)*

Heart Rate ☐☐☐ beats/min

SaO_2 ☐☐☐ %

Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

"How short of breath do you feel right now?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Post-exercise breathlessness score ☐☐.☐

INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise test (rest for at least 10 minutes) before performing the pulmonary function tests.

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Protocol	Patient Number	Patient Initials	Visit 8 Week 16
207499/156	[redacted]		

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 confirm that the pulmonary function tests were performed

[1] ☐ Not Performed

[2] ☐ Performed

PREGNANCY TEST

Is the patient a female of child-bearing potential?

☐ No

☐ Yes → *If 'Yes' please perform a urine pregnancy test locally.*

Urine Sample Date ☐☐ ☐☐☐ ☐☐
Day Month Yr

Is the patient pregnant?

☐ No

☐ Yes → *If 'Yes' please withdraw the patient from the study, complete the Serious Adverse Experiences form and forward it to SB within 24 hours. Complete the assessments scheduled at this visit and the Assessments for Patients Withdrawing at Visit 8. The SGRQ and SF-36 should be completed before any additional assessments.*

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Protocol	Patient Number	Patient Initials	Visit 8 Week 16
207499/156	[redacted]		

STUDY MEDICATION LABEL

Issue the patient a 35 day supply of study medication (1 bottles, 70 tablets). Attach the tear-off label from the study medication bottle dispensed at this visit in the space below. Record the start date in the Study Medication Record section in the next visit section. Issue the patient an albuterol inhaler and retrieve their old inhaler for 'as-required' use.

Attach study medication label here

Enter 6-digit Code as it appears on the study medication label | | | | | | |

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

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 8

- *If the patient **is not continuing** in the study, please complete the assessments for Visit 8 and the Assessments for Patients Withdrawing at Visit 8.*
- *If the patient **is continuing** in the study, please:*
  - *Issue the patient a diary card and and remind the patient to use the card to record if they feel differently since starting the study.*
  - *Ask the patient to return for the next visit in 28 +/- 6 days at the same time of day as at Visit 3.*
  - ***Remind the patient:***

    i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after breakfast.*

    ii ***not** to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).*

    iii *to refrain from using albuterol or anticholinergic agents during the **4 hours** immediately preceding the 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 albuterol inhaler and spacer, and the diary card.*

    vi *to continue to take the anticholinergic medication, if prescribed, at a constant dose.*

    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, diarrhea, 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.*

PATIENT ACTIVITY POSTCARD

Please complete the patient activity postcard for ***Visit 8*** located in the postcard section of this CRF. Detach the postcard and mail promptly. Postage has been prepaid.

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Protocol		Patient Number	Patient Initials		Withdrawal at Visit 8 Week 16
207499/156		[redacted]			

ASSESSMENTS FOR PATIENTS WITHDRAWING AT VISIT 8

Complete the assessments below only for patients who are withdrawing from the study.

ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

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

INVESTIGATOR GLOBAL ASSESSMENT

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

PATIENT GLOBAL ASSESSMENT

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	Patient Initials		Withdrawal at Visit 8 Week 16
207499/156		[redacted]			

COUGH AND SPUTUM PRODUCTION ASSESSMENTS

*Please ask the patient the following questions and record the answers below (Mark **one** box per section only.)*

COUGH

How troubled have you been by cough today?

[0] ☐ No symptoms at all

[1] ☐ Some symptoms, but hardly noticeable

[2] ☐ Symptoms noticeable and a little uncomfortable

[3] ☐ Symptoms definitely noticeable and uncomfortable

[4] ☐ Symptoms very bad and extremely uncomfortable

SPUTUM PRODUCTION

How much sputum have you produced today?

[0] ☐ No sputum at all

[1] ☐ Some sputum, but not as much as usual

[2] ☐ As much as usual

[3] ☐ More than usual

[4] ☐ A lot more than usual

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a **clinically significant worsening** in the patient's physical condition since the previous examination?

☐ No

☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of this module.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Withdrawal at Visit 8 Week 16
207499/156		[redacted]			

LABORATORY TESTS

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 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.

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes', please record the findings and/or diagnosis in the Adverse Experiences section (If a re-test is necessary, please use the Repeat Lab page at the end of this book)*

FECAL OCCULT BLOOD TEST

Issue the patient the fecal occult blood test kit. Instruct the patient to follow the Patient Instructions provided with the kit. Samples should be collected as specified on three consecutive bowel movements or three bowel movements closely spaced in time and returned to the clinic as soon as possible.

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

Are these findings clinically significant?

☐ No

☐ Yes → *If 'Yes' please record the details in the Adverse Experience section at the back of this module.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Withdrawal at Visit 8 Week 16
207499/156		[redacted]			

VITAL SIGNS - ORTHOSTATIC CHANGE

1st Measurement: After 5 Minutes Supine

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
___ / ___	___

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
___ / ___	___

Are there any **clincially significant worsenings** since Baseline?

☐ No

☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of this module.*

INVESTIGATOR INSTRUCTIONS

Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return for the Safety Follow-Up Visit in 7 +/- 3 days.

VISIT 9, WEEK 20

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Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	
207499/156		[redacted]			Visit 9 Week 20

PRESENTATION TO CLINIC

Record time of presentation to clinic ☐☐ 24hr:min

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?

☐ NA → Patient is not using beta$_2$ agonist.

☐ 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?

☐ NA → Patient is not using anticholinergic.

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: ☐☐☐ 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 : ☐☐

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes

SmithKline Beecham Pharmaceuticals

Protocol	Patient Number	Patient Initials	Visit 9 Week 20
207499/156	[redacted]		

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes → *If 'Yes' please record details below. If the patient has had more than three Level 2 or 3 exacerbations since the start of double-blind medication, patient may be withdrawn after consultation with Medical Monitor. If withdrawing, complete the assessments scheduled at this visit and the Assessments for Patients Withdrawing at Visit 9. The SGRQ and SF-36 should be completed before any additional assessments.*

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

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

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

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of excerbation (maximum level)	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1
	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2
	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations, including an increase in usual COPD medications, must be recorded in the COPD Medications or Procedures pages.

RESOURCE UTILIZATION

Please complete the Resource Utilization section at the back of this module. If the patient has received any COPD exacerbation-related medical care since the last visit, record details in the Resource Utilization section at the back of this module.

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials	Visit 9 Week 20
207499/156	[redacted]		

INDIRECT COST

Does the patient work?

☐ No

☐ Yes → *If 'Yes'*, has the patient missed work due to COPD-related symptoms, excluding scheduled protocol visits, since the last visit?

☐ No

☐ Yes → *If 'Yes', please record lost work days below:*

Start Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence

How many days since your last visit have you been restricted in performing your leisure activities, due to your COPD-related symptoms? *(please enter number of days below, if not restricted, enter 0)*

☐☐ Days

Since your last visit, how many hours per week did you require paid or unpaid assistance by a relative, friend or professional with your daily activities such as dressing, bathing, cooking, etc., due to your COPD-related symptoms? *(please enter number of hours below, if no paid or unpaid assistance, enter 0 in each instance)*

☐☐☐ Hours per week of **paid** assistance

☐☐☐ Hours per week of **unpaid** assistance

ADVERSE EXPERIENCES

Please complete the Adverse Experience section at the back of this module. If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

SmithKline Beecham
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Protocol		Patient Number	Patient Initials		Visit 9 Week 20
207499/156		[redacted]			

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.

"AS NEEDED" ALBUTEROL USE

Record the patient's evaluation of their 'as needed' albuterol use since the last visit.

[1] ☐ Much less than usual
[2] ☐ Less than usual
[3] ☐ About the same as usual
[4] ☐ More than usual
[5] ☐ Much more than usual

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	Patient Initials	Visit 9 Week 20
207499/156	[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. bid)

Date and time of last dose of study medication prior to the study visit ☐☐☐☐☐☐ ☐☐☐☐
Day Month Yr 24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
70	☐☐	☐☐	☐☐	☐☐	☐☐☐

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance < 80% or >120%?

☐ No

☐ Yes → *If 'Yes' please check the percent compliance at the previous visit. If compliance was <80% or >120% at the last visit, please contact the Medical Monitor to discuss patient withdrawal. If the patient is to be withdrawn, complete the assessments scheduled at this visit and the Assessments for Patients Withdrawing at Visit 9. The SGRQ and SF-36 should be completed before any additional assessments.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 9 Week 20
207499/156		[redacted]			

OVERALL BREATHLESSNESS ASSESSMENT

Give the patient a copy of the following scale when assessing breathlessness.

Please ask the patient the following question and record the answer below.

"Generally speaking, how has your breathlessness been during the previous week when you carried out tasks that usually cause you to be short of breath (e.g. walking, carrying shopping, climbing stairs, etc)?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Overall breathlessness score ☐☐.☐

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 Exercise Tolerance Test) must be performed greater than 4 hours after the patient's last albuterol administration.

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 9 Week 20
207499/156		[redacted]			

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
☐☐☐ / ☐☐☐	☐☐☐

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes.

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant changes noted at this examination compared to the last visit?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of this module.*

EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted? The distance walked should be entered even if the patient did not walk for 6 minutes.

☐ No

☐ Yes → *If 'Yes', Distance walked* ☐☐☐ Meters ☐

Yards ☐

Record any adverse experiences which occur during the exercise tolerance test in the Adverse Experience section at the back of this module.

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Protocol		Patient Number	Patient Initials		Visit 9 Week 20
207499/156		[redacted]			

POST-EXERCISE ASSESSMENTS *(Immediately after the patient completes the exercise tolerance)*

Heart Rate ☐☐☐ beats/min

SaO_2 ☐☐☐ %

Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

"How short of breath do you feel right now?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Post-exercise breathlessness score ☐☐.☐

INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise test (rest for at least 10 minutes) before performing the pulmonary function tests.

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 9 Week 20
207499/156		[redacted]			

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 confirm that the pulmonary function tests were performed

[1] ☐ Not Performed

[2] ☐ Performed

PREGNANCY TEST

Is the patient a female of child-bearing potential?

☐ No

☐ Yes → *If 'Yes' please perform a urine pregnancy test locally.*

Urine Sample Date ☐☐☐ Day Month Yr

Is the patient pregnant?

☐ No

☐ Yes → *If 'Yes' please withdraw the patient from the study, complete the Serious Adverse Experiences form and forward it to SB within 24 hours. Complete the assessments scheduled at this visit and the Assessments for Patients Withdrawing at Visit 9. The SGRQ and SF-36 should be completed before any additional assessments.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 9 Week 20
207499/156		[redacted]			

STUDY MEDICATION LABEL

Issue the patient a 35 day supply of study medication (1 bottle, 70 tablets). Attach the tear-off label from the study medication bottle dispensed at this visit in the space below. Record the start date in the Study Medication Record section in the next visit section. Issue the patient an albuterol inhaler and retrieve their old inhaler for 'as-required' use.

Attach study medication label here

Enter 6-digit Code as it appears on the study medication label | | | | | | |

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

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 9

- *If the patient **is not continuing** in the study, please complete the assessments for Visit 9 and the Assessments for Patients Withdrawing at Visit 9.*
- *If the patient **is continuing** in the study, please:*
  - *Issue the patient a diary card and and remind the patient to use the card to record if they feel differently since starting the study.*
  - *Issue the patient the fecal occult blood test kit. Instruct the patient to follow the Patient Instructions provided with the kit. Samples should be collected as specified and returned by the next visit.*
  - *Ask the patient to return for the next visit in 28 +/- 6 days at the same time of day as at Visit 3.*
  - ***Remind the patient:***

    i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after breakfast.*

    ii ***not** to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).*

    iii *to refrain from using albuterol or anticholinergic agents during the **4 hours** immediately preceding the 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 albuterol inhaler and spacer, and the diary card.*

    vi *to continue to take the anticholinergic medication, if prescribed, at a constant dose.*

    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, diarrhea, 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.*

PATIENT ACTIVITY POSTCARD

Please complete the patient activity postcard for ***Visit 9*** located in the postcard section of this CRF. Detach the postcard and mail promptly. Postage has been prepaid.

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Withdrawal at Visit 9 Week 20
207499/156		[redacted]			

ASSESSMENTS FOR PATIENTS WITHDRAWING AT VISIT 9

Complete the assessments below only for patients who are withdrawing from the study.

ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

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INVESTIGATOR GLOBAL ASSESSMENT

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PATIENT GLOBAL ASSESSMENT

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Pharmaceuticals

Protocol		Patient Number	Patient Initials		Withdrawal at Visit 9 Week 20
207499/156		[redacted]			

COUGH AND SPUTUM PRODUCTION ASSESSMENTS

*Please ask the patient the following questions and record the answers below (Mark **one** box per section only.)*

COUGH

How troubled have you been by cough today?

[0] ☐ No symptoms at all

[1] ☐ Some symptoms, but hardly noticeable

[2] ☐ Symptoms noticeable and a little uncomfortable

[3] ☐ Symptoms definitely noticeable and uncomfortable

[4] ☐ Symptoms very bad and extremely uncomfortable

SPUTUM PRODUCTION

How much sputum have you produced today?

[0] ☐ No sputum at all

[1] ☐ Some sputum, but not as much as usual

[2] ☐ As much as usual

[3] ☐ More than usual

[4] ☐ A lot more than usual

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a **clinically significant worsening** in the patient's physical condition since the previous examination?

☐ No

☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of this module.*

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Pharmaceuticals

Protocol		Patient Number	Patient Initials		Withdrawal at Visit 9 Week 20
207499/156		[redacted]			

LABORATORY TESTS

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 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.

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes', please record the findings and/or diagnosis in the Adverse Experiences section (If a re-test is necessary, please use the Repeat Lab page at the end of this book)*

FECAL OCCULT BLOOD TEST

Issue the patient the fecal occult blood test kit. Instruct the patient to follow the Patient Instructions provided with the kit. Samples should be collected as specified on three consecutive bowel movements or three bowel movements closely spaced in time and returned to the clinic as soon as possible.

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

Are these findings clinically significant?

☐ No

☐ Yes → *If 'Yes' please record the details in the Adverse Experience section at the back of this module.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Withdrawal at Visit 9 Week 20
207499/156		[redacted]			

VITAL SIGNS - ORTHOSTATIC CHANGE

1st Measurement: After 5 Minutes Supine

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
___ / ___	___

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
___ / ___	___

Are there any **clincially significant worsenings** since Baseline?

☐ No

☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of this module.*

INVESTIGATOR INSTRUCTIONS

Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return for the Safety Follow-Up Visit in 7 +/- 3 days.

ADVERSE EXPERIENCES (Non-serious)

DEFINITIONS

INTENSITY (Maximum)

MILD	*Adverse experience which is easily tolerated*
MODERATE	*Adverse experience sufficiently discomforting to interfere with daily activities*
SEVERE	*Adverse experience which prevents normal everyday activities*

RELATIONSHIP TO INVESTIGATIONAL DRUG

NOT RELATED	*The adverse experience is definitely not related to the test drug*
UNLIKELY	*There are other more likely causes and the drug is not suspected as a cause*
SUSPECTED (REASONABLE POSSIBILITY)	*A direct cause and effect relationship between the drug and the adverse experience has not been demonstrated but there is a reasonable possibility that the experience was caused by the drug*
PROBABLE	*There probably is a direct cause and effect relationship between the adverse experience and the study drug*

SERIOUS ADVERSE EXPERIENCE (SAE)

An SAE is any 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	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

ADVERSE EXPERIENCES (Non-serious)

*Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Have you felt different in any way since starting the treatment or since the previous 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).

If no adverse experiences occured since the previous module (i.e., since Visit 7), please mark this box. ☐

Adverse Experience *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***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) *See definitions page for Adverse Experience*	[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 and/or Medical Procedures section if appropriate* →	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No

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Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

ADVERSE EXPERIENCES (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 previous 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).

If no adverse experiences occured since the previous module (i.e., since Visit 7), please mark this box. ☐

Adverse Experience *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***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) *See definitions page for Adverse Experience*	[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 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	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

ADVERSE EXPERIENCES (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 previous 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).

If no adverse experiences occured since the previous module (i.e., since Visit 7), please mark this box. ☐

Adverse Experience *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***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) *See definitions page for Adverse Experience*	[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 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)

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

CONCOMITANT MEDICATION

Record any changes in concomitant medication taken since the previous module (i.e., since Visit 7). (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 (albuterol) use, using the date the study inhaler was returned.

☐ No concomitant medication changes since the previous module (i.e., since Visit 7)

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 Route, see General Instructions for acceptable abbreviations.*

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 (albuterol) 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 Route, see General Instructions for acceptable abbreviations.*

MEDICAL PROCEDURES
excluding treatment for COPD Exacerbations
(These are recorded in the COPD Exacerbations section)

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 (i.e., since Visit 7)?

☐ 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			

COPD EXACERBATION SECTION

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 previous module (i.e., since Visit 7) should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages***

If no COPD Exacerbations since previous module (i.e., since Visit 7), please mark this box. ☐

Adverse Experience	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***If patient died, STOP: go to SAE COPD Exacerbation pages.***	[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) *See definitions page for Adverse Experience form*	[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 COPD Medications and/or Medical Procedures page*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

DETAILS OF COPD EXACERBATIONS - CONTINUED

*An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy.*
All exacerbations of COPD since the previous module (i.e., since Visit 7) should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). ***COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages***

If no COPD Exacerbations since previous module (i.e., since Visit 7), please mark this box. ☐

Adverse Experience	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***If patient died, STOP: go to SAE COPD Exacerbation pages.***	[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) *See definitions page for Adverse Experience form*	[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 COPD Medications and/or Medical Procedures page*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

DETAILS OF COPD EXACERBATIONS - CONTINUED

*An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy.*
*All exacerbations of COPD since the previous module (i.e., since Visit 7) should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages***

If no COPD Exacerbations since previous module (i.e., since Visit 7), please mark this box. ☐

Adverse Experience	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***If patient died, STOP: go to SAE COPD Exacerbation pages.*** →	[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) *See definitions page for Adverse Experience form*	[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 COPD Medications and/or Medical Procedures page* →	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No

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	Center Number	Patient Number	Patient Initials	SB Receipt Date Day Month Year
207499/156		[redacted]		

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation

Person Reporting SAE _____ *(Please print clearly)*

AEGIS Number

Serious Adverse Experience *(Please print clearly)*: **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

Specify reason(s) for considering this a serious AE. Mark all that apply.

- [1] ☐ fatal
- [2] ☐ life threatening
- [3] ☐ disabling/incapacitating
- [4] ☐ results in hospitalization (excluding elective surgery or routine clinical procedures)
- [5] ☐ hospitalization 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 COPD Medication or Medical Procedures section*: ☐ Yes ☐ No

Was patient withdrawn due to this specific SAE ?: ☐ Yes ☐ No

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation (cont)

Relevant Laboratory Data
Please provide relevant abnormal laboratory data below

Test	Date	Value	Units	Normal Range
	Day Month Yr			
	Day Month Yr			
	Day Month Yr			
	Day Month Yr			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomization code broken at investigational site? ☐ No ☐ Yes

Randomization 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 _____

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

SERIOUS ADVERSE EXPERIENCE - COPD EXACERBATION (Cont.) PHARMACOKINETIC EVALUATION

If the patient presents to the clinic within 24 hours of the onset of a serious adverse experience (SAE) COPD Exacerbation or with an ongoing SAE COPD Exacerbation, please collect a blood sample (5mL) for pharmacokinetic evaluation.

Was a pharmacokinetic sample taken?

☐ No

☐ Yes → *If 'Yes',* 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 taken prior to the onset of the serious adverse experience - COPD exacerbation

☐☐ ☐☐☐ ☐☐ 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 serious adverse experience - COPD exacerbation?

☐ No

☐ Yes → *If 'Yes',* record date and time of last dose of study medication taken prior to collection of the pharmacokinetic sample.

☐☐ ☐☐☐ ☐☐ Day Month Yr ☐☐ 24hr:min

Was this dose taken with food?

☐ No

☐ Yes

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

MEDICATION FOR COPD EXACERBATIONS

Has the patient taken any medication for COPD exacerbations since the previous module (i.e., since Visit 7)?

☐ No

☐ Yes → *If 'Yes', please record details below*

Drug Name (Trade Name Preferred)	Unit Dose (eg 500mg)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible) Day Mth Yr	End Date (or if Continuing mark box) Day Mth Yr	
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							

* *For Route, see General Instructions for acceptable abbreviations.*

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

MEDICAL PROCEDURES FOR COPD EXACERBATIONS

Have any non-medication, therapeutic, diagnostic or surgical procedures been performed for COPD exacerbations since the previous module (i.e., since Visit 7)?

☐ 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		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			

RESOURCE UTILIZATION

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

RESOURCE UTILIZATION

Has the patient utilized any COPD Exacerbation-related medical care since the previous module (i.e., since Visit 7)?

☐ No

☐ Yes → *If 'Yes', please record details below*

Has the patient had any **Physician Visits** (COPD care excluding scheduled protocol visits) since the previous module (i.e., since Visit 7)?

☐ No

☐ Yes → *If 'Yes', please record details below*

Date of Visit Day Mth Yr	Reason for Visit

Has the patient had any **Emergency Room (ER)/Urgent Care Visits/Procedures (i.e., lung surgery)** between since the previous module (i.e., since Visit 7)?

☐ No

☐ Yes → *If 'Yes', please record details below*

Date of Visit Day Mth Yr	Reason for Visit	Patient Admitted from ER? Yes	No
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

RESOURCE UTILIZATION - (cont)

Has the patient had any **Hospitalizations** since the previous module (i.e., since Visit 7)?

☐ No

☐ Yes → *If 'Yes', please record details below* ***(also record details of any hospitalization in the Serious Adverse Experience - COPD Exacerbation section)***

Name of Hospital & City	Date of Admission Day Mth Yr	Date of Discharge Day Mth Yr	Reason for Admission

Has the patient had any **Intensive Care Unit (ICU) stays** ***(did the patient stay in the ICU during any of the above hospitalizations?)*** since the previous module (i.e., since Visit 7)?

☐ 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

VISIT 10, WEEK 24

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

MOD6

Please do not split modules

Module 6 : **Visit 10, Adverse Experiences, Concomitant Medications, Medical Procedures, COPD Exacerbations, Resource Utilization**

CRF Pages **241 - 280**

Unprocessed Forms : **Within this module the following occur which will generate attachments that need to be brought in-house.**

None

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	Visit 10 Week 24
207499/156		[redacted]			

PRESENTATION TO CLINIC

Record time of presentation to clinic ☐☐ 24hr:min

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?

☐ NA → Patient is not using beta$_2$ agonist.

☐ 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?

☐ NA → Patient is not using anticholinergic.

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: ☐☐☐ 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 : ☐☐

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes

ST. GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

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

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 10 Week 24
207499/156		[redacted]			

ST. GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE (PAGE 1 OF 5)

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SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day / Month / Year)	Visit 10 Week 24
207499/156		[redacted]			

SF - 36 (HEALTH STATUS QUESTIONNAIRE) (Page 1 of 5)

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Protocol	Patient Number	Patient Initials	Visit 10 Week 24
207499/156	[redacted]		

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes ⟶ *If 'Yes' please record details below.*

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

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

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

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of excerbation (maximum level)	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1
	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2
	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations, including an increase in usual COPD medications, must be recorded in the COPD Medications or Procedures pages.

RESOURCE UTILIZATION

Please complete the Resource Utilization section at the back of this module. If the patient has received any COPD exacerbation related medical care since the previous visit, please complete the COPD Resource Utilization section at the back of this module.

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Protocol		Patient Number	Patient Initials		Visit 10 Week 24
207499/156		[redacted]			

INDIRECT COST

Does the patient work?

☐ No

☐ Yes → *If 'Yes'*, has the patient missed work due to COPD-related symptoms, excluding scheduled protocol visits, since the last visit?

☐ No

☐ Yes → *If 'Yes', please record lost work days below:*

Start Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence

How many days since your last visit have you been restricted in performing your leisure activities, due to your COPD-related symptoms? *(please enter number of days below, if not restricted, enter 0)*

☐☐ Days

Since your last visit, how many hours per week did you require paid or unpaid assistance by a relative, friend or professional with your daily activities such as dressing, bathing, cooking, etc., due to your COPD-related symptoms? *(please enter number of hours below, if no paid or unpaid assistance, enter 0 in each instance)*

☐☐☐ Hours per week of **paid** assistance

☐☐☐ Hours per week of **unpaid** assistance

ADVERSE EXPERIENCES

Please complete the Adverse Experience section at the back of this module. If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

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Protocol		Patient Number	Patient Initials		Visit 10 Week 24
207499/156		[redacted]			

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.

"AS NEEDED" ALBUTEROL USE

Record the patient's evaluation of their 'as needed' albuterol use since the last visit.

[1] ☐ Much less than usual
[2] ☐ Less than usual
[3] ☐ About the same as usual
[4] ☐ More than usual
[5] ☐ Much more than usual

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.

FECAL OCCULT BLOOD TEST

The fecal occult blood test should be performed on three consecutive bowel movements or on bowel movements closely spaced in time between Visits 9 and 10.

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

Are these findings clinically significant?

☐ No

☐ Yes → *If 'Yes' please record the details in the Adverse Experience section at the back of this module.*

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Protocol		Patient Number	Patient Initials		Visit 10 Week 24
207499/156		[redacted]			

INVESTIGATOR GLOBAL ASSESSMENT

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PATIENT GLOBAL ASSESSMENT

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

COUGH AND SPUTUM PRODUCTION ASSESSMENTS

*Please ask the patient the following questions and record the answers below (Mark **one** box per section only.)*

COUGH

How troubled have you been by cough today?

[0] ☐ No symptoms at all

[1] ☐ Some symptoms, but hardly noticeable

[2] ☐ Symptoms noticeable and a little uncomfortable

[3] ☐ Symptoms definitely noticeable and uncomfortable

[4] ☐ Symptoms very bad and extremely uncomfortable

SPUTUM PRODUCTION

How much sputum have you produced today?

[0] ☐ No sputum at all

[1] ☐ Some sputum, but not as much as usual

[2] ☐ As much as usual

[3] ☐ More than usual

[4] ☐ A lot more than usual

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Protocol	Patient Number	Patient Initials	Visit 10 Week 24
207499/156	[redacted]		

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a **clinically significant worsening** in the patient's physical condition since the previous examination?

☐ No

☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of this module.*

OVERALL BREATHLESSNESS ASSESSMENT

Give the patient a copy of the following scale when assessing breathlessness.

Please ask the patient the following question and record the answer below.

"Generally speaking, how has your breathlessness been during the previous week when you carried out tasks that usually cause you to be short of breath (e.g. walking, carrying shopping, climbing stairs, etc)?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Overall breathlessness score ☐☐.☐

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 Exercise Tolerance Test) must be performed greater than 4 hours after the patient's last albuterol administration.

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Protocol		Patient Number	Patient Initials		Visit 10 Week 24
207499/156		[redacted]			

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
___ / ___	___

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

VITAL SIGNS - ORTHOSTATIC CHANGE

1st Measurement: After 5 Minutes Supine

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
___ / ___	___

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
___ / ___	___

Are there any clinically significant worsenings since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 10 Week 24
207499/156		[redacted]			

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes.

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant changes noted at this examination compared to the last visit?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of this module.*

RESTING SaO_2

Measure Resting SaO_2 by pulse oximetry for all patients with an FEV_1 < 40% of predicted for age, height and gender at Visit 1.

[1] ☐ Measurement not required (patient's FEV_1 at Visit 1 ≥ 40% of predicted)

[2] ☐ Measurement required but not performed

[3] ☐ Measurement taken, *please record value below:*

Resting SaO_2 ☐☐☐ %

EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted? The distance walked should be entered even if the patient did not walk for 6 minutes.

☐ No

☐ Yes → *If 'Yes', Distance walked* ☐☐☐ [M] Meters ☐

[YD] Yards ☐

Record any adverse experiences which occur during the exercise tolerance test in the Adverse Experience section at the back of this module.

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 10 Week 24
207499/156		[redacted]			

POST-EXERCISE ASSESSMENTS *(Immediately after the patient completes the exercise tolerance)*

Heart Rate ☐☐☐ beats/min

SaO_2 ☐☐☐ %

Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

"How short of breath do you feel right now?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Post-exercise breathlessness score ☐☐.☐

INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise tolerance test (rest for at least 10 minutes) before performing the pulmonary function tests.

SmithKline Beecham
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Protocol		Patient Number	Patient Initials		Visit 10 Week 24
207499/156		[redacted]			

PULMONARY FUNCTION TESTS (PRE-ALBUTEROL)

Pulmonary function tests will be assessed at least 4 hours after the last dose of inhaled beta-$_2$ agonist or anticholinergic agent.
NOTE: Additional pulmonary function tests will be performed after a dose of study albuterol is given in the clinic (see next page).

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 confirm that the pulmonary function tests were performed

[1] ☐ Not Performed

[2] ☐ Performed

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. If the pregnancy test is positive, complete the Serious Adverse Experiences form and forward it to SB within 24 hours.

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes', please record the findings and/or diagnosis in the Adverse Experiences section (If a re-test is necessary, please use the Repeat Lab page at the end of this book)*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 10 Week 24
207499/156		[redacted]			

ARTERIAL BLOOD GASES

If a resting SaO2 test was required at this visit AND the patient's resting SaO2 < 88% OR the patient lives at a high altitude, please take an arterial blood gas sample for analysis if feasible. The patient should be rested (5 to 10 minute rest) after pulmonary function tests.

☐ Not required

☐ Sample required but not taken

PO_2 (mmHg)	PCO_2 (mmHg)	HCO_3- (mEq/L)	pH	SaO_2 %
☐☐☐	☐☐	☐☐	☐.☐☐	☐☐☐

POST-ALBUTEROL PULMONARY FUNCTION TESTS

Administer 180mcg (2 puffs) of albuterol via MDI with a spacer using the study inhaler provided for "as required" rescue-medication use.

Record the time of albuterol inhalation ☐☐ 24hr:min

Wait 30 minutes *(+/-5 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 manuals).*** *For each set of three FEV_1 measurements, one FEV_1 must be within 10% of the highest.*

Please confirm that the pulmonary function tests were performed

[1] ☐ Not Performed

[2] ☐ Performed

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 10 Week 24
207499/156		[redacted]			

PHARMACOKINETIC EVALUATIONS - PRE-DOSE BLOOD SAMPLE

Record the date and time of the previous two doses of study medication.

Study Medication Taken	Date Day Mth Yr	Time 24hr:min	Did the patient take this dose with food ?	
Yesterday's Morning Dose			☐ Yes	☐ No
Yesterday's Evening Dose			☐ Yes	☐ No

Collect a pre-dose blood sample (5mL) for pharmacokinetic evaluation.

Was a pharmacokinetic sample taken?

☐ No

☐ Yes → *If 'Yes',* 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)

Did the patient accidentally take this morning's dose prior to attending the clinic?

☐ No

☐ Yes → *If 'Yes', check that the Study Medication Record for this visit is recorded correctly.*

ADMINISTRATION OF STUDY MEDICATION

Give the patient their dose of study medication (from the bottle dispensed at Visit 9) with food and record the date and time of administration below.

Date and time of administration Day Month Yr 24hr:min

Note: If this is a morning visit, patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 10 Week 24
207499/156		[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 (and should reflect the date of the dose given in the clinic at Visit 10). Record interruptions or changes in dose on separate lines.

Start Date Day Mth Yr	End Date Day Mth Yr	Number of tablets per dose	Frequency (e.g. bid)

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
70					

Note: Include the dose of study medication given to the patient at this visit.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance < 80% or > 120%?

☐ No

☐ Yes

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials	Visit 10 Week 24
207499/156	[redacted]		

POST-DOSE PULMONARY FUNCTION TESTS

Pulmonary function tests will be completed every hour in the 4-hour period following administration of the dose of study medication.

Ask the patient to avoid using their albuterol or anticholinergic medication and to refrain from smoking if at all possible.

If the patient uses their albuterol or anticholinergic medication during this period, the tests should be abandoned.

Time post-dose	Completed?	
	Yes	No
1 Hour	☐	☐
2 Hours	☐	☐
3 Hours	**Perform ECG**	
3 Hours	☐	☐
4 Hours	☐	☐

Record any adverse experiences which occur during the pulmonary function tests in the Adverse Experience section at the back of this module.

12 LEAD ELECTROCARDIOGRAM - 3 HOURS POST DOSE

The ECG should be performed before the 3-hour post-dose pulmonary function test and after the patient has been semi-supine for 5 minutes.

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant changes noted at this examination compared to the ECG performed earlier in this visit?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of this module.*

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 10

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 previous COPD medications as appropriate.*
- ***Remind the patient:***

  i *to refrain from using albuterol or anticholinergic agents during the **4 hours** immediately preceding the visit.*

  ii *to refrain from smoking for **2 hours** immediately preceding the visit.*

  iii *to bring the study albuterol inhaler and spacer to the visit.*

  iv *to call the investigator as soon as possible to report any gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhea, 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.*

PATIENT ACTIVITY POSTCARD

Please complete the patient activity postcard for ***Visit 10*** located in the postcard section of this CRF. Detach the postcard and mail promptly. Postage has been prepaid.

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	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

ADVERSE EXPERIENCES (Non-serious)

*Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Have you felt different in any way since starting the treatment or since the previous 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).

If no adverse experiences occured since the last visit, please mark this box. ☐

Adverse Experience *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***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) *See definitions page for Adverse Experience*	[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 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
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Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

ADVERSE EXPERIENCES (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 previous 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).

If no adverse experiences occured since the last visit, please mark this box. ☐

Adverse Experience *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***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) *See definitions page for Adverse Experience*	[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 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	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

ADVERSE EXPERIENCES (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 previous 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).

If no adverse experiences occured since the last visit, please mark this box. ☐

Adverse Experience *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***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) *See definitions page for Adverse Experience*	[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 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)

SmithKline Beecham
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Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

CONCOMITANT MEDICATION

Record any changes in concomitant medication taken since the last 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 (albuterol) use, using the date the study inhaler was returned.

☐ No concomitant medication changes since the last visit

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 Route, see General Instructions for acceptable abbreviations.*

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 (albuterol) 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 Route, see General Instructions for acceptable abbreviations.*

MEDICAL PROCEDURES
excluding treatment for COPD Exacerbations
(These are recorded in the COPD Exacerbations section)

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 visit?

☐ 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			

COPD EXACERBATION SECTION

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[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 visit should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages***

If no COPD Exacerbations since the last visit, please mark this box. ☐

Adverse Experience	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***If patient died, STOP: go to SAE COPD Exacerbation pages.*** →	[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) *See definitions page for Adverse Experience*	[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 COPD Medication 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	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

DETAILS OF COPD EXACERBATIONS - CONTINUED

*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 since the last visit should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages***

If no COPD Exacerbations since the last visit, please mark this box. ☐

Adverse Experience	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***If patient died, STOP: go to SAE COPD Exacerbation pages.***	[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) *See definitions page for Adverse Experience*	[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 COPD Medication 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	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

DETAILS OF COPD EXACERBATIONS - CONTINUED

*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 since the last visit should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages***

If no COPD Exacerbations since the last visit, please mark this box. ☐

Adverse Experience	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***If patient died, STOP: go to SAE COPD Exacerbation pages.***	[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) *See definitions page for Adverse Experience*	[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 COPD Medication and/or Medical Procedures section if appropriate*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No

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	Center Number	Patient Number	Patient Initials	SB Receipt Date (Day Month Year)
207499/156		[redacted]		

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation

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 hospitalization (excluding elective surgery or routine clinical procedures)
[5] ☐ hospitalization 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 COPD Medication or Medical Procedures section* ←
☐ Yes ☐ No

Was patient withdrawn due to this specific SAE ?
☐ Yes ☐ No

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation (cont)

Relevant Laboratory Data
Please provide relevant abnormal laboratory data below

Test	Date	Value	Units	Normal Range
	Day Month Yr			
	Day Month Yr			
	Day Month Yr			
	Day Month Yr			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomization code broken at investigational site? ☐ No ☐ Yes

Randomization 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

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

SERIOUS ADVERSE EXPERIENCE - COPD EXACERBATION (Cont.) PHARMACOKINETIC EVALUATION

If the patient presents to the clinic within 24 hours of the onset of a serious adverse experience (SAE) COPD Exacerbation or with an ongoing SAE COPD Exacerbation, please collect a blood sample (5mL) for pharmacokinetic evaluation.

Was a pharmacokinetic sample taken?

☐ No

☐ Yes → *If 'Yes',* 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 taken prior to the onset of the serious adverse experience - COPD exacerbation

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 serious adverse experience - COPD exacerbation?

☐ No

☐ Yes → *If 'Yes',* record date and time of last dose of study medication taken prior to collection of the pharmacokinetic sample.

Day Month Yr 24hr:min

Was this dose taken with food?

☐ No

☐ Yes

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

MEDICATION FOR COPD EXACERBATIONS

Has the patient taken any medication for COPD exacerbations since the previous visit?

☐ No

☐ Yes → *If 'Yes', please record details below*

Drug Name (Trade Name Preferred)	Unit Dose (eg 500mg)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible) Day Mth Yr	End Date (or if Continuing mark box) Day Mth Yr	
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							

** For Route, see General Instructions for acceptable abbreviations.*

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

MEDICAL PROCEDURES FOR COPD EXACERBATIONS

Have any non-medication, therapeutic, diagnostic or surgical procedures been performed for COPD exacerbations since the previous visit?

☐ 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		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			

RESOURCE UTILIZATION

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

RESOURCE UTILIZATION

Has the patient utilized any COPD Exacerbation-related medical care since the last visit?

☐ No

☐ Yes → *If 'Yes', please record details below*

Has the patient had any **Physician Visits** (COPD care excluding scheduled protocol visits) since the last visit?

☐ No

☐ Yes → *If 'Yes', please record details below*

Date of Visit Day Mth Yr	Reason for Visit

Has the patient had any **Emergency Room (ER)/Urgent Care Visits/Procedures (i.e., lung surgery)** since the last visit?

☐ No

☐ Yes → *If 'Yes', please record details below*

Date of Visit Day Mth Yr	Reason for Visit	Patient Admitted from ER? Yes	No
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

RESOURCE UTILIZATION - (cont)

Has the patient had any **Hospitalizations** since the last visit?

☐ No

☐ Yes → *If 'Yes', please record details below* ***(also record details of any hospitalization in the Serious Adverse Experience - COPD Exacerbation section)***

Name of Hospital & City	Date of Admission Day Mth Yr	Date of Discharge Day Mth Yr	Reason for Admission

Has the patient had any **Intensive Care Unit (ICU) stays** ***(did the patient stay in the ICU during any of the above hospitalizations?)*** since the last visit?

☐ 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

EARLY WITHDRAWAL BETWEEN SCHEDULED VISITS

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

EW2

Please do not split modules

Module : **Early Withdrawal Between Scheduled Visits**

CRF Pages **281 - 291**

Unprocessed Forms : **Within this module the following occur which will generate attachments that need to be brought in-house.**

Early Withdrawal:
SGRQ Quality of Life Assessment
SF-36 Quality of Life Assessment

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

Complete these assessments ONLY for patients who withdraw from the study between scheduled clinic visits. These assessments should be completed within 24 hours of stopping study medication.

PRESENTATION TO CLINIC

Record time of presentation to clinic ☐☐ 24hr:min

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?

☐ NA → Patient is not using $beta_2$ agonist.

☐ 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?

☐ NA → Patient is not using anticholinergic.

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: ☐☐☐ 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 : ☐☐

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

ST. GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

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

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes ⟶ *If 'Yes' please record details below.*

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

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

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

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of excerbation (maximum level)	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1
	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2
	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of the module which contains the visit (or visit interval) at which the patient withdrew, 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 UTILIZATION

If the patient has received any COPD exacerbation related medical care since the previous visit, record details in the Resource Utilization section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

INDIRECT COST

Does the patient work?

☐ No

☐ Yes → *If 'Yes'*, has the patient missed work due to COPD-related symptoms, excluding scheduled protocol visits, since the last visit?

☐ No

☐ Yes → *If 'Yes', please record lost work days below:*

Start Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence

How many days since your last visit have you been restricted in performing your leisure activities, due to your COPD-related symptoms? *(please enter number of days below, if not restricted, enter 0)*

☐☐ Days

Since your last visit, how many hours per week did you require paid or unpaid assistance by a relative, friend or professional with your daily activities such as dressing, bathing, cooking, etc., due to your COPD-related symptoms? *(please enter number of hours below, if no paid or unpaid assistance, enter 0 in each instance)*

☐☐☐ Hours per week of **paid** assistance

☐☐☐ Hours per week of **unpaid** assistance

ADVERSE EXPERIENCES

If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of the module which contains the visit (or visit interval) at which the patient withdrew. The patient should refer to the notes in their diary when answering this question.

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

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 the module which contains the visit (or visit interval) at which the patient withdrew.

"AS NEEDED" ALBUTEROL USE

Record the patient's evaluation of their 'as needed' albuterol use since the last visit.

[1] ☐ Much less than usual
[2] ☐ Less than usual
[3] ☐ About the same as usual
[4] ☐ More than usual
[5] ☐ Much more than usual

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 the module which contains the visit (or visit interval) at which the patient withdrew.

INVESTIGATOR GLOBAL ASSESSMENT

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

PATIENT GLOBAL ASSESSMENT

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

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Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

COUGH AND SPUTUM PRODUCTION ASSESSMENTS

*Please ask the patient the following questions and record the answers below (Mark **one** box per section only.)*

COUGH

How troubled have you been by cough today?

[0] ☐ No symptoms at all

[1] ☐ Some symptoms, but hardly noticeable

[2] ☐ Symptoms noticeable and a little uncomfortable

[3] ☐ Symptoms definitely noticeable and uncomfortable

[4] ☐ Symptoms very bad and extremely uncomfortable

SPUTUM PRODUCTION

How much sputum have you produced today?

[0] ☐ No sputum at all

[1] ☐ Some sputum, but not as much as usual

[2] ☐ As much as usual

[3] ☐ More than usual

[4] ☐ A lot more than usual

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a **clinically significant worsening** in the patient's physical condition since the previous examination?

☐ No

☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

FECAL OCCULT BLOOD TEST

Issue the patient the fecal occult blood test kit. Instruct the patient to follow the Patient Instructions provided with the kit. Samples should be collected as specified on three consecutive bowel movements or three bowel movements closely spaced in time and returned to the clinic as soon as possible.

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

Are these findings clinically significant?

☐ No

☐ Yes → *If 'Yes' please record the details in the Adverse Experience section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[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. bid)

Date and time of last dose of study medication prior to the study visit ☐☐☐ Day Month Yr ☐☐ 24hr:min

Did the patient take their last dose with food?

☐ No

☐ Yes

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
☐☐	☐☐	☐☐	☐☐	☐☐	☐☐☐

Note: If this is a morning visit, patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance ≥ 80% and ≤120%?

☐ No

☐ Yes

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials	Early Withdrawal between Scheduled Visits
207499/156	[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 and ECG) must be performed greater than 4 hours after the patient's last albuterol administration.

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
☐☐☐ / ☐☐☐	☐☐☐

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

VITAL SIGNS - ORTHOSTATIC CHANGE

1st Measurement: After 5 Minutes Supine

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
☐☐☐ / ☐☐☐	☐☐☐

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
☐☐☐ / ☐☐☐	☐☐☐

Are there any clinically significant worsenings since Baseline?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes.

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant changes noted at this examination compared to the last visit?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted? The distance walked should be entered even if the patient did not walk for 6 minutes.

☐ No

☐ Yes → *If 'Yes', Distance walked* ☐☐☐ [M] Meters ☐

[YD] Yards ☐

Record any adverse experiences which occur during the exercise tolerance test in the Adverse Experience section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.

POST-EXERCISE ASSESSMENTS *(Immediately after the patient completes the exercise tolerance)*

Heart Rate ☐☐☐ beats/min

SaO_2 ☐☐☐ %

Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

"How short of breath do you feel right now?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0 Nothing at all

1 Very, very slight (just noticeable)

2 Very slight

3 Moderate

4 Somewhat severe

5 Severe

6

7 Very severe

8

9 Very, very severe (almost maximal)

10 Maximal

Post-exercise breathlessness score ☐☐.☐

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise test (rest for at least 10 minutes) before performing the pulmonary function tests.

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 confirm that the pulmonary function tests were performed

[1] ☐ Not Performed

[2] ☐ Performed

LABORATORY TESTS

Please take blood samples for hematology, 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. If the pregnancy test is positive, please complete the Serious Adverse Experiences form and forward it to SB within 24 hours.

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes', please record the findings and/or diagnosis in the Adverse Experiences section (If a re-test is necessary, please use the Repeat Lab page at the end of this book)*

INSTRUCTION TO THE INVESTIGATOR

Please complete the Study Conclusion page at the end of this book.

Ask the patient to return for the Safety Follow-Up Visit in 7 +/- 3 days.

PATIENT ACTIVITY POSTCARD

Please complete the patient activity postcard for ***Early Withdrawal Between Scheduled Visits*** located in the postcard section of this CRF. Detach the postcard and mail promptly. Postage has been prepaid.

SAFETY FOLLOW-UP

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

SFU2

Please do not split modules

Module : Safety Follow-Up

CRF Pages 292 - 297

Unprocessed Forms : Within this module the following occur which will generate attachments that need to be brought in-house.

None

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	
207499/156		[redacted]			Safety Follow-Up

INVESTIGATOR INSTRUCTIONS

Complete these assessments for those patients who withdrew early from the study or for patients who have completed Visit 10. These assessments should be completed within 7 +/- 3 days after discontinuation of study medication.

PRESENTATION TO CLINIC

Record time of presentation to clinic ☐☐ 24hr:min

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?

☐ NA → Patient is not using beta$_2$ agonist.

☐ 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?

☐ NA → Patient is not using anticholinergic.

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: ☐☐☐ 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 : ☐☐

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Safety Follow-Up
207499/156		[redacted]			

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes ⟶ *If 'Yes' please record details below.*

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

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

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

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of excerbation (maximum level)	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1
	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2
	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of the module which contains the visit (or visit interval) at which the patient withdrew or after Visit 10, if applicable, 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 UTILIZATION

If the patient has received any COPD exacerbation related medical care since the previous visit, record details in the Resource Utilization section at the back of the module which contains the visit (or visit interval) at which the patient withdrew or after Visit 10, if applicable.

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Safety Follow-Up
207499/156		[redacted]			

INDIRECT COST

Does the patient work?

☐ No

☐ Yes → *If 'Yes'*, has the patient missed work due to COPD-related symptoms, excluding scheduled protocol visits, since the last visit?

☐ No

☐ Yes → *If 'Yes', please record lost work days below:*

Start Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence

How many days since your last visit have you been restricted in performing your leisure activities, due to your COPD-related symptoms? *(please enter number of days below, if not restricted, enter 0)*

☐☐ Days

Since your last visit, how many hours per week did you require paid or unpaid assistance by a relative, friend or professional with your daily activities such as dressing, bathing, cooking, etc., due to your COPD-related symptoms? *(please enter number of hours below, if no paid or unpaid assistance, enter 0 in each instance)*

☐☐☐ Hours per week of **paid** assistance

☐☐☐ Hours per week of **unpaid** assistance

ADVERSE EXPERIENCES

If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of the module which contains the visit (or visit interval) at which the patient withdrew or after Visit 10, if applicable.

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Safety Follow-Up
207499/156		[redacted]			

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 the module which contains the visit (or visit interval) at which the patient withdrew or after Visit 10, if applicable.

At the patient's final study visit, record the end date for prn study rescue medication (albuterol) use, using the date the study inhaler was returned.

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 the module which contains the visit (or visit interval) at which the patient withdrew or after Visit 10, if applicable.

PULMONARY REHABILITATION PROGRAM

Has the patient entered a Pulmonary Rehabilitation Program since the last visit?

☐ No

☐ Yes

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
☐☐☐ / ☐☐☐	☐☐☐

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of the module which contains the visit (or visit interval) at which the patient withdrew or after Visit 10, if applicable.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Safety Follow-Up
207499/156		[redacted]			

12 LEAD ELECTROCARDIOGRAM

If any abnormalities were observed at the last visit, please perform a 12-lead ECG. The ECG should be performed after the patient has been semi-supine for 5 minutes.

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant changes noted at this examination compared to the last visit?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of the module which contains the visit (or visit interval) at which the patient withdrew or after Visit 10, if applicable.*

LABORATORY TESTS

If abnormal laboratory results were reported at the previous visit, 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 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.

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes', please record the findings and/or diagnosis in the Adverse Experiences section at the back of the module which contains the visit (or visit interval) at which the patient withdrew or after Visit 10, if applicable. (If a re-test is necessary, please use the Repeat Lab page at the end of this book)*

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials	Safety Follow-Up
207499/156	[redacted]		

PREGNANCY TEST

Is the patient a female of child-bearing potential?

☐ No

☐ Yes → *If 'Yes' please perform a urine pregnancy test locally.*

Urine Sample Date ☐☐ ☐☐☐ ☐☐
Day Month Yr

Is the patient pregnant?

☐ No

☐ Yes → *If the pregnancy test is positive, complete the Serious Adverse Experiences form and forward it to SB within 24 hours.*

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

If any abnormalities were noted at the last visit, please perform a physical examination (including respiratory examination).

Were any clinically significant changes noted at this examination compared to the last visit?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of the module which contains the visit (or visit interval) at which the patient withdrew or after Visit 10, if applicable.*

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 confirm that the pulmonary function tests were performed

[1] ☐ Not Performed

[2] ☐ Performed

PATIENT ACTIVITY POSTCARD

Please complete the patient activity postcard for ***Safety Follow-Up Visit*** located in the postcard section of this CRF. Detach the postcard and mail promptly. Postage has been prepaid.

STUDY CONCLUSION

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

CONC3

Please do not split modules

Module : **Study Conclusion**

CRF Pages **298**

Unprocessed Forms : **Within this module the following occur which will generate attachments that need to be brought in-house.**

None

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

STUDY CONCLUSION

Did the patient complete the double-blind phase of the study as planned?

☐ Yes

☐ No → *If 'No' please mark the **PRIMARY** cause of withdrawal. (Mark one box only).*

[1] ☐ Adverse experience (complete AE form)

[2] ☐ Insufficient therapeutic effect

[3] ☐ Protocol deviation (including non-compliance)

[4] ☐ Lost to follow-up

[7] ☐ Other - specify: _____

Date of Final Visit ☐☐ ☐☐☐ ☐☐
Day Month Yr

Date of Final Dose ☐☐ ☐☐☐ ☐☐
Day Month Yr

INVESTIGATOR SIGNATURE

I certify that I have reviewed the data on this case report form, 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	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

SAE3

Please do not split modules

Module : Serious Adverse Experiences

CRF Pages 299 - 301

Unprocessed Forms : Within this module the following occur which will generate attachments that need to be brought in-house.

None

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	SB Receipt Date (Day Month Year)
207499/156		[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 hospitalization (excluding elective surgery or routine clinical procedures)
[5] ☐ hospitalization 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 section
☐ Yes ☐ No

Was patient withdrawn due to this specific SAE ?
☐ Yes ☐ No

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 randomization code broken at investigational site? ☐ No ☐ Yes

Randomization 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 _____

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		
207499/156		[redacted]			

SERIOUS ADVERSE EXPERIENCE (Cont.) PHARMACOKINETIC EVALUATION

If the patient presents to the clinic within 24 hours of the onset of a serious adverse experience (SAE) or with an ongoing SAE, please collect a blood sample (5mL) for pharmacokinetic evaluation.

Was a pharmacokinetic sample taken?

☐ No

☐ Yes → *If 'Yes',* 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 taken prior to the onset of the serious adverse experience

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 serious adverse experience?

☐ No

☐ Yes → *If 'Yes',* record date and time of last dose of study medication taken prior to collection of the pharmacokinetic sample.

Day Month Yr 24hr:min

Was this dose taken with food?

☐ No

☐ Yes

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

FORMD3

Please do not split modules

Module: Form D

CRF Pages: 302

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

FORM D

Certified Cause of Death _____

Date of Death Day Month Yr → *Please complete Serious Adverse Experience section.*

Was a post-mortem examination carried out?

☐ No

☐ Yes → *If 'Yes' please summarize findings (include diagnosis):*

_____

_____

_____

_____

Reporting Physician's Signature _____ Date Day Month Yr

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			OPTIONAL Repeat Lab

RPLAB3

Please do not split modules

Module: Repeat Lab

CRF Pages: 303

Unprocessed Forms: Within this module, the following tests / procedures occur which may generate attachments.

None

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		OPTIONAL Repeat Lab
207499/156		[redacted]			

REPEAT 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, complete the Early Withdrawal between Scheduled Visits 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.*

REPEAT 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, complete the Early Withdrawal between Scheduled Visits 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	Center Number	Patient Number	Patient Initials	Investigator
207499/156		[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	
MOD5	V8, V9, AE, CM, MPro, COPD, RU	197 - 240	☐	☐	
MOD6	V10, AE, CM, Med Pro, COPD, RU	241 - 280	☐	☐	
EW2	Early Withdrawal	281 - 291	☐	☐	
SFU2	Safety Follow-Up	292 - 297	☐	☐	
CONC3	Conclusion	298	☐	☐	
SAE3	Serious Adverse Experiences	299 - 301	☐	☐	
FORMD3	Form D	302	☐	☐	
RPLAB3	Repeat Labs	303	☐	☐	

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	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

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

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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) which cause concern or interfere with usual activity (including eating and sleeping) at any time during the study.

Report this gastrointestinal symptom(s) to the SB Medical Monitor by telephone within 24 hours of the first assessment and fax the completed Supplemental Gastrointestinal Adverse Experience Report within 24 hours of the first assessment.

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.

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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 on page 3) specify: _____

☐ Back

☐ Groin

☐ Shoulder tip

☐ Other, specify: _____ _____

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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	☐	☐
Abdominal masses	☐	☐
Peritoneal signs	☐	☐

Other clinically significant GI physical examination findings, please specify: _ _ _ _ _ _ _ _ _ _ _ _ _ _

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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: _____

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: _____

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			Supplemental Report

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

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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

_____ Day Month Yr 24hr:min

_____ Day Month Yr 24hr:min

_____ Day Month Yr 24hr:min

Investigator's Signature: _____

Telephone Number: ( ) __-_____

Please PRINT name: _____

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Investigator
207499/156		[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)

_____

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_____

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Site Monitor's Signature _____ Date Submitted ☐☐ ☐☐ ☐☐
Day Month Yr

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

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

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[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:				
	☐	☐	☐	☐
	☐	☐	☐	☐
	☐	☐	☐	☐

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[redacted]			

SUPPLEMENTAL REPORT FOR GASTROINTESTINAL ADVERSE EXPERIENCE - FOLLOW UP

PHYSICAL EXAMINATION (*continued*)

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

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[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: _____

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: _____

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[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.

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Investigator
207499/156		[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)

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Site Monitor's Signature _____ Date Submitted ☐☐ Day ☐☐ Month ☐☐ Yr

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number
207499/156	

PATIENT ASSIGNMENT SHEET

Investigator _____ For SB Date Day Month Yr

Directions: *Do not enter the patient on this form until he/she is randomized (starts double-blind medication).*

Final Status: C = *Completed study*
W = *Withdrawn from study*

	Patient Initials	Patient Number	Randomization Number	Date of Randomization Day Mth Yr	Status (C/W)	Ad Referral (for SB) Yes	Ad Referral (for SB) No
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							
16							
17							
18							

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number
207499/156	

PATIENT LOG

Investigator _____

Directions: *Enter **all** patients who have been considered for the study and who have been interviewed. Indicate if the patient was referred for the study through a study advertisement. For patients not entering the trial, note the reason for exclusion in the designated column.*

Patient Initials	Interview Date Day Mth Yr	Ad Referral Yes	Ad Referral No	Reason for Exclusion
		☐	☐	
		☐	☐	
		☐	☐	
		☐	☐	
		☐	☐	
		☐	☐	
		☐	☐	
		☐	☐	
		☐	☐	
		☐	☐	
		☐	☐	
		☐	☐	
		☐	☐	
		☐	☐	
		☐	☐	
		☐	☐	
		☐	☐	
		☐	☐	
		☐	☐	

SB 207499/156

SB

SmithKline Beecham

Pharmaceuticals

PATIENT DIARY

This diary is a **very important** part of the study.

Remember:

- Complete the diary card if you feel different since starting the study medication.
- All visits should be in the morning between 10am and 12 noon, therefore on the day of your next visit do NOT take your morning dose of study medication before attending the clinic. In the exceptional case that your appointment has to be in the afternoon, please contact your doctor for instructions regarding your morning dose of study medication.
- DO NOT use your inhaler during the 4 hours before your next appointment unless you really have to.
- DO NOT smoke 2 hours before your next appointment.
- Bring all empty study medication bottles, any unused study medication, and the study inhaler and spacer to your next appointment.
- Bring this diary with you to your next appointment.
- At your next appointment, you will be asked to recall the time at which you took your study medication on the day before the visit.
- If you experience gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhea, or vomiting) that interfere with your usual activities (including eating and sleeping) or cause concern, please telephone the number below as soon as possible.

In an emergency, telephone:

_____
name

at:_____
phone number

Date and time of next appointment | | | | | | |
Day Month Yr 24hr:min

If you feel different since starting the study medication, please write in the space below and include the date:

Date

Date

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

QU1

Please do not split modules

Module QU1 : SGRQ Withdrawal

CRF Pages SG1 - SG5

Unprocessed Forms : Within this module the following occur which will generate attachments that need to be brought in-house.

None

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day / Month / Year)
207499/156		[redacted]		

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. US version adapted and modified with permission by Judith Barr, Sc.D., Northeastern Univ., Boston, MA.

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Investigator
207499/156		[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	
QU1	SGRQ Withdrawal	SG1 - SG5	☐	☐	_____

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	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

QU2

Please do not split modules

Module QU2 : **SF-36 Withdrawal**

CRF Pages **SF1 - SF5**

Unprocessed Forms : **Within this module the following occur which will generate attachments that need to be brought in-house.**

None

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day / Month / Year)
207499/156		[redacted]		

SF - 36 (HEALTH STATUS 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.

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SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Investigator
207499/156		[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	
QU2	SF-36 Withdrawal	SF1 - SF5	☐	☐	_____

If multiple modules are submitted together, please ensure they are sorted according to the order above

Site Monitor's Comments (e.g. protocol violations or deviations)

_____

_____

_____

_____

_____

_____

Site Monitor's Signature _____ Date Submitted ☐☐ Day ☐☐ Month ☐☐ Yr

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

CONFIDENTIAL

SmithKline Beecham
Pharmaceuticals

PROTOCOL 207499/156

BOOK 1 : SCREENING TO RANDOMIZATION

A RANDOMIZED, 24-WEEK, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY, SAFETY AND TOLERABILITY OF ARIFLO™ (15 MG BID) IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

GENERAL INSTRUCTIONS

- *Write clearly in capital letters using a ball point pen.*
- *Do not write in shaded areas*
- *Answer ALL questions on every page*
- *Enter "N/A" if information requested is not available*
- *Initial and date all changes, additions or deletions. Use a single pen stroke to remove an incorrect entry*
- *Enter the patient initials on all pages on which information has been entered and the patient number and center number where required*

DATE

Please use the following three-letter abbreviations for the months

January	JAN
February	FEB
March	MAR
April	APR
May	MAY
June	JUN
July	JUL
August	AUG
September	SEP
October	OCT
November	NOV
December	DEC

e.g. | 0 1 | J A N | 0 0 | = *1st January 2000*

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

PATIENT INITIALS

Please use the following format:

e.g. [redacted]

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*

STUDY PROCEDURES CHART 207499/156

Visit	1	2	3	3a	4	5	6	7	8	9	10		
	Screen		Baseline								End Double-blind	Early Withdrawal[1]	Final Safety Follow-up
Time relative to baseline (weeks)	-4	-2	0	+1	+2	+4	+8	+12	+16	+20	+24		+25
Signed written informed consent	x												
Medical & surgical history	x												
Physical examination[2]	x		x								x	x	x[3]
Pulmonary history & symptoms	x												
Postero-anterior chest radiograph[4]	x												
Exacerbation assessment/resource use	x	x	x	x	x	x	x	x	x	x	x	x	x
Medication history	x												
Overall breathlessness (modified Borg)	x	x	x		x	x	x	x	x	x	x		
Resting 12-lead ECG	x		x	x	x	x	x	x	x	x	x	x	x[3]
Vital signs (BP, HR)	x[5]	x	x[5]	x	x	x	x	x	x	x	x[5]	x[5]	x
Exercise Tolerance (6-Minute walk)	x	x	x			x	x	x	x	x	x	x	
Post-exercise SaO2 & breathlessness	x	x	x			x	x	x	x	x	x	x	
CO Diffusing Capacity (DLCO)[6]	x												
Albuterol reversibility[7]	x												
Laboratory tests	x		x[8]	x	x	x	x	x	x[9]	x[9]	x[8]	x[8]	x[3,9]
Dispense single-blind medication	x	x											
Albuterol Use		x	x	x	x	x	x	x	x	x	x		
Concomitant medication/medical procedures		x	x	x	x	x	x	x	x	x	x	x	x
PFTs (in absence of albuterol)[10]		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	
Baseline signs and symptoms/AEs[11]		x	x	x	x	x	x	x	x	x	x	x	x
Health status assessment: SGRQ			x					x			x	x	
Quality of life assessment: SF-36			x								x	x	
Cough and sputum assessments			x					x			x	x	
Pharmacokinetic evaluations[12]			x			x		x			x		
Arterial blood gas/SaO2[13]			x								x		
Hourly PFTs for 4 hrs post first/last dose [14]			x								x		
Dispense double-blind medication			x	x	x	x	x	x	x	x			
Investigator/Patient global assessment											x	x	
Study conclusion record												x	x

1 Patients who stop taking study medication between clinic visits will attend the clinic within 24 hours for an early withdrawal visit.

2 To include a respiratory examination.

3 If abnormalities at previous visit for patients who complete Visit 10 or withdraw from the study.

4 Postero-anterior chest X-ray must be performed at Visit 1 unless the film from a chest X-ray within the 12 weeks prior to Visit 1 is available to the Investigator.

5 Including Orthostatic vital signs.

6 DLCO should be done between Visit 1 and Visit 3 if not performed during the previous 24 weeks or if the results are unavailable.

7 Before and 15 to 30 (± 5) minutes after administration of 180 mcg albuterol via a MDI with a spacer to determine % predicted FEV_1, FVC, FEF_{25-75}, PEFR, and FEV_1: FVC.

8 In addition to usual laboratory tests, three fecal occult blood tests will be performed between Visits 1 and 3, between Visits 9 and 10, and at early withdrawal; amylase will be measured at Visit 3.

9 Urinary beta-HCG tests will be performed in females of childbearing potential. No other laboratory samples will be collected at Visits 8 and 9.

10 Includes FEV_1, FVC, FEF_{25-75}, PEFR, and FEV_1:FVC measured by centralized spirometry by the same person at each visit.

11 A diary will be used to record if patients feel different since starting study medication.

12 Visit 3: 3 hours post-dose. Visit 5: trough and 0.5-3 hours post-dose. Visit 7: trough and 3-10 hours post-dose. Visit 10: trough only.

13 In patients with <40% of predicted FEV_1 at Visit 1 and resting SaO_2 <88% or if the patient lives at a high altitude.

14 Pulmonary function tests 30 (± 5) minutes after albuterol followed by 4-hour post-double-blind drug assessments at Visits 3 and 10.

VISIT 1 - SCREENING

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Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

MOD1

Please do not split modules

Module 1 : **Visit 1 Screening**

CRF Pages **1 - 18**

Unprocessed Forms : **Within this module the following occur which will generate attachments that need to be brought in-house.**

None

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Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	
207499/156		[redacted]			Visit 1 Screening

PRESENTATION TO CLINIC

Record time of presentation to clinic ☐☐ 24hr:min

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?

☐ NA → Patient is not using beta$_2$ agonist.

☐ 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?

☐ NA → Patient is not using anticholinergic.

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: ☐☐☐☐ Day Month Yr ☐☐ 24hr:min

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.

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:* ☐☐

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes

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Protocol	Patient Number	Patient Initials	Visit
207499/156	[redacted]		Visit 1 Screening

CONSENT

Date of signed informed consent to participate in this study ☐☐ ☐☐ ☐☐ Day Month Yr

DEMOGRAPHY

Date of Birth ☐☐ ☐☐ ☐☐ Day Month Year

Gender

[M] ☐ Male

[F] ☐ Female

Race

[1] ☐ White

[2] ☐ Black

[3] ☐ Oriental

[4] ☐ Other → *specify:* _____

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Protocol	Patient Number	Patient Initials	Visit 1 Screening
207499/156	[redacted]		

SIGNIFICANT MEDICAL/SURGICAL HISTORY AND PHYSICAL EXAMINATION
(INCLUDING RESPIRATORY EXAMINATION)

Is the patient suffering from or has he/she ever suffered from any **significant** medical or surgical condition, including any significant medical conditions detected during the physical examination?

☐ No

☑ Yes → *If 'Yes' please list below one diagnosis per line.*

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	[1] Past	[2] Ongoing
CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)	☐☐☐☐	☐	☑
For SB			
For SB	☐☐☐☐	☐	☐
For SB	☐☐☐☐	☐	☐
For SB	☐☐☐☐	☐	☐
For SB	☐☐☐☐	☐	☐
For SB	☐☐☐☐	☐	☐
For SB	☐☐☐☐	☐	☐
For SB	☐☐☐☐	☐	☐
For SB	☐☐☐☐	☐	☐

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Protocol		Patient Number	Patient Initials		Visit 1 Screening
207499/156		[redacted]			

SIGNIFICANT MEDICAL/SURGICAL HISTORY AND PHYSICAL EXAMINATION (cont)

Diagnosis	Year of first diagnosis	[1] Past	[2] Ongoing
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			

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®
Selected short-acting inhaled beta$_2$-agonists	All **except** Ventolin®
Long-acting inhaled beta$_2$-agonists	Serevent®
Oral beta$_2$-agonists	Proventil®, Ventolin®, Volmax®, Brethine®
Nebulized beta$_2$-agonists	albuterol, metaproterenol, Alupent®, Isuprel®, Proventil®, Tornalate®, Ventolin®
Nebulized anticholinergics	Atrovent®
Inhaled cromolyn sodium	Intal®
Inhaled nedocromil	Tilade®
Oral xanthines	Slo-Bid®, Theo-Dur®
Leukotriene modifiers	Accolate®, Zyflo®, Singulair®
Mucolytics*	Mucomyst®, Mucosal®
Long-term oxygen therapy (LTOT)**	N/A

* Mucolytic administration should not be started during the study. Stable doses taken prior to study start may continue.

** 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. bid, prn)	**Route***	**Medical Illness/ Diagnosis** (or symptom in absence of a diagnosis)	**Start Date** (be as precise as possible) Day Mth Yr	**End Date** (or if Continuing mark box) Day Mth Yr	
TRADE NAME HERE	***200mcg***	***bid***	***IH***	***COPD***	15 JUN 00		✓
For SB							
For SB							

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Protocol		Patient Number	Patient Initials		Visit 1 Screening
207499/156		[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.*

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. 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.*

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Protocol	Patient Number	Patient Initials	
207499/156	[redacted]		Visit 1 Screening

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. 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 SB							

* For Route, see general instructions for acceptable abbreviations.

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials	Visit 1 Screening
207499/156	[redacted]		

AVERAGE ALCOHOL INTAKE

Number of units per week ☐☐

Note : A unit of alcohol is defined as 8 oz. (250 mL, half a pint) of beer, 4 oz. (125 mL, a medium-sized glass) of wine or 1 oz. (24mL, a measure) of spirits.

CHEST X-RAY

Perform a postero-anterior (PA) chest X-ray (unless one has been performed in the previous 12 weeks 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.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 1 Screening
207499/156		[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 or antibiotics, that required treatment to be prescribed by a physician, or for which the patient was hospitalized?

   ☐ No

   ☐ Yes → *If 'Yes' please withdraw the patient and complete the Study Continuation / Withdrawal page at the back of this book.*

SmithKline Beecham
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Protocol	Patient Number	Patient Initials	Visit 1 Screening
207499/156	[redacted]		

HEALTHCARE RESOURCE UTILIZATION

1. COPD-related emergency department visits

How many times did the patient go to the emergency room / Urgent Care Center for COPD treatment during the past year?

[0] ☐ 0
[1] ☐ 1
[2] ☐ 2
[3] ☐ 3 - 4
[4] ☐ 5 or more

2. COPD-related hospitalization

How many times was the patient admitted to the hospital for COPD treatment during the past year?

[0] ☐ 0
[1] ☐ 1
[2] ☐ 2
[3] ☐ 3 - 4
[4] ☐ 5 or more

INDIRECT COST

Does the patient perform work for which they are paid?

☐ No
☐ Yes → *If 'Yes', on average, how many hours per **week** does the patient work?*

☐☐.☐ Hours

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Protocol	Patient Number	Patient Initials		Visit 1 Screening
207499/156	[redacted]			

OVERALL BREATHLESSNESS ASSESSMENT

Give the patient a copy of the following scale when assessing breathlessness.

Please ask the patient the following question and record the answer below.

"Generally speaking, how has your breathlessness been during the previous week when you carried out tasks that usually cause you to be short of breath (e.g. walking, carrying shopping, climbing stairs, etc)?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Overall breathlessness score ☐☐.☐

SmithKline Beecham
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Protocol	Patient Number	Patient Initials	
207499/156	[redacted]		Visit 1 Screening

INVESTIGATOR INSTRUCTIONS

The following procedures (Vital Signs, ECG, and Exercise Tolerance Test) must be performed greater than 4 hours after the patient's last albuterol administration.

VITAL SIGNS

Height	Weight (light clothes, no shoes)	After Sitting for 5 Minutes	
		Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
☐ cm ☐ in	☐ kg ☐ lb		
☐☐☐.☐	☐☐☐.☐	☐☐☐/☐☐☐	☐☐☐

Were any clinically significant abnormalities noted?

☐ No

☐ Yes → *Record on the Significant Medical/Surgical History and Physical Examination page*

VITAL SIGNS - ORTHOSTATIC CHANGE

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)
☐☐☐/☐☐☐	☐☐☐	☐☐☐/☐☐☐	☐☐☐

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 ≥10 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'.*

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Protocol	Patient Number	Patient Initials	Visit
207499/156	[redacted]		Visit 1 Screening

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant abnormalities noted at this examination?

☐ No

☐ Yes → *If 'Yes', enter details on the Significant Medical/Surgical History and Physical Examination page.*

EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted? The distance walked should be entered even if the patient did not walk for 6 minutes.

☐ No

☐ Yes → *If 'Yes', Distance walked* ☐☐☐ [M] Meters ☐

[YD] Yards ☐

Record any adverse experiences which occur during the exercise tolerance test in the Baseline Signs and Symptoms section.

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Protocol	Patient Number	Patient Initials	Visit
207499/156	[redacted]		Visit 1 Screening

POST-EXERCISE ASSESSMENTS *(Immediately after the patient completes the exercise tolerance)*

Heart Rate ☐☐☐ beats/min

SaO_2 ☐☐☐ %

Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

"How short of breath do you feel right now?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Post-exercise breathlessness score ☐☐.☐

INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise test (rest for at least 10 minutes) before performing the pulmonary function tests.

CARBON MONOXIDE DIFFUSING CAPACITY (DLCO)

A carbon monoxide diffusing capacity test (DLCO) should be done if one has not been performed within the previous 24 weeks or the results are not available. DLCO assessments may be scheduled between Visits 1 and 3.

Date of DLCO test ☐☐☐ Day Month Yr

Mean DLCO ☐☐.☐☐

Units *(Mark appropriate)*

☐ $mL.min^{-1}.mmHg^{-1}$

☐ $mmol.min^{-1}.kPa^{-1}$

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials	
207499/156	[redacted]		Visit 1 Screening

PRE-ALBUTEROL 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 confirm that the pulmonary function tests were performed

[1] ☐ Not performed

[2] ☐ Performed

Is the patient's pre-albuterol 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-albuterol Pulmonary Function Tests.*

POST-ALBUTEROL PULMONARY FUNCTION TESTS

Provide the patient with an albuterol MDI and spacer. Administer 180 mcg (2 puffs) of albuterol via MDI with a spacer. Remind the patient to use this inhaler (with or without the spacer), rather than any albuterol inhaler they may have at home, for "as required" rescue-medication use during the study. ***Record the start date for this prn albuterol use in the Prior and Concomitant medication section.***

Record the time of albuterol inhalation ☐☐:☐☐ 24hr:min

Wait 15 - 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 confirm that the pulmonary function tests were performed

[1] ☐ Not performed

[2] ☐ Performed

Does the patient have a ≤ 15% and/or ≤ 200 ml increase in FEV_1 after administration of albuterol?

☐ 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-albuterol 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

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Protocol	Patient Number	Patient Initials		Visit 1 Screening
207499/156	[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)*

SmithKline Beecham
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Protocol	Patient Number	Patient Initials		Visit 1 Screening
207499/156	[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. Patients with a clinical diagnosis of COPD, as defined by American Thoracic Society Guidelines (see Appendix G of the protocol).	☐	☐
3. Patients with a cigarette smoking history of ≥10 pack years (1 pack year = 20 cigarettes smoked per day for 1 year or the equivalent). Both current smokers and ex-smokers are eligible.	☐	☐
4. Patients with a pre-albuterol FEV_1 to FVC ratio (FEV_1:FVC) ≤ 0.7 at Visit 1 (Screening).	☐	☐
5. Patients with fixed airway obstruction, defined by ≤ 15% **or** ≤ 200 ml (or both) increase in FEV_1 after the administration of albuterol 180 mcg via MDI with a spacer at Visit 1 (Screening).	☐	☐
6. Patients with a post-albuterol FEV_1 between ≥30% and ≤ 70% of predicted normal for height, age and gender at Visit 1. Patients will be assessed 15 to 30 (± 5) minutes after receiving albuterol 180 mcg via MDI with a spacer.	☐	☐
7. Patients who give their signed written informed consent to participate.	☐	☐

Do not admit the patient to this study if any "NO" box has been marked.

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Protocol	Patient Number	Patient Initials	
207499/156	[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. Patients with poorly controlled COPD, defined as the occurrence of any of the following in the 2 weeks prior to Visit 1: acute worsening of COPD that is managed by the patient at home by self-treatment with corticosteroids or antibiotics, that requires treatment prescribed by a physician, or for which the patient is hospitalized.	☐	☐
4. Patients with active tuberculosis, lung cancer, or clinically overt bronchiectasis.	☐	☐
5. Patients with clinically significant cardiovascular, neurological, renal, endocrine, or hematological abnormalities that are uncontrolled on permitted therapy.	☐	☐
6. Patients with clinically significant gastrointestinal or hepatic abnormalities.	☐	☐
7. Patients with clinically significant orthostatic changes in blood pressure or heart rate at Visit 1 (Protocol Section 5.4.2).	☐	☐
8. Patients with a history of hypersensitivity to PDE4 inhibitors.	☐	☐
9. Patients with a history (or suspected history) of alcohol misuse or any other recreational substance abuse.	☐	☐
10. Patients who require treatment with inhaled cromolyn sodium or nedocromil, inhaled long-acting beta$_2$-agonists, oral beta$_2$-agonists, nebulized beta$_2$-agonists, nebulized anticholinergics, xanthines, leukotriene modifiers or oral/inhaled corticosteroids beyond Visit 1. All COPD medications except anticholinergic medication or albuterol via MDI should be withdrawn prior to or at Visit 1 (Screening).	☐	☐
11. Patients receiving treatment with long term oxygen therapy (LTOT), patients who require supplemental oxygen more often than on an occasional (prn) basis, or patients who require nocturnal positive pressure for sleep apnea.	☐	☐
12. Patients who have participated in a Pulmonary Rehabilitation Program within 4 weeks prior to Visit 1 (Screening) or who will enter a Pulmonary Rehabilitation Program during the study.	☐	☐
13. Patients 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).	☐	☐
14. Patients who have previously participated in an Ariflo (SB 207499) study and who received randomized study medication.	☐	☐
15. Patients unable to comply with study procedures (including completion of the health status questionnaires).	☐	☐

Do not admit the patient to this study if any "YES" box has been marked.
Additional Exclusion Criteria will be evaluated at Visit 3.

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 1

- *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 a diary card and remind the patient to use the card to record if they feel differently since starting the study.*

  - *Issue the patient the fecal occult blood test kit. Instruct the patient to follow the Patient Instructions provided with the kit. 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 10am + / - 2 hours.*

  - ***Remind the patient:***

    i *__not__ to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit (eg if study medication is taken at 08:00, the visit must be 16:00 or later).*

    ii *to refrain from using albuterol or anticholinergic agents during the **4 hours** immediately preceding the 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 albuterol inhaler and spacer, and the diary card.*

    v *to continue to take the anticholinergic medication, if prescribed, at a constant dose.*

    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, diarrhea, 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	Patient Initials	
207499/156	[redacted]		Visit 1 Screening

STUDY MEDICATION LABEL

Register the patient with SB's Registration and Medication Ordering System (RAMOS) by calling 1-866-726-6760. Issue the patient 20 days supply of **single-blind study medication** (2 bottles). The first 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.

Attach the tear-off labels from the study medication bottles 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	Attach label here

Date and time visit dose was taken ___ ___ ___ (Day Month Yr) ___ ___ (24hr:min)

PATIENT ACTIVITY POSTCARD

Please complete the patient activity postcard for ***Visit 1 Screening*** located in the postcard section of this CRF. Detach the postcard and mail promptly. Postage has been prepaid.

VISIT 2, WEEK -2
SINGLE-BLIND RUN-IN

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

MOD2

Please do not split modules

Module 2 : Visit 2, Visit 3 (Pre-Randomization), Baseline Signs and Symptoms, Concomitant Medications, Medical Procedures, COPD Exacerbations, Resource Utilization

CRF Pages 19 - 63

Unprocessed Forms : Within this module the following occur which will generate attachments that need to be brought in-house.

None

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Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	
207499/156		[redacted]			Visit 2 Single-blind Run-in Week -2

PRESENTATION TO CLINIC

Record time of presentation to clinic ☐☐ 24hr:min

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?

☐ NA → Patient is not using beta$_2$ agonist.

☐ 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?

☐ NA → Patient is not using anticholinergic.

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: ☐☐☐ 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 : ☐☐

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials	Visit 2 Single-blind Run-in Week -2
207499/156	[redacted]		

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes → If 'Yes' please record details below.

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

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

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

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of excerbation (maximum level)	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1
	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2
	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3

If a patient experienced a COPD exacerbation that was treated with corticosteroids or antibiotics, 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.

RESOURCE UTILIZATION

If the patient has received any COPD exacerbation-related medical care since the last visit, record details in the Resource Utilization section at the back of this module.

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Protocol	Patient Number	Patient Initials	Visit 2 Single-blind Run-in Week -2
207499/156	[redacted]		

INDIRECT COST

Does the patient work?

☐ No

☐ Yes → *If 'Yes'*, has the patient missed work due to COPD-related symptoms, excluding scheduled protocol visits, since the last visit?

☐ No

☐ Yes → *If 'Yes', please record lost work days below:*

Start Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence

How many days since your last visit have you been restricted in performing your leisure activities, due to your COPD-related symptoms? *(please enter number of days below, if not restricted, enter 0)*

☐☐ Days

Since your last visit, how many hours per week did you require paid or unpaid assistance by a relative, friend or professional with your daily activities such as dressing, bathing, cooking, etc., due to your COPD-related symptoms? *(please enter number of hours below, if no paid or unpaid assistance, enter 0 in each instance)*

☐☐☐ Hours per week of **paid** assistance

☐☐☐ Hours per week of **unpaid** assistance

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 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.

SmithKline Beecham
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Protocol	Patient Number	Patient Initials	Visit 2 Single-blind Run-in Week -2
207499/156	[redacted]		

"AS NEEDED" ALBUTEROL USE

Record the patient's evaluation of their 'as needed' albuterol use since the last visit.

[1] ☐ Much less than usual
[2] ☐ Less than usual
[3] ☐ About the same as usual
[4] ☐ More than usual
[5] ☐ Much more than usual

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.

FECAL OCCULT BLOOD TEST

The fecal 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.

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

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'.

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Protocol	Patient Number	Patient Initials	Visit 2 Single-blind Run-in Week -2
207499/156	[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. bid)

Date and time of last dose of study medication prior to the study visit ____ ____ ____ ____ ____
Day Month Yr 24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
40					

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance ≥ 80% and ≤120%?

☐ No → *If 'No' please remind the patient of the importance of taking the medication according to the protocol.*

☐ Yes

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Protocol	Patient Number	Patient Initials	Visit 2 Single-blind Run-in Week -2
207499/156	[redacted]		

OVERALL BREATHLESSNESS ASSESSMENT

Give the patient a copy of the following scale when assessing breathlessness.

Please ask the patient the following question and record the answer below.

"Generally speaking, how has your breathlessness been during the previous week when you carried out tasks that usually cause you to be short of breath (e.g. walking, carrying shopping, climbing stairs, etc)?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Overall breathlessness score ☐☐.☐

PULMONARY REHABILITATION PROGRAM

Has the patient entered a Pulmonary Rehabilitation Program since the last visit?

☐ No

☐ Yes

INVESTIGATOR INSTRUCTIONS

The following procedures (Vital Signs and Exercise Tolerance Test) must be performed more than 4 hours after the patient's last albuterol administration.

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Protocol	Patient Number	Patient Initials	Visit
207499/156	[redacted]		Visit 2 Single-blind Run-in Week -2

VITAL SIGNS

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 module.*

EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted? The distance walked should be entered even if the patient did not walk for 6 minutes.

☐ No

☐ Yes → *If 'Yes', Distance walked* ☐☐☐ Meters ☐

Yards ☐

Record any adverse experiences which occur during the exercise tolerance test in the Baseline Signs and Symptoms section.

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Protocol	Patient Number	Patient Initials	Visit 2 Single-blind Run-in Week -2
207499/156	[redacted]		

POST-EXERCISE ASSESSMENTS *(Immediately after the patient completes the exercise tolerance)*

Heart Rate ☐☐☐ beats/min

SaO_2 ☐☐☐ %

Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

"How short of breath do you feel right now?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Post-exercise breathlessness score ☐☐.☐

INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise tolerance test (rest for at least 10 minutes) before performing the pulmonary function tests.

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Protocol	Patient Number	Patient Initials	Visit 2 Single-blind Run-in Week -2
207499/156	[redacted]		

PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed at least 4 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 confirm that the pulmonary function tests were performed

[1] ☐ Not performed

[2] ☐ Performed

Has the patient's absolute value of FEV$_1$ increased or decreased by > 20% between Visits 1 and 2?

☐ No

☐ Yes → *If 'Yes please withdraw the patient and complete the Study Continuation/Withdrawal page at the back of this book.*

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 2

- *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 a new diary card and remind the patient to use the card to record if they feel differently since starting the study.*

    - *Ask the patient to return for the next visit in 14 +/- 3 days at 10:00 +/- 2 hours.*

    - ***Remind the patient:***

        i *__not__ to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).*

        ii *to refrain from using albuterol or anticholinergic agents during the **4 hours** immediately preceding the 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 albuterol inhaler and spacer, and the diary card.*

        v *to continue to take the anticholinergic medication, if prescribed, at a constant dose.*

        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, diarrhea, 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 fecal occult blood test(s) by the next visit if not already done.*

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Protocol	Patient Number	Patient Initials	Visit 2 Single-blind Run-in Week -2
207499/156	[redacted]		

STUDY MEDICATION LABEL

Issue the patient 20 days supply of **single-blind study medication** (2 bottles) and an albuterol MDI and spacer for 'as required' use if applicable (remind the patient to use this inhaler rather than any albuterol inhaler they may have at home). The first 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.

Attach the tear-off labels from the study medication bottles 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

Attach label here

Date and time visit dose was taken ____ ____ ____ (Day Month Yr) ____ ____ (24hr:min)

PATIENT ACTIVITY POSTCARD

Please complete the patient activity postcard for ***Visit 2 Single Blind Run-In*** located in the postcard section of this CRF. Detach the postcard and mail promptly. Postage has been prepaid.

VISIT 3, DAY 1
BASELINE
(PRE-RANDOMIZATION)

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Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	Visit 3 Baseline Pre-randomization Day1
207499/156		[redacted]			

PRESENTATION TO CLINIC

Record time of presentation to clinic ☐☐ 24hr:min

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?

☐ NA → Patient is not using beta$_2$ agonist.

☐ 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?

☐ NA → Patient is not using anticholinergic.

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: ☐☐☐ 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 : ☐☐

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes

ST. GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

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

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Protocol		Patient Number	Patient Initials		Visit 3
207499/156		[redacted]			

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.

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Protocol		Patient Number	Patient Initials		
207499/156		[redacted]			Visit 3

SF - 36 (HEALTH STATUS QUESTIONNAIRE) (Page 1 of 5)

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Protocol		Patient Number	Patient Initials		Visit 3 Baseline Pre-randomization Day1
207499/156		[redacted]			

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes → *If 'Yes' please record details below.*

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

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

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

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of excerbation (maximum level)	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1
	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2
	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3

If a patient experienced a COPD exacerbation that was treated with corticosteroids or antibiotics, 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.

RESOURCE UTILIZATION

Please complete the COPD Resource Utilization section at the back of this module.

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Protocol		Patient Number	Patient Initials		Visit 3 Baseline Pre-randomization Day1
207499/156		[redacted]			

INDIRECT COST

Does the patient work?

☐ No

☐ Yes → *If 'Yes'*, has the patient missed work due to COPD-related symptoms, excluding scheduled protocol visits, since the last visit?

☐ No

☐ Yes → *If 'Yes', please record lost work days below:*

Start Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence

How many days since your last visit have you been restricted in performing your leisure activities, due to your COPD-related symptoms? *(please enter number of days below, if not restricted, enter 0)*

☐☐ Days

Since your last visit, how many hours per week did you require paid or unpaid assistance by a relative, friend or professional with your daily activities such as dressing, bathing, cooking, etc., due to your COPD-related symptoms? *(please enter number of hours below, if no paid or unpaid assistance, enter 0 in each instance)*

☐☐☐ Hours per week of **paid** assistance

☐☐☐ Hours per week of **unpaid** assistance

BASELINE SIGNS AND SYMPTOMS

Please complete the Baseline Signs and Symptoms 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 Baseline Signs and Symptoms section at the back of this module. The patient should refer to the notes in their diary when answering this question.

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Protocol		Patient Number	Patient Initials		Visit 3 Baseline Pre-randomization Day1
207499/156		[redacted]			

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.

"AS NEEDED" ALBUTEROL USE

Record the patient's evaluation of their 'as needed' albuterol use since the last visit.

[1] ☐ Much less than usual
[2] ☐ Less than usual
[3] ☐ About the same as usual
[4] ☐ More than usual
[5] ☐ Much more than usual

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.

FECAL OCCULT BLOOD TEST

If not completed previously, record results from the test(s) in the Fecal Occult Blood Test section in Visit 2.

Has the patient had a positive fecal 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 module.*

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Protocol	Patient Number	Patient Initials	Visit 3 Baseline Pre-randomization Day1
207499/156	[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. bid)

Date and time of last dose of study medication prior to the study visit Day Month Yr 24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
40					

Note: If this is a morning visit, patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance ≥ 80% and ≤120%?

☐ No → *If 'No' please withdraw the patient and complete the Study Continuation/Withdrawal page at the back of this book.*

☐ Yes

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Protocol	Patient Number	Patient Initials	Visit 3 Baseline Pre-randomization Day1
207499/156	[redacted]		

OVERALL BREATHLESSNESS ASSESSMENT

Give the patient a copy of the following scale when assessing breathlessness.

Please ask the patient the following question and record the answer below.

"Generally speaking, how short of breath have you been during the previous week when you carried out tasks that usually cause you to be short of breath (e.g. walking, carrying shopping, climbing stairs, etc)?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Overall breathlessness score ☐☐.☐

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Protocol	Patient Number	Patient Initials	Visit 3 Baseline Pre-randomization Day1
207499/156	[redacted]		

COUGH AND SPUTUM PRODUCTION ASSESSMENTS

*Please ask the patient the following questions and record the answers below (Mark **one** box per section only.)*

COUGH

How troubled have you been by cough today?

[0] ☐ No symptoms at all

[1] ☐ Some symptoms, but hardly noticeable

[2] ☐ Symptoms noticeable and a little uncomfortable

[3] ☐ Symptoms definitely noticeable and uncomfortable

[4] ☐ Symptoms very bad and extremely uncomfortable

SPUTUM PRODUCTION

How much sputum have you produced today?

[0] ☐ No sputum at all

[1] ☐ Some sputum, but not as much as usual

[2] ☐ As much as usual

[3] ☐ More than usual

[4] ☐ A lot more than usual

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 Exercise Tolerance Test) must be performed greater than 4 hours after the patient's last albuterol administration.

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials	Visit 3 Baseline Pre-randomization Day1
207499/156	[redacted]		

VITAL SIGNS

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 module.*

VITAL SIGNS - ORTHOSTATIC CHANGE

1st Measurement: After 5 Minutes Supine

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
___ / ___	___

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
___ / ___	___

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 ≥ 10 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'.*

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Pharmaceuticals

Protocol	Patient Number	Patient Initials	Visit 3 Baseline Pre-randomization Day1
207499/156	[redacted]		

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant changes noted at this examination compared to Screening?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Baseline Signs and Symptoms section at the back of this module.*

RESTING SaO_2

Measure Resting SaO_2 by pulse oximetry for all patients with an FEV_1 < 40% of predicted for age, height and gender at Visit 1.

[1] ☐ Measurement not required (patient's FEV_1 at Visit 1 ≥ 40% of predicted)

[2] ☐ Measurement required but not performed

[3] ☐ Measurement taken, *please record value below:*

Resting SaO_2 ☐☐☐ %

EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted? The distance walked should be entered even if the patient did not walk for 6 minutes.

☐ No

☐ Yes → *If 'Yes', Distance walked* ☐☐☐ Meters [M] ☐

Yards [YD] ☐

Record any adverse experiences which occur during the exercise tolerance test in the Baseline Signs and Symptoms section at the back of this module.

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Protocol	Patient Number	Patient Initials		Visit 3 Baseline Pre-randomization Day1
207499/156	[redacted]			

POST-EXERCISE ASSESSMENTS *(Immediately after the patient completes the exercise tolerance test)*

Heart Rate ☐☐☐ beats/min

SaO_2 ☐☐☐ %

Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

"How short of breath do you feel right now?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Post-exercise breathlessness score ☐☐.☐

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials	Visit 3 Baseline Pre-randomization Day1
207499/156	[redacted]		

INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise tolerance test (rest for at least 10 minutes) before performing the pulmonary function tests.

PULMONARY FUNCTION TESTS - PRE-ALBUTEROL

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 randomized, additional pulmonary function tests will be performed after a dose of study albuterol is given in the clinic (Book 2) AND prior to the first dose of randomized 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 confirm that the pulmonary function tests were performed

[1] ☐ Not performed

[2] ☐ Performed

RANDOMIZATION CRITERION

Has the patient's absolute value of FEV_1 increased or decreased by > 20% between Visits 1 and 3?

☐ Yes → *If 'Yes' please withdraw the patient and complete the Study Continuation/Withdrawal page at the back of this book.*

☐ No

ADDITIONAL EXCLUSION CRITERIA

Complete the following exclusion criteria.	Yes	No
1. The patient has had a positive fecal occult blood test result between Visit 1 and 3.	☐	☐
2. The patient has a clinically significant orthostatic change in blood pressure or heart rate at Visit 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.

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 is 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 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 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

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[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)

If no baseline events prior to randomization into study please mark this box ☐

Baseline Event *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***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 randomization	[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 Concomitant Medication and/or Medical Procedures section if appropriate*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific event?	☐ Yes ☐ No	☐ Yes ☐ No

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials
207499/156	[redacted]	

BASELINE SIGNS AND SYMPTOMS (or events, or diagnoses) - Continued

*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)

If no baseline events prior to randomization into study please mark this box ☐

Baseline Event *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***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 randomization	[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 Concomitant Medication and/or Medical Procedures section if appropriate*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific event?	☐ Yes ☐ No	☐ Yes ☐ No

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials
207499/156	[redacted]	

BASELINE SIGNS AND SYMPTOMS (or events, or diagnoses) - Continued

*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)

If no baseline events prior to randomization into study please mark this box ☐

Baseline Event *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr ☐☐ 24hr:min ☐☐	Day Month Yr ☐☐ 24hr:min ☐☐
End Date and Time *(If ongoing please leave blank)*	Day Month Yr ☐☐ 24hr:min ☐☐	Day Month Yr ☐☐ 24hr:min ☐☐
Outcome ***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 randomization	[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 Concomitant Medication and/or Medical Procedures section if appropriate*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific event?	☐ Yes ☐ No	☐ Yes ☐ No

CONCOMITANT MEDICATION
excluding treatment for COPD Exacerbations
(These are recorded in the COPD Exacerbations section)

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 (albuterol) 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 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 Route, see General Instructions for acceptable abbreviations.

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 (albuterol) 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 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 Route, see General Instructions for acceptable abbreviations.*

MEDICAL PROCEDURES
excluding treatment for COPD Exacerbations
(These are recorded in the COPD Exacerbations section)

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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			

COPD EXACERBATION SECTION

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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***

If no COPD Exacerbations prior to randomization please mark this box. ☐

Baseline Event	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***If patient died, STOP: go to SAE COPD Exacerbation pages.***	[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) *See definitions page for Baseline Signs & Symptoms form.*	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Relationship to study procedures performed prior to randomization	[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 on the COPD Medications or Procedures page*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific event prior to randomization?	☐ Yes ☐ No	☐ Yes ☐ No

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

DETAILS OF COPD EXACERBATIONS - CONTINUED

*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***

If no COPD Exacerbations prior to randomization please mark this box. ☐

Baseline Event	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***If patient died, STOP: go to SAE COPD Exacerbation pages.***	[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) *See definitions page for Baseline Signs & Symptoms form.*	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Relationship to study procedures performed prior to randomization	[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 on the COPD Medications or Procedures page*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific event prior to randomization?	☐ Yes ☐ No	☐ Yes ☐ No

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 minimize 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	Center Number	Patient Number	Patient Initials
207499/156		[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 hospitalization (excluding elective surgery or routine clinical procedures)
[5] ☐ hospitalization 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 _____

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 randomization code broken at investigational site? ☐ No ☐ Yes

Randomization 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 _____

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible) Day Mth Yr	End Date (or if Continuing mark box) Day Mth Yr	
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							

* *For Route, see General Instructions for acceptable abbreviations.*

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			

RESOURCE UTILIZATION

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

RESOURCE UTILIZATION

Has the patient utilized any COPD Exacerbation-related medical care between Visits 1 and 3?

☐ No

☐ Yes → *If 'Yes', please record details below*

Has the patient had any **Physician Visits** (COPD care excluding scheduled protocol visits) between Visits 1 and 3?

☐ No

☐ Yes → *If 'Yes', please record details below*

Date of Visit Day Mth Yr	Reason for Visit

Has the patient had any **Emergency Room (ER)/Urgent Care Visits/Procedures (i.e., lung surgery)** between Visits 1 and 3?

☐ No

☐ Yes → *If 'Yes', please record details below*

Date of Visit Day Mth Yr	Reason for Visit	Patient Admitted from ER? Yes	No
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

RESOURCE UTILIZATION - (cont)

Has the patient had any **Hospitalizations** between Visits 1 and 3?

☐ No

☐ Yes → *If 'Yes', please record details below* ***(also record details of any hospitalization in the Serious Adverse Experience - COPD Exacerbation section)***

Name of Hospital & City	Date of Admission Day Mth Yr	Date of Discharge Day Mth Yr	Reason for Admission

Has the patient had any **Intensive Care Unit (ICU) stays** ***(did the patient stay in the ICU during any of the above hospitalizations?)*** between Visits 1 and 3?

☐ 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

STUDY CONTINUATION / WITHDRAWAL

SmithKline Beecham
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Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

CONC1

Please do not split modules

Module: Study Continuation / Withdrawal

CRF Pages: 64

Unprocessed Forms: Within this module, the following occur which will generate attachments that need to be brought in-house.

None

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Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

STUDY CONTINUATION/WITHDRAWAL

Is the patient continuing into the double-blind treatment phase of the study?

☐ Yes → *If 'Yes' please sign in the appropriate space below and continue immediately to Book 2.*

☐ No → *If 'No' please mark the **PRIMARY** cause of withdrawal and sign the box below.*

[1] ☐ Baseline sign/symptom (complete BS&S form)

[10] ☐ Does not meet inclusion/exclusion criteria

[3] ☐ Protocol deviation (including non-compliance)

[4] ☐ Lost to follow-up

[5] ☐ Other - specify: _____

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

PATIENT ACTIVITY POSTCARD

Please complete the patient activity postcard for ***Visit 3 Pre-randomization***, located in the postcard section of this CRF. Detach the postcard and mail promptly. Postage has been prepaid.

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	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

SAE1

Please do not split modules

Module: Serious Adverse Experiences

CRF Pages: 65 - 66

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	SB Receipt Date (Day Month Year)
207499/156		[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

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 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 hospitalization (excluding elective surgery or routine clinical procedures)
[5] ☐ hospitalization 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 _____

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 randomization code broken at investigational site? ☐ No ☐ Yes

Randomization 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 _____

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

FORMD1

Please do not split modules

Module: Form D

CRF Pages: 67

SmithKline Beecham
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Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

FORM D

Certified Cause of Death _____

Date of Death Day Month Yr → *Please complete Serious Adverse Experience section.*

Was a post-mortem examination carried out?

☐ No

☐ Yes → *If 'Yes' please summarize findings (include diagnosis):*

_____

_____

_____

_____

Reporting Physician's Signature _____ Date Day Month Yr

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Protocol	Center Number	Patient Number	Patient Initials		OPTIONAL Repeat Lab
207499/156		[redacted]			

RPLAB1

Please do not split modules

Module: Repeat Lab

CRF Pages: 68

Unprocessed Forms: Within this module, the following tests / procedures occur which may generate attachments.

None

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Protocol	Center Number	Patient Number	Patient Initials		OPTIONAL Repeat Lab
207499/156		[redacted]			

REPEAT 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.*

REPEAT 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.*

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Protocol	Center Number	Patient Number	Patient Initials	Investigator
207499/156		[redacted]		

CRF TRACKING/REVIEW FORM

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 - 18	☐	☐	
MOD2	V2, V3, BSS, CM, MP, COPD, RU	19 - 63	☐	☐	
CONC1	Continuation/Withdrawal	64	☐	☐	
SAE1	Serious Adverse Experiences	65 - 66	☐	☐	
FORMD1	Form D	67	☐	☐	
RPLAB1	Repeat Labs	68	☐	☐	

If multiple modules are submitted together, please ensure they are sorted according to the order above

Site Monitor's Comments (e.g. protocol violations or deviations)

Site Monitor's Signature _____ Date Submitted ☐☐ ☐☐ ☐☐
Day Month Yr

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

CONFIDENTIAL

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Pharmaceuticals

PROTOCOL 207499/156

BOOK 3 : VISIT 8 TO STUDY CONCLUSION

A RANDOMIZED, 24-WEEK, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY, SAFETY AND TOLERABILITY OF ARIFLO™ (15 MG BID) IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

GENERAL INSTRUCTIONS

- *Write clearly in capital letters using a black ball point pen and press firmly so that all copies are legible*
- *Do not write in shaded areas*
- *Answer ALL questions on every page*
- *Enter "N/A" if information requested is not available*
- *Initial and date all changes, additions or deletions. Use a single pen stroke to remove an incorrect entry*
- *Enter the patient initials on all pages on which information has been entered and the patient number and center number where required*

Do not enter additional data/information after the set of CRF pages has been split/separated

The cover flap or plastic writing board should be used to divide each set of pages before writing on them with a ball point pen

DATE

Please use the following three-letter abbreviations for the months

January	JAN
February	FEB
March	MAR
April	APR
May	MAY
June	JUN
July	JUL
August	AUG
September	SEP
October	OCT
November	NOV
December	DEC

e.g. | 0 1 | J A N | 0 0 | = *1st January 2000*

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

PATIENT INITIALS

Please use the following format:

e.g. [redacted]

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*

STUDY PROCEDURES CHART 207499/156

Visit	1	2	3	3a	4	5	6	7	8	9	10		
Time relative to baseline (weeks)	Screen -4	-2	Baseline 0	+1	+2	+4	+8	+12	+16	+20	End Double-blind +24	Early Withdrawal[1]	Final Safety Follow-up +25
Signed written informed consent	x												
Medical & surgical history	x												
Physical examination[2]	x		x								x	x	x[3]
Pulmonary history & symptoms	x												
Postero-anterior chest radiograph[4]	x												
Exacerbation assessment/resource use	x	x	x	x	x	x	x	x	x	x	x	x	x
Medication history	x												
Overall breathlessness (modified Borg)	x	x	x		x	x	x	x	x	x	x		
Resting 12-lead ECG	x		x	x	x	x	x	x	x	x	x	x	x[3]
Vital signs (BP, HR)	x[5]	x	x[5]	x	x	x	x	x	x	x	x[5]	x[5]	x
Exercise Tolerance (6-Minute walk)	x	x	x			x	x	x	x	x	x	x	
Post-exercise SaO2 & breathlessness	x	x	x			x	x	x	x	x	x	x	
CO Diffusing Capacity (DLCO)[6]	x												
Albuterol reversibility[7]	x												
Laboratory tests	x		x[8]	x	x	x	x	x	x[9]	x[9]	x[8]	x[8]	x[3,9]
Dispense single-blind medication	x	x											
Albuterol Use		x	x	x	x	x	x	x	x	x	x		
Concomitant medication/medical procedures		x	x	x	x	x	x	x	x	x	x	x	x
PFTs (in absence of albuterol)[10]		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	
Baseline signs and symptoms/AEs[11]		x	x	x	x	x	x	x	x	x	x	x	x
Health status assessment: SGRQ			x					x			x	x	
Quality of life assessment: SF-36			x								x	x	
Cough and sputum assessments			x					x			x	x	
Pharmacokinetic evaluations[12]			x			x		x			x		
Arterial blood gas/SaO2[13]			x								x		
Hourly PFTs for 4 hrs post first/last dose [14]			x								x		
Dispense double-blind medication			x	x	x	x	x	x	x	x			
Investigator/Patient global assessment											x	x	
Study conclusion record												x	x

1 Patients who stop taking study medication between clinic visits will attend the clinic within 24 hours for an early withdrawal visit.

2 To include a respiratory examination.

3 If abnormalities at previous visit for patients who complete Visit 10 or withdraw from the study.

4 Postero-anterior chest X-ray must be performed at Visit 1 unless the film from a chest X-ray within the 12 weeks prior to Visit 1 is available to the Investigator.

5 Including Orthostatic vital signs.

6 DLCO should be done between Visit 1 and Visit 3 if not performed during the previous 24 weeks or if the results are unavailable.

7 Before and 15 to 30 (± 5) minutes after administration of 180 mcg albuterol via a MDI with a spacer to determine % predicted FEV_1, FVC, FEF_{25-75}, PEFR, and FEV_1: FVC.

8 In addition to usual laboratory tests, three fecal occult blood tests will be performed between Visits 1 and 3, between Visits 9 and 10, and at early withdrawal; amylase will be measured at Visit 3.

9 Urinary beta-HCG tests will be performed in females of childbearing potential. No other laboratory samples will be collected at Visits 8 and 9.

10 Includes FEV_1, FVC, FEF_{25-75}, PEFR, and FEV_1:FVC measured by centralized spirometry by the same person at each visit.

11 A diary will be used to record if patients feel different since starting study medication.

12 Visit 3: 3 hours post-dose. Visit 5: trough and 0.5-3 hours post-dose. Visit 7: trough and 3-10 hours post-dose. Visit 10: trough only.

13 In patients with <40% of predicted FEV_1 at Visit 1 and resting SaO_2 <88% or if the patient lives at a high altitude.

14 Pulmonary function tests 30 (± 5) minutes after albuterol followed by 4-hour post-double-blind drug assessments at Visits 3 and 10.

VISIT 8, WEEK 16

SmithKline Beecham
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Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

MOD5

Please do not split modules

Module 5 :	**Visit 8, Visit 9, Adverse Experiences, Concomitant Medications, Medical Procedures, COPD Exacerbations, Resource Utilization**
CRF Pages	**197 - 240**
Unprocessed Forms :	**Within this module the following occur which will generate attachments that need to be brought in-house.**
	None

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Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	
207499/156		[redacted]			Visit 8 Week 16

PRESENTATION TO CLINIC

Record time of presentation to clinic ☐☐ 24hr:min

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?

☐ NA → Patient is not using beta$_2$ agonist.

☐ 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?

☐ NA → Patient is not using anticholinergic.

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: ☐☐☐ 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 : ☐☐

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes

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Protocol		Patient Number	Patient Initials		Visit 8 Week 16
207499/156		[redacted]			

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes → *If 'Yes' please record details below. If the patient has had more than three Level 2 or 3 exacerbations since the start of double-blind medication, patient may be withdrawn after consultation with the Medical Monitor. If withdrawing, complete the assessments scheduled at this visit and the Assessments for Patients Withdrawing at Visit 8. The SGRQ and SF-36 should be completed before any additional assessments.*

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

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

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

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of excerbation (maximum level)	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1
	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2
	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations, including an increase in usual COPD medications, must be recorded in the COPD Medications or Procedures pages.

RESOURCE UTILIZATION

If the patient has received any COPD exacerbation-related medical care since the last visit, record details in the Resource Utilization section at the back of this module.

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Protocol		Patient Number	Patient Initials		Visit 8 Week 16
207499/156		[redacted]			

INDIRECT COST

Does the patient work?

☐ No

☐ Yes → *If 'Yes'*, has the patient missed work due to COPD-related symptoms, excluding scheduled protocol visits, since the last visit?

☐ No

☐ Yes → *If 'Yes', please record lost work days below:*

Start Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence

How many days since your last visit have you been restricted in performing your leisure activities, due to your COPD-related symptoms? *(please enter number of days below, if not restricted, enter 0)*

☐☐ Days

Since your last visit, how many hours per week did you require paid or unpaid assistance by a relative, friend or professional with your daily activities such as dressing, bathing, cooking, etc., due to your COPD-related symptoms? *(please enter number of hours below, if no paid or unpaid assistance, enter 0 in each instance)*

☐☐☐ Hours per week of **paid** assistance

☐☐☐ Hours per week of **unpaid** assistance

ADVERSE EXPERIENCES

If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

CONCOMITANT MEDICATION

If there has been any change in the patient's concomitant medication excluding treatment for COPD exacerbations (this is recorded in the COPD Exacerbations section) since the last visit, please record details in the Concomitant Medication section at the back of this module.

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Protocol		Patient Number	Patient Initials		Visit 8 Week 16
207499/156		[redacted]			

"AS NEEDED" ALBUTEROL USE

Record the patient's evaluation of their 'as needed' albuterol use since the last visit.

[1] ☐ Much less than usual
[2] ☐ Less than usual
[3] ☐ About the same as usual
[4] ☐ More than usual
[5] ☐ Much more than usual

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	Patient Initials		Visit 8 Week 16
207499/156	[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. bid)

Date and time of last dose of study medication prior to the study visit ____ ____ ____ (Day Month Yr) ____ ____ (24hr:min)

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
70					

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance < 80% or > 120%?

☐ No

☐ Yes → *If 'Yes' please check the percent compliance at the previous visit. If compliance was <80% or >120% at the last visit, please contact the Medical Monitor to discuss patient withdrawal. If the patient is to be withdrawn, complete the assessments scheduled at this visit and the Assessments for Patients Withdrawing at Visit 8. The SGRQ and SF-36 should be completed before any additional assessments.*

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Protocol	Patient Number	Patient Initials	Visit 8 Week 16
207499/156	[redacted]		

OVERALL BREATHLESSNESS ASSESSMENT

Give the patient a copy of the following scale when assessing breathlessness.

Please ask the patient the following question and record the answer below.

"Generally speaking, how has your breathlessness been during the previous week when you carried out tasks that usually cause you to be short of breath (e.g. walking, carrying shopping, climbing stairs, etc)?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Overall breathlessness score ☐☐.☐

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 Exercise Tolerance Test) must be performed greater than 4 hours after the patient's last albuterol administration.

SmithKline Beecham Pharmaceuticals

Protocol	Patient Number	Patient Initials	Visit 8 Week 16
207499/156	[redacted]		

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
☐☐☐/☐☐☐	☐☐☐

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes.

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant changes noted at this examination compared to the last visit?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of this module.*

EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted? The distance walked should be entered even if the patient did not walk for 6 minutes.

☐ No

☐ Yes → *If 'Yes', Distance walked* ☐☐☐ Meters ☐

Yards ☐

Record any adverse experiences which occur during the exercise tolerance test in the Adverse Experience section at the back of this module.

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 8 Week 16
207499/156		[redacted]			

POST-EXERCISE ASSESSMENTS *(Immediately after the patient completes the exercise tolerance)*

Heart Rate ☐☐☐ beats/min

SaO_2 ☐☐☐ %

Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

"How short of breath do you feel right now?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Post-exercise breathlessness score ☐☐.☐

INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise test (rest for at least 10 minutes) before performing the pulmonary function tests.

SmithKline Beecham Pharmaceuticals

Protocol	Patient Number	Patient Initials		Visit 8 Week 16
207499/156	[redacted]			

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 confirm that the pulmonary function tests were performed

[1] ☐ Not Performed

[2] ☐ Performed

PREGNANCY TEST

Is the patient a female of child-bearing potential?

☐ No

☐ Yes → *If 'Yes' please perform a urine pregnancy test locally.*

Urine Sample Date ☐☐ ☐☐ ☐☐ Day Month Yr

Is the patient pregnant?

☐ No

☐ Yes → *If 'Yes' please withdraw the patient from the study, complete the Serious Adverse Experiences form and forward it to SB within 24 hours. Complete the assessments scheduled at this visit and the Assessments for Patients Withdrawing at Visit 8. The SGRQ and SF-36 should be completed before any additional assessments.*

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials		Visit 8 Week 16
207499/156	[redacted]			

STUDY MEDICATION LABEL

Issue the patient a 35 day supply of study medication (1 bottles, 70 tablets). Attach the tear-off label from the study medication bottle dispensed at this visit in the space below. Record the start date in the Study Medication Record section in the next visit section. Issue the patient an albuterol inhaler and retrieve their old inhaler for 'as-required' use.

Attach study medication label here

Enter 6-digit Code as it appears on the study medication label | | | | | | |

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

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 8

- *If the patient **is not continuing** in the study, please complete the assessments for Visit 8 and the Assessments for Patients Withdrawing at Visit 8.*
- *If the patient **is continuing** in the study, please:*
  - *Issue the patient a diary card and and remind the patient to use the card to record if they feel differently since starting the study.*
  - *Ask the patient to return for the next visit in 28 +/- 6 days at the same time of day as at Visit 3.*
  - ***Remind the patient:***

    i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after breakfast.*

    ii ***not** to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).*

    iii *to refrain from using albuterol or anticholinergic agents during the **4 hours** immediately preceding the 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 albuterol inhaler and spacer, and the diary card.*

    vi *to continue to take the anticholinergic medication, if prescribed, at a constant dose.*

    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, diarrhea, 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.*

PATIENT ACTIVITY POSTCARD

Please complete the patient activity postcard for ***Visit 8*** located in the postcard section of this CRF. Detach the postcard and mail promptly. Postage has been prepaid.

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Withdrawal at Visit 8 Week 16
207499/156		[redacted]			

ASSESSMENTS FOR PATIENTS WITHDRAWING AT VISIT 8

Complete the assessments below only for patients who are withdrawing from the study.

ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

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

INVESTIGATOR GLOBAL ASSESSMENT

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

PATIENT GLOBAL ASSESSMENT

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	Patient Initials		Withdrawal at Visit 8 Week 16
207499/156		[redacted]			

COUGH AND SPUTUM PRODUCTION ASSESSMENTS

*Please ask the patient the following questions and record the answers below (Mark **one** box per section only.)*

COUGH

How troubled have you been by cough today?

[0] ☐ No symptoms at all

[1] ☐ Some symptoms, but hardly noticeable

[2] ☐ Symptoms noticeable and a little uncomfortable

[3] ☐ Symptoms definitely noticeable and uncomfortable

[4] ☐ Symptoms very bad and extremely uncomfortable

SPUTUM PRODUCTION

How much sputum have you produced today?

[0] ☐ No sputum at all

[1] ☐ Some sputum, but not as much as usual

[2] ☐ As much as usual

[3] ☐ More than usual

[4] ☐ A lot more than usual

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a **clinically significant worsening** in the patient's physical condition since the previous examination?

☐ No

☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of this module.*

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Withdrawal at Visit 8 Week 16
207499/156		[redacted]			

LABORATORY TESTS

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 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.

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes', please record the findings and/or diagnosis in the Adverse Experiences section (If a re-test is necessary, please use the Repeat Lab page at the end of this book)*

FECAL OCCULT BLOOD TEST

Issue the patient the fecal occult blood test kit. Instruct the patient to follow the Patient Instructions provided with the kit. Samples should be collected as specified on three consecutive bowel movements or three bowel movements closely spaced in time and returned to the clinic as soon as possible.

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

Are these findings clinically significant?

☐ No

☐ Yes → *If 'Yes' please record the details in the Adverse Experience section at the back of this module.*

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials	Withdrawal at Visit 8 Week 16
207499/156	[redacted]		

VITAL SIGNS - ORTHOSTATIC CHANGE

1st Measurement: After 5 Minutes Supine

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
___ / ___	___

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
___ / ___	___

Are there any **clincially significant worsenings** since Baseline?

☐ No

☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of this module.*

INVESTIGATOR INSTRUCTIONS

Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return for the Safety Follow-Up Visit in 7 +/- 3 days.

VISIT 9, WEEK 20

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	Visit 9 Week 20
207499/156		[redacted]			

PRESENTATION TO CLINIC

Record time of presentation to clinic ☐☐ 24hr:min

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?

☐ NA → Patient is not using beta$_2$ agonist.

☐ 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?

☐ NA → Patient is not using anticholinergic.

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: ☐☐☐ (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 : ☐☐

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes

SmithKline Beecham Pharmaceuticals

Protocol	Patient Number	Patient Initials	Visit 9 Week 20
207499/156	[redacted]		

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes → *If 'Yes' please record details below. If the patient has had more than three Level 2 or 3 exacerbations since the start of double-blind medication, patient may be withdrawn after consultation with Medical Monitor. If withdrawing, complete the assessments scheduled at this visit and the Assessments for Patients Withdrawing at Visit 9. The SGRQ and SF-36 should be completed before any additional assessments.*

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

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

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

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of excerbation (maximum level)	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1
	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2
	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations, including an increase in usual COPD medications, must be recorded in the COPD Medications or Procedures pages.

RESOURCE UTILIZATION

Please complete the Resource Utilization section at the back of this module. If the patient has received any COPD exacerbation-related medical care since the last visit, record details in the Resource Utilization section at the back of this module.

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 9 Week 20
207499/156		[redacted]			

INDIRECT COST

Does the patient work?

☐ No

☐ Yes → *If 'Yes', has the patient missed work due to COPD-related symptoms, excluding scheduled protocol visits, since the last visit?*

☐ No

☐ Yes → *If 'Yes', please record lost work days below:*

Start Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence

How many days since your last visit have you been restricted in performing your leisure activities, due to your COPD-related symptoms? *(please enter number of days below, if not restricted, enter 0)*

☐☐ Days

Since your last visit, how many hours per week did you require paid or unpaid assistance by a relative, friend or professional with your daily activities such as dressing, bathing, cooking, etc., due to your COPD-related symptoms? *(please enter number of hours below, if no paid or unpaid assistance, enter 0 in each instance)*

☐☐☐ Hours per week of **paid** assistance

☐☐☐ Hours per week of **unpaid** assistance

ADVERSE EXPERIENCES

Please complete the Adverse Experience section at the back of this module. If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials		Visit 9 Week 20
207499/156	[redacted]			

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.

"AS NEEDED" ALBUTEROL USE

Record the patient's evaluation of their 'as needed' albuterol use since the last visit.

[1] ☐ Much less than usual
[2] ☐ Less than usual
[3] ☐ About the same as usual
[4] ☐ More than usual
[5] ☐ Much more than usual

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	Patient Initials	Visit 9 Week 20
207499/156	[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. bid)

Date and time of last dose of study medication prior to the study visit ____ Day Month Yr ____ 24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
70					

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance < 80% or >120%?

☐ No

☐ Yes → *If 'Yes' please check the percent compliance at the previous visit. If compliance was <80% or >120% at the last visit, please contact the Medical Monitor to discuss patient withdrawal. If the patient is to be withdrawn, complete the assessments scheduled at this visit and the Assessments for Patients Withdrawing at Visit 9. The SGRQ and SF-36 should be completed before any additional assessments.*

SmithKline Beecham Pharmaceuticals

Protocol	Patient Number	Patient Initials	Visit 9 Week 20
207499/156	[redacted]		

OVERALL BREATHLESSNESS ASSESSMENT

Give the patient a copy of the following scale when assessing breathlessness.

Please ask the patient the following question and record the answer below.

"Generally speaking, how has your breathlessness been during the previous week when you carried out tasks that usually cause you to be short of breath (e.g. walking, carrying shopping, climbing stairs, etc)?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Overall breathlessness score ☐☐.☐

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 Exercise Tolerance Test) must be performed greater than 4 hours after the patient's last albuterol administration.

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials	Visit 9 Week 20
207499/156	[redacted]		

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
☐☐☐/☐☐☐	☐☐☐

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes.

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant changes noted at this examination compared to the last visit?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of this module.*

EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted? The distance walked should be entered even if the patient did not walk for 6 minutes.

☐ No

☐ Yes → *If 'Yes', Distance walked* ☐☐☐ Meters ☐

Yards ☐

Record any adverse experiences which occur during the exercise tolerance test in the Adverse Experience section at the back of this module.

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials	Visit 9 Week 20
207499/156	[redacted]		

POST-EXERCISE ASSESSMENTS *(Immediately after the patient completes the exercise tolerance)*

Heart Rate ☐☐☐ beats/min

SaO_2 ☐☐☐ %

Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

"How short of breath do you feel right now?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Post-exercise breathlessness score ☐☐.☐

INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise test (rest for at least 10 minutes) before performing the pulmonary function tests.

SmithKline Beecham Pharmaceuticals

Protocol	Patient Number	Patient Initials	Visit 9 Week 20
207499/156	[redacted]		

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 confirm that the pulmonary function tests were performed

[1] ☐ Not Performed

[2] ☐ Performed

PREGNANCY TEST

Is the patient a female of child-bearing potential?

☐ No

☐ Yes → *If 'Yes' please perform a urine pregnancy test locally.*

Urine Sample Date ☐☐ ☐☐☐ ☐☐ Day Month Yr

Is the patient pregnant?

☐ No

☐ Yes → *If 'Yes' please withdraw the patient from the study, complete the Serious Adverse Experiences form and forward it to SB within 24 hours. Complete the assessments scheduled at this visit and the Assessments for Patients Withdrawing at Visit 9. The SGRQ and SF-36 should be completed before any additional assessments.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 9 Week 20
207499/156		[redacted]			

STUDY MEDICATION LABEL

Issue the patient a 35 day supply of study medication (1 bottle, 70 tablets). Attach the tear-off label from the study medication bottle dispensed at this visit in the space below. Record the start date in the Study Medication Record section in the next visit section. Issue the patient an albuterol inhaler and retrieve their old inhaler for 'as-required' use.

Attach study medication label here

Enter 6-digit Code as it appears on the study medication label ☐☐☐☐☐☐

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

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 9

- *If the patient **is not continuing** in the study, please complete the assessments for Visit 9 and the Assessments for Patients Withdrawing at Visit 9.*
- *If the patient **is continuing** in the study, please:*
  - *Issue the patient a diary card and and remind the patient to use the card to record if they feel differently since starting the study.*
  - *Issue the patient the fecal occult blood test kit. Instruct the patient to follow the Patient Instructions provided with the kit. Samples should be collected as specified and returned by the next visit.*
  - *Ask the patient to return for the next visit in 28 +/- 6 days at the same time of day as at Visit 3.*
  - ***Remind the patient:***

    i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after breakfast.*

    ii ***not** to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).*

    iii *to refrain from using albuterol or anticholinergic agents during the **4 hours** immediately preceding the 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 albuterol inhaler and spacer, and the diary card.*

    vi *to continue to take the anticholinergic medication, if prescribed, at a constant dose.*

    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, diarrhea, 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.*

PATIENT ACTIVITY POSTCARD

Please complete the patient activity postcard for ***Visit 9*** located in the postcard section of this CRF. Detach the postcard and mail promptly. Postage has been prepaid.

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Withdrawal at Visit 9 Week 20
207499/156		[redacted]			

ASSESSMENTS FOR PATIENTS WITHDRAWING AT VISIT 9

Complete the assessments below only for patients who are withdrawing from the study.

ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

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

INVESTIGATOR GLOBAL ASSESSMENT

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

PATIENT GLOBAL ASSESSMENT

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	Patient Initials	Withdrawal at Visit 9 Week 20
207499/156	[redacted]		

COUGH AND SPUTUM PRODUCTION ASSESSMENTS

*Please ask the patient the following questions and record the answers below (Mark **one** box per section only.)*

COUGH

How troubled have you been by cough today?

[0] ☐ No symptoms at all

[1] ☐ Some symptoms, but hardly noticeable

[2] ☐ Symptoms noticeable and a little uncomfortable

[3] ☐ Symptoms definitely noticeable and uncomfortable

[4] ☐ Symptoms very bad and extremely uncomfortable

SPUTUM PRODUCTION

How much sputum have you produced today?

[0] ☐ No sputum at all

[1] ☐ Some sputum, but not as much as usual

[2] ☐ As much as usual

[3] ☐ More than usual

[4] ☐ A lot more than usual

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a **clinically significant worsening** in the patient's physical condition since the previous examination?

☐ No

☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of this module.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Withdrawal at Visit 9 Week 20
207499/156		[redacted]			

LABORATORY TESTS

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 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.

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes', please record the findings and/or diagnosis in the Adverse Experiences section (If a re-test is necessary, please use the Repeat Lab page at the end of this book)*

FECAL OCCULT BLOOD TEST

Issue the patient the fecal occult blood test kit. Instruct the patient to follow the Patient Instructions provided with the kit. Samples should be collected as specified on three consecutive bowel movements or three bowel movements closely spaced in time and returned to the clinic as soon as possible.

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

Are these findings clinically significant?

☐ No

☐ Yes → *If 'Yes' please record the details in the Adverse Experience section at the back of this module.*

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials	Withdrawal at Visit 9 Week 20
207499/156	[redacted]		

VITAL SIGNS - ORTHOSTATIC CHANGE

1st Measurement: After 5 Minutes Supine

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
☐☐☐ / ☐☐☐	☐☐☐

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
☐☐☐ / ☐☐☐	☐☐☐

Are there any **clincially significant worsenings** since Baseline?

☐ No

☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of this module.*

INVESTIGATOR INSTRUCTIONS

Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return for the Safety Follow-Up Visit in 7 +/- 3 days.

ADVERSE EXPERIENCES (Non-serious)

DEFINITIONS

INTENSITY (Maximum)

MILD	*Adverse experience which is easily tolerated*
MODERATE	*Adverse experience sufficiently discomforting to interfere with daily activities*
SEVERE	*Adverse experience which prevents normal everyday activities*

RELATIONSHIP TO INVESTIGATIONAL DRUG

NOT RELATED	*The adverse experience is definitely not related to the test drug*
UNLIKELY	*There are other more likely causes and the drug is not suspected as a cause*
SUSPECTED (REASONABLE POSSIBILITY)	*A direct cause and effect relationship between the drug and the adverse experience has not been demonstrated but there is a reasonable possibility that the experience was caused by the drug*
PROBABLE	*There probably is a direct cause and effect relationship between the adverse experience and the study drug*

SERIOUS ADVERSE EXPERIENCE (SAE)

An SAE is any 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	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

ADVERSE EXPERIENCES (Non-serious)

*Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Have you felt different in any way since starting the treatment or since the previous 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).

If no adverse experiences occured since the previous module (i.e., since Visit 7), please mark this box. ☐

Adverse Experience *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***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) *See definitions page for Adverse Experience*	[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 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	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

ADVERSE EXPERIENCES (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 previous 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).

If no adverse experiences occured since the previous module (i.e., since Visit 7), please mark this box. ☐

Adverse Experience *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***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) *See definitions page for Adverse Experience*	[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 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	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

ADVERSE EXPERIENCES (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 previous 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).

If no adverse experiences occured since the previous module (i.e., since Visit 7), please mark this box. ☐

Adverse Experience *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***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) *See definitions page for Adverse Experience*	[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 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)

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

CONCOMITANT MEDICATION

Record any changes in concomitant medication taken since the previous module (i.e., since Visit 7). (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 (albuterol) use, using the date the study inhaler was returned.

☐ No concomitant medication changes since the previous module (i.e., since Visit 7)

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 Route, see General Instructions for acceptable abbreviations.*

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 (albuterol) 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 Route, see General Instructions for acceptable abbreviations.

MEDICAL PROCEDURES
excluding treatment for COPD Exacerbations
(These are recorded in the COPD Exacerbations section)

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 (i.e., since Visit 7)?

☐ 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			

COPD EXACERBATION SECTION

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 previous module (i.e., since Visit 7) should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages***

If no COPD Exacerbations since previous module (i.e., since Visit 7), please mark this box. ☐

Adverse Experience	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***If patient died, STOP: go to SAE COPD Exacerbation pages.***	[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) *See definitions page for Adverse Experience form*	[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 COPD Medications and/or Medical Procedures page*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

DETAILS OF COPD EXACERBATIONS - CONTINUED

*An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy.*
*All exacerbations of COPD since the previous module (i.e., since Visit 7) should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages***

If no COPD Exacerbations since previous module (i.e., since Visit 7), please mark this box. ☐

Adverse Experience	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***If patient died, STOP: go to SAE COPD Exacerbation pages.***	[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) *See definitions page for Adverse Experience form*	[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 COPD Medications and/or Medical Procedures page*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

DETAILS OF COPD EXACERBATIONS - CONTINUED

*An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy.*
All exacerbations of COPD since the previous module (i.e., since Visit 7) should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). ***COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages***

If no COPD Exacerbations since previous module (i.e., since Visit 7), please mark this box. ☐

Adverse Experience	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***If patient died, STOP: go to SAE COPD Exacerbation pages.***	[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) *See definitions page for Adverse Experience form*	[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 COPD Medications and/or Medical Procedures page*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No

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	Center Number	Patient Number	Patient Initials	SB Receipt Date Day Month Year
207499/156		[redacted]		

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation

Person Reporting SAE _____ *(Please print clearly)*

AEGIS Number

Serious Adverse Experience *(Please print clearly)*: **COPD Exacerbation**

→ *Specify reason(s) for considering this a serious AE. Mark all that apply.*

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 Medication or Medical Procedures section* ← ☐ Yes ☐ No

Was patient withdrawn due to this specific SAE ? ☐ Yes ☐ No

- [1] ☐ fatal
- [2] ☐ life threatening
- [3] ☐ disabling/incapacitating
- [4] ☐ results in hospitalization (excluding elective surgery or routine clinical procedures)
- [5] ☐ hospitalization 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 _____

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation (cont)

Relevant Laboratory Data
Please provide relevant abnormal laboratory data below

Test	Date	Value	Units	Normal Range
	Day Month Yr			
	Day Month Yr			
	Day Month Yr			
	Day Month Yr			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomization code broken at investigational site? ☐ No ☐ Yes

Randomization 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 _____

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

SERIOUS ADVERSE EXPERIENCE - COPD EXACERBATION (Cont.) PHARMACOKINETIC EVALUATION

If the patient presents to the clinic within 24 hours of the onset of a serious adverse experience (SAE) COPD Exacerbation or with an ongoing SAE COPD Exacerbation, please collect a blood sample (5mL) for pharmacokinetic evaluation.

Was a pharmacokinetic sample taken?

☐ No

☐ Yes → *If 'Yes',* 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 taken prior to the onset of the serious adverse experience - COPD exacerbation

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 serious adverse experience - COPD exacerbation?

☐ No

☐ Yes → *If 'Yes',* record date and time of last dose of study medication taken prior to collection of the pharmacokinetic sample.

Day Month Yr 24hr:min

Was this dose taken with food?

☐ No

☐ Yes

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

MEDICATION FOR COPD EXACERBATIONS

Has the patient taken any medication for COPD exacerbations since the previous module (i.e., since Visit 7)?

☐ No

☐ Yes → *If 'Yes', please record details below*

Drug Name (Trade Name Preferred)	Unit Dose (eg 500mg)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible) Day Mth Yr	End Date (or if Continuing mark box) Day Mth Yr	
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							

** For Route, see General Instructions for acceptable abbreviations.*

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

MEDICAL PROCEDURES FOR COPD EXACERBATIONS

Have any non-medication, therapeutic, diagnostic or surgical procedures been performed for COPD exacerbations since the previous module (i.e., since Visit 7)?

☐ 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		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			

RESOURCE UTILIZATION

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Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

RESOURCE UTILIZATION

Has the patient utilized any COPD Exacerbation-related medical care since the previous module (i.e., since Visit 7)?

☐ No

☐ Yes → *If 'Yes', please record details below*

Has the patient had any **Physician Visits** (COPD care excluding scheduled protocol visits) since the previous module (i.e., since Visit 7)?

☐ No

☐ Yes → *If 'Yes', please record details below*

Date of Visit Day Mth Yr	Reason for Visit

Has the patient had any **Emergency Room (ER)/Urgent Care Visits/Procedures (i.e., lung surgery)** between since the previous module (i.e., since Visit 7)?

☐ No

☐ Yes → *If 'Yes', please record details below*

Date of Visit Day Mth Yr	Reason for Visit	Patient Admitted from ER? Yes	No
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐

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Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

RESOURCE UTILIZATION - (cont)

Has the patient had any **Hospitalizations** since the previous module (i.e., since Visit 7)?

☐ No

☐ Yes → *If 'Yes', please record details below* ***(also record details of any hospitalization in the Serious Adverse Experience - COPD Exacerbation section)***

Name of Hospital & City	Date of Admission Day Mth Yr	Date of Discharge Day Mth Yr	Reason for Admission

Has the patient had any **Intensive Care Unit (ICU) stays** ***(did the patient stay in the ICU during any of the above hospitalizations?)*** since the previous module (i.e., since Visit 7)?

☐ 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

VISIT 10, WEEK 24

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Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

MOD6

Please do not split modules

Module 6 : **Visit 10, Adverse Experiences, Concomitant Medications, Medical Procedures, COPD Exacerbations, Resource Utilization**

CRF Pages **241 - 280**

Unprocessed Forms : **Within this module the following occur which will generate attachments that need to be brought in-house.**

None

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Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	Visit 10 Week 24
207499/156		[redacted]			

PRESENTATION TO CLINIC

Record time of presentation to clinic ☐☐ 24hr:min

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?

☐ NA → Patient is not using beta$_2$ agonist.

☐ 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?

☐ NA → Patient is not using anticholinergic.

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: ☐☐☐ (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 : ☐☐

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes

ST. GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

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

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Protocol		Patient Number	Patient Initials		Visit 10 Week 24
207499/156		[redacted]			

ST. GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE (PAGE 1 OF 5)

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St. George's Hospital Respiratory Questionnaire. Reproduced and used with permission from PW Jones. US version adapted and modified with permission by Judith Barr, Sc.D., Northeastern Univ., Boston, MA.

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Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day / Month / Year)	Visit 10 Week 24
207499/156		[redacted]			

SF - 36 (HEALTH STATUS QUESTIONNAIRE) (Page 1 of 5)

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Protocol		Patient Number	Patient Initials		Visit 10 Week 24
207499/156		[redacted]			

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes → *If 'Yes' please record details below.*

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

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

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

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of excerbation (maximum level)	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1
	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2
	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations, including an increase in usual COPD medications, must be recorded in the COPD Medications or Procedures pages.

RESOURCE UTILIZATION

Please complete the Resource Utilization section at the back of this module. If the patient has received any COPD exacerbation related medical care since the previous visit, please complete the COPD Resource Utilization section at the back of this module.

SmithKline Beecham
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Protocol	Patient Number	Patient Initials	Visit 10 Week 24
207499/156	[redacted]		

INDIRECT COST

Does the patient work?

☐ No

☐ Yes → *If 'Yes'*, has the patient missed work due to COPD-related symptoms, excluding scheduled protocol visits, since the last visit?

☐ No

☐ Yes → *If 'Yes', please record lost work days below:*

Start Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence

How many days since your last visit have you been restricted in performing your leisure activities, due to your COPD-related symptoms? *(please enter number of days below, if not restricted, enter 0)*

☐☐ Days

Since your last visit, how many hours per week did you require paid or unpaid assistance by a relative, friend or professional with your daily activities such as dressing, bathing, cooking, etc., due to your COPD-related symptoms? *(please enter number of hours below, if no paid or unpaid assistance, enter 0 in each instance)*

☐☐☐ Hours per week of **paid** assistance

☐☐☐ Hours per week of **unpaid** assistance

ADVERSE EXPERIENCES

Please complete the Adverse Experience section at the back of this module. If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

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Protocol	Patient Number	Patient Initials	Visit 10 Week 24
207499/156	[redacted]		

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.

"AS NEEDED" ALBUTEROL USE

Record the patient's evaluation of their 'as needed' albuterol use since the last visit.

[1] ☐ Much less than usual
[2] ☐ Less than usual
[3] ☐ About the same as usual
[4] ☐ More than usual
[5] ☐ Much more than usual

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.

FECAL OCCULT BLOOD TEST

The fecal occult blood test should be performed on three consecutive bowel movements or on bowel movements closely spaced in time between Visits 9 and 10.

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

Are these findings clinically significant?

☐ No

☐ Yes → *If 'Yes' please record the details in the Adverse Experience section at the back of this module.*

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Protocol	Patient Number	Patient Initials	Visit 10 Week 24
207499/156	[redacted]		

INVESTIGATOR GLOBAL ASSESSMENT

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

PATIENT GLOBAL ASSESSMENT

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

COUGH AND SPUTUM PRODUCTION ASSESSMENTS

*Please ask the patient the following questions and record the answers below (Mark **one** box per section only.)*

COUGH

How troubled have you been by cough today?

[0] ☐ No symptoms at all

[1] ☐ Some symptoms, but hardly noticeable

[2] ☐ Symptoms noticeable and a little uncomfortable

[3] ☐ Symptoms definitely noticeable and uncomfortable

[4] ☐ Symptoms very bad and extremely uncomfortable

SPUTUM PRODUCTION

How much sputum have you produced today?

[0] ☐ No sputum at all

[1] ☐ Some sputum, but not as much as usual

[2] ☐ As much as usual

[3] ☐ More than usual

[4] ☐ A lot more than usual

SmithKline Beecham
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Protocol	Patient Number	Patient Initials	Visit 10 Week 24
207499/156	[redacted]		

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a **clinically significant worsening** in the patient's physical condition since the previous examination?

☐ No

☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of this module.*

OVERALL BREATHLESSNESS ASSESSMENT

Give the patient a copy of the following scale when assessing breathlessness.

Please ask the patient the following question and record the answer below.

"Generally speaking, how has your breathlessness been during the previous week when you carried out tasks that usually cause you to be short of breath (e.g. walking, carrying shopping, climbing stairs, etc)?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Overall breathlessness score ☐☐.☐

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 Exercise Tolerance Test) must be performed greater than 4 hours after the patient's last albuterol administration.

SmithKline Beecham
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Protocol	Patient Number	Patient Initials	Visit 10 Week 24
207499/156	[redacted]		

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
___ / ___	___

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

VITAL SIGNS - ORTHOSTATIC CHANGE

1st Measurement: After 5 Minutes Supine

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
___ / ___	___

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
___ / ___	___

Are there any clinically significant worsenings since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

SmithKline Beecham
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Protocol	Patient Number	Patient Initials	Visit 10 Week 24
207499/156	[redacted]		

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes.

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant changes noted at this examination compared to the last visit?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of this module.*

RESTING SaO_2

Measure Resting SaO_2 by pulse oximetry for all patients with an FEV_1 < 40% of predicted for age, height and gender at Visit 1.

[1] ☐ Measurement not required (patient's FEV_1 at Visit 1 ≥ 40% of predicted)

[2] ☐ Measurement required but not performed

[3] ☐ Measurement taken, *please record value below:*

Resting SaO_2 ☐☐☐ %

EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted? The distance walked should be entered even if the patient did not walk for 6 minutes.

☐ No

☐ Yes → *If 'Yes', Distance walked* ☐☐☐ [M] Meters ☐

[YD] Yards ☐

Record any adverse experiences which occur during the exercise tolerance test in the Adverse Experience section at the back of this module.

SmithKline Beecham
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Protocol	Patient Number	Patient Initials	Visit 10 Week 24
207499/156	[redacted]		

POST-EXERCISE ASSESSMENTS *(Immediately after the patient completes the exercise tolerance)*

Heart Rate ☐☐☐ beats/min

SaO_2 ☐☐☐ %

Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

"How short of breath do you feel right now?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Post-exercise breathlessness score ☐☐.☐

INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise tolerance test (rest for at least 10 minutes) before performing the pulmonary function tests.

SmithKline Beecham
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Protocol	Patient Number	Patient Initials	Visit 10 Week 24
207499/156	[redacted]		

PULMONARY FUNCTION TESTS (PRE-ALBUTEROL)

Pulmonary function tests will be assessed at least 4 hours after the last dose of inhaled beta-$_2$ agonist or anticholinergic agent.
NOTE: Additional pulmonary function tests will be performed after a dose of study albuterol is given in the clinic (see next page).

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 confirm that the pulmonary function tests were performed

[1] ☐ Not Performed

[2] ☐ Performed

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. If the pregnancy test is positive, complete the Serious Adverse Experiences form and forward it to SB within 24 hours.

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes', please record the findings and/or diagnosis in the Adverse Experiences section (If a re-test is necessary, please use the Repeat Lab page at the end of this book)*

SmithKline Beecham
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Protocol		Patient Number	Patient Initials		Visit 10 Week 24
207499/156		[redacted]			

ARTERIAL BLOOD GASES

If a resting SaO2 test was required at this visit AND the patient's resting SaO2 < 88% OR the patient lives at a high altitude, please take an arterial blood gas sample for analysis if feasible. The patient should be rested (5 to 10 minute rest) after pulmonary function tests.

☐ Not required

☐ Sample required but not taken

PO_2 (mmHg)	PCO_2 (mmHg)	HCO_3- (mEq/L)	pH	SaO_2 %

POST-ALBUTEROL PULMONARY FUNCTION TESTS

Administer 180mcg (2 puffs) of albuterol via MDI with a spacer using the study inhaler provided for "as required" rescue-medication use.

Record the time of albuterol inhalation ☐☐ 24hr:min

Wait 30 minutes *(+/-5 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 manuals).*** *For each set of three FEV_1 measurements, one FEV_1 must be within 10% of the highest.*

Please confirm that the pulmonary function tests were performed

[1] ☐ Not Performed

[2] ☐ Performed

SmithKline Beecham
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Protocol	Patient Number	Patient Initials	
207499/156	[redacted]		Visit 10 Week 24

PHARMACOKINETIC EVALUATIONS - PRE-DOSE BLOOD SAMPLE

Record the date and time of the previous two doses of study medication.

Study Medication Taken	Date Day Mth Yr	Time 24hr:min	Did the patient take this dose with food ?	
Yesterday's Morning Dose			☐ Yes	☐ No
Yesterday's Evening Dose			☐ Yes	☐ No

Collect a pre-dose blood sample (5mL) for pharmacokinetic evaluation.

Was a pharmacokinetic sample taken?

☐ No

☐ Yes → *If 'Yes',* 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)

Did the patient accidentally take this morning's dose prior to attending the clinic?

☐ No

☐ Yes → *If 'Yes', check that the Study Medication Record for this visit is recorded correctly.*

ADMINISTRATION OF STUDY MEDICATION

Give the patient their dose of study medication (from the bottle dispensed at Visit 9) with food and record the date and time of administration below.

Date and time of administration Day Month Yr 24hr:min

Note: If this is a morning visit, patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

SmithKline Beecham
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Protocol	Patient Number	Patient Initials	Visit 10 Week 24
207499/156	[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 (and should reflect the date of the dose given in the clinic at Visit 10). Record interruptions or changes in dose on separate lines.

Start Date Day Mth Yr	End Date Day Mth Yr	Number of tablets per dose	Frequency (e.g. bid)

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
70					

Note: Include the dose of study medication given to the patient at this visit.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance < 80% or >120%?

☐ No

☐ Yes

SmithKline Beecham
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Protocol	Patient Number	Patient Initials	
207499/156	[redacted]		Visit 10 Week 24

POST-DOSE PULMONARY FUNCTION TESTS

Pulmonary function tests will be completed every hour in the 4-hour period following administration of the dose of study medication.

Ask the patient to avoid using their albuterol or anticholinergic medication and to refrain from smoking if at all possible.

If the patient uses their albuterol or anticholinergic medication during this period, the tests should be abandoned.

Time post-dose	Completed?	
	Yes	No
1 Hour	☐	☐
2 Hours	☐	☐
3 Hours	**Perform ECG**	
3 Hours	☐	☐
4 Hours	☐	☐

Record any adverse experiences which occur during the pulmonary function tests in the Adverse Experience section at the back of this module.

12 LEAD ELECTROCARDIOGRAM - 3 HOURS POST DOSE

The ECG should be performed before the 3-hour post-dose pulmonary function test and after the patient has been semi-supine for 5 minutes.

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant changes noted at this examination compared to the ECG performed earlier in this visit?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of this module.*

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 10

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 previous COPD medications as appropriate.*
- ***Remind the patient:***

  i *to refrain from using albuterol or anticholinergic agents during the **4 hours** immediately preceding the visit.*

  ii *to refrain from smoking for **2 hours** immediately preceding the visit.*

  iii *to bring the study albuterol inhaler and spacer to the visit.*

  iv *to call the investigator as soon as possible to report any gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhea, 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.*

PATIENT ACTIVITY POSTCARD

Please complete the patient activity postcard for ***Visit 10*** located in the postcard section of this CRF. Detach the postcard and mail promptly. Postage has been prepaid.

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
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Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

ADVERSE EXPERIENCES (Non-serious)

*Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Have you felt different in any way since starting the treatment or since the previous 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).

If no adverse experiences occured since the last visit, please mark this box. ☐

Adverse Experience *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***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) *See definitions page for Adverse Experience*	[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 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
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Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

ADVERSE EXPERIENCES (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 previous 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).

If no adverse experiences occured since the last visit, please mark this box. ☐

Adverse Experience *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***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) *See definitions page for Adverse Experience*	[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 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	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

ADVERSE EXPERIENCES (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 previous 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).

If no adverse experiences occured since the last visit, please mark this box. ☐

Adverse Experience *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***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) *See definitions page for Adverse Experience*	[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 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)

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

CONCOMITANT MEDICATION

Record any changes in concomitant medication taken since the last 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 (albuterol) use, using the date the study inhaler was returned.

☐ No concomitant medication changes since the last visit

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 Route, see General Instructions for acceptable abbreviations.*

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 (albuterol) 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 Route, see General Instructions for acceptable abbreviations.

MEDICAL PROCEDURES
excluding treatment for COPD Exacerbations
(These are recorded in the COPD Exacerbations section)

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 visit?

☐ 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			

COPD EXACERBATION SECTION

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 visit should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages***

If no COPD Exacerbations since the last visit, please mark this box. ☐

Adverse Experience	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***If patient died, STOP: go to SAE COPD Exacerbation pages.***	[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) *See definitions page for Adverse Experience*	[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 COPD Medication 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	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

DETAILS OF COPD EXACERBATIONS - CONTINUED

*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 since the last visit should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages***

If no COPD Exacerbations since the last visit, please mark this box. ☐

Adverse Experience	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***If patient died, STOP: go to SAE COPD Exacerbation pages.***	[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) *See definitions page for Adverse Experience*	[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 COPD Medication 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	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

DETAILS OF COPD EXACERBATIONS - CONTINUED

*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 since the last visit should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages***

If no COPD Exacerbations since the last visit, please mark this box. ☐

Adverse Experience	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***If patient died, STOP: go to SAE COPD Exacerbation pages.***	[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) *See definitions page for Adverse Experience*	[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 COPD Medication and/or Medical Procedures section if appropriate*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No

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	Center Number	Patient Number	Patient Initials	SB Receipt Date (Day Month Year)
207499/156		[redacted]		

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation

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

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 Medication or Medical Procedures 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 hospitalization (excluding elective surgery or routine clinical procedures)
[5] ☐ hospitalization 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 _____

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation (cont)

Relevant Laboratory Data
Please provide relevant abnormal laboratory data below

Test	Date	Value	Units	Normal Range
	Day Month Yr			
	Day Month Yr			
	Day Month Yr			
	Day Month Yr			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomization code broken at investigational site? ☐ No ☐ Yes

Randomization 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 _____

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

SERIOUS ADVERSE EXPERIENCE - COPD EXACERBATION (Cont.) PHARMACOKINETIC EVALUATION

If the patient presents to the clinic within 24 hours of the onset of a serious adverse experience (SAE) COPD Exacerbation or with an ongoing SAE COPD Exacerbation, please collect a blood sample (5mL) for pharmacokinetic evaluation.

Was a pharmacokinetic sample taken?

☐ No

☐ Yes → *If 'Yes',* 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 taken prior to the onset of the serious adverse experience - COPD exacerbation

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 serious adverse experience - COPD exacerbation?

☐ No

☐ Yes → *If 'Yes',* record date and time of last dose of study medication taken prior to collection of the pharmacokinetic sample.

Day Month Yr 24hr:min

Was this dose taken with food?

☐ No

☐ Yes

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

MEDICATION FOR COPD EXACERBATIONS

Has the patient taken any medication for COPD exacerbations since the previous visit?

☐ No

☐ Yes → *If 'Yes', please record details below*

Drug Name (Trade Name Preferred)	Unit Dose (eg 500mg)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible) Day Mth Yr	End Date (or if Continuing mark box) Day Mth Yr	
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							

** For Route, see General Instructions for acceptable abbreviations.*

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

MEDICAL PROCEDURES FOR COPD EXACERBATIONS

Have any non-medication, therapeutic, diagnostic or surgical procedures been performed for COPD exacerbations since the previous visit?

☐ 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		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			

RESOURCE UTILIZATION

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

RESOURCE UTILIZATION

Has the patient utilized any COPD Exacerbation-related medical care since the last visit?

☐ No

☐ Yes → *If 'Yes', please record details below*

Has the patient had any **Physician Visits** (COPD care excluding scheduled protocol visits) since the last visit?

☐ No

☐ Yes → *If 'Yes', please record details below*

Date of Visit Day Mth Yr	Reason for Visit

Has the patient had any **Emergency Room (ER)/Urgent Care Visits/Procedures (i.e., lung surgery)** since the last visit?

☐ No

☐ Yes → *If 'Yes', please record details below*

Date of Visit Day Mth Yr	Reason for Visit	Patient Admitted from ER? Yes	No
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

RESOURCE UTILIZATION - (cont)

Has the patient had any **Hospitalizations** since the last visit?

☐ No

☐ Yes → *If 'Yes', please record details below* ***(also record details of any hospitalization in the Serious Adverse Experience - COPD Exacerbation section)***

Name of Hospital & City	Date of Admission Day Mth Yr	Date of Discharge Day Mth Yr	Reason for Admission

Has the patient had any **Intensive Care Unit (ICU) stays** ***(did the patient stay in the ICU during any of the above hospitalizations?)*** since the last visit?

☐ 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

EARLY WITHDRAWAL BETWEEN SCHEDULED VISITS

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

EW2

Please do not split modules

Module : Early Withdrawal Between Scheduled Visits

CRF Pages 281 - 291

Unprocessed Forms : Within this module the following occur which will generate attachments that need to be brought in-house.

Early Withdrawal:
- SGRQ Quality of Life Assessment
- SF-36 Quality of Life Assessment

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

Complete these assessments ONLY for patients who withdraw from the study between scheduled clinic visits. These assessments should be completed within 24 hours of stopping study medication.

PRESENTATION TO CLINIC

Record time of presentation to clinic ☐☐ 24hr:min

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?

☐ NA → Patient is not using beta$_2$ agonist.

☐ 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?

☐ NA → Patient is not using anticholinergic.

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: ☐☐☐ 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 : ☐☐

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes

SmithKline Beecham Pharmaceuticals

Protocol	Patient Number	Patient Initials	Early Withdrawal between Scheduled Visits
207499/156	[redacted]		

ST. GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

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

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes ⟶ *If 'Yes' please record details below.*

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

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

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

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of excerbation (maximum level)	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1
	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2
	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of the module which contains the visit (or visit interval) at which the patient withdrew, 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 UTILIZATION

If the patient has received any COPD exacerbation related medical care since the previous visit, record details in the Resource Utilization section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

INDIRECT COST

Does the patient work?

☐ No

☐ Yes → *If 'Yes'*, has the patient missed work due to COPD-related symptoms, excluding scheduled protocol visits, since the last visit?

☐ No

☐ Yes → *If 'Yes', please record lost work days below:*

Start Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence

How many days since your last visit have you been restricted in performing your leisure activities, due to your COPD-related symptoms? *(please enter number of days below, if not restricted, enter 0)*

☐☐ Days

Since your last visit, how many hours per week did you require paid or unpaid assistance by a relative, friend or professional with your daily activities such as dressing, bathing, cooking, etc., due to your COPD-related symptoms? *(please enter number of hours below, if no paid or unpaid assistance, enter 0 in each instance)*

☐☐☐ Hours per week of **paid** assistance

☐☐☐ Hours per week of **unpaid** assistance

ADVERSE EXPERIENCES

If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of the module which contains the visit (or visit interval) at which the patient withdrew. The patient should refer to the notes in their diary when answering this question.

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials	Early Withdrawal between Scheduled Visits
207499/156	[redacted]		

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 the module which contains the visit (or visit interval) at which the patient withdrew.

"AS NEEDED" ALBUTEROL USE

Record the patient's evaluation of their 'as needed' albuterol use since the last visit.

[1] ☐ Much less than usual
[2] ☐ Less than usual
[3] ☐ About the same as usual
[4] ☐ More than usual
[5] ☐ Much more than usual

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 the module which contains the visit (or visit interval) at which the patient withdrew.

INVESTIGATOR GLOBAL ASSESSMENT

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

PATIENT GLOBAL ASSESSMENT

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	Patient Initials	Early Withdrawal between Scheduled Visits
207499/156	[redacted]		

COUGH AND SPUTUM PRODUCTION ASSESSMENTS

*Please ask the patient the following questions and record the answers below (Mark **one** box per section only.)*

COUGH

How troubled have you been by cough today?

[0] ☐ No symptoms at all

[1] ☐ Some symptoms, but hardly noticeable

[2] ☐ Symptoms noticeable and a little uncomfortable

[3] ☐ Symptoms definitely noticeable and uncomfortable

[4] ☐ Symptoms very bad and extremely uncomfortable

SPUTUM PRODUCTION

How much sputum have you produced today?

[0] ☐ No sputum at all

[1] ☐ Some sputum, but not as much as usual

[2] ☐ As much as usual

[3] ☐ More than usual

[4] ☐ A lot more than usual

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a **clinically significant worsening** in the patient's physical condition since the previous examination?

☐ No

☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.*

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials	Early Withdrawal between Scheduled Visits
207499/156	[redacted]		

FECAL OCCULT BLOOD TEST

Issue the patient the fecal occult blood test kit. Instruct the patient to follow the Patient Instructions provided with the kit. Samples should be collected as specified on three consecutive bowel movements or three bowel movements closely spaced in time and returned to the clinic as soon as possible.

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

Are these findings clinically significant?

☐ No

☐ Yes → *If 'Yes' please record the details in the Adverse Experience section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[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. bid)

Date and time of last dose of study medication prior to the study visit ☐☐ ☐☐☐ ☐☐ (Day Month Yr) ☐☐ (24hr:min)

Did the patient take their last dose with food?

☐ No

☐ Yes

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
☐☐	☐☐	☐☐	☐☐	☐☐	☐☐☐

Note: If this is a morning visit, patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance ≥ 80% and ≤120%?

☐ No

☐ Yes

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials	Early Withdrawal between Scheduled Visits
207499/156	[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 and ECG) must be performed greater than 4 hours after the patient's last albuterol administration.

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
☐☐☐ / ☐☐☐	☐☐☐

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.*

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

VITAL SIGNS - ORTHOSTATIC CHANGE

1st Measurement: After 5 Minutes Supine

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
☐☐☐ / ☐☐☐	☐☐☐

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
☐☐☐ / ☐☐☐	☐☐☐

Are there any clinically significant worsenings since Baseline?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes.

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant changes noted at this examination compared to the last visit?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.*

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Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted? The distance walked should be entered even if the patient did not walk for 6 minutes.

☐ No

☐ Yes → *If 'Yes', Distance walked* ☐☐☐ [M] Meters ☐

[YD] Yards ☐

Record any adverse experiences which occur during the exercise tolerance test in the Adverse Experience section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.

POST-EXERCISE ASSESSMENTS *(Immediately after the patient completes the exercise tolerance)*

Heart Rate ☐☐☐ beats/min

SaO_2 ☐☐☐ %

Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

"How short of breath do you feel right now?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0 Nothing at all

1 Very, very slight (just noticeable)

2 Very slight

3 Moderate

4 Somewhat severe

5 Severe

6

7 Very severe

8

9 Very, very severe (almost maximal)

10 Maximal

Post-exercise breathlessness score ☐☐.☐

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise test (rest for at least 10 minutes) before performing the pulmonary function tests.

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 confirm that the pulmonary function tests were performed

[1] ☐ Not Performed

[2] ☐ Performed

LABORATORY TESTS

Please take blood samples for hematology, 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. If the pregnancy test is positive, please complete the Serious Adverse Experiences form and forward it to SB within 24 hours.

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes', please record the findings and/or diagnosis in the Adverse Experiences section (If a re-test is necessary, please use the Repeat Lab page at the end of this book)*

INSTRUCTION TO THE INVESTIGATOR

Please complete the Study Conclusion page at the end of this book.

Ask the patient to return for the Safety Follow-Up Visit in 7 +/- 3 days.

PATIENT ACTIVITY POSTCARD

Please complete the patient activity postcard for ***Early Withdrawal Between Scheduled Visits*** located in the postcard section of this CRF. Detach the postcard and mail promptly. Postage has been prepaid.

SAFETY FOLLOW-UP

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

SFU2

Please do not split modules

Module : Safety Follow-Up

CRF Pages 292 - 297

Unprocessed Forms : Within this module the following occur which will generate attachments that need to be brought in-house.

None

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	
207499/156		[redacted]			Safety Follow-Up

INVESTIGATOR INSTRUCTIONS

Complete these assessments for those patients who withdrew early from the study or for patients who have completed Visit 10. These assessments should be completed within 7 +/- 3 days after discontinuation of study medication.

PRESENTATION TO CLINIC

Record time of presentation to clinic ☐☐ 24hr:min

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?

☐ NA → Patient is not using beta$_2$ agonist.

☐ 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?

☐ NA → Patient is not using anticholinergic.

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: ☐☐☐ 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 : ☐☐

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials	Safety Follow-Up
207499/156	[redacted]		

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes → *If 'Yes' please record details below.*

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

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

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

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of excerbation (maximum level)	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1
	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2
	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of the module which contains the visit (or visit interval) at which the patient withdrew or after Visit 10, if applicable, 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 UTILIZATION

If the patient has received any COPD exacerbation related medical care since the previous visit, record details in the Resource Utilization section at the back of the module which contains the visit (or visit interval) at which the patient withdrew or after Visit 10, if applicable.

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials	
207499/156	[redacted]		Safety Follow-Up

INDIRECT COST

Does the patient work?

☐ No

☐ Yes → *If 'Yes'*, has the patient missed work due to COPD-related symptoms, excluding scheduled protocol visits, since the last visit?

☐ No

☐ Yes → *If 'Yes', please record lost work days below:*

Start Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence

How many days since your last visit have you been restricted in performing your leisure activities, due to your COPD-related symptoms? *(please enter number of days below, if not restricted, enter 0)*

☐☐ Days

Since your last visit, how many hours per week did you require paid or unpaid assistance by a relative, friend or professional with your daily activities such as dressing, bathing, cooking, etc., due to your COPD-related symptoms? *(please enter number of hours below, if no paid or unpaid assistance, enter 0 in each instance)*

☐☐☐ Hours per week of **paid** assistance

☐☐☐ Hours per week of **unpaid** assistance

ADVERSE EXPERIENCES

If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of the module which contains the visit (or visit interval) at which the patient withdrew or after Visit 10, if applicable.

SmithKline Beecham Pharmaceuticals

Protocol	Patient Number	Patient Initials	Safety Follow-Up
207499/156	[redacted]		

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 the module which contains the visit (or visit interval) at which the patient withdrew or after Visit 10, if applicable.

At the patient's final study visit, record the end date for prn study rescue medication (albuterol) use, using the date the study inhaler was returned.

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 the module which contains the visit (or visit interval) at which the patient withdrew or after Visit 10, if applicable.

PULMONARY REHABILITATION PROGRAM

Has the patient entered a Pulmonary Rehabilitation Program since the last visit?

☐ No

☐ Yes

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
☐☐☐ / ☐☐☐	☐☐☐

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of the module which contains the visit (or visit interval) at which the patient withdrew or after Visit 10, if applicable.*

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials	Safety Follow-Up
207499/156	[redacted]		

12 LEAD ELECTROCARDIOGRAM

If any abnormalities were observed at the last visit, please perform a 12-lead ECG. The ECG should be performed after the patient has been semi-supine for 5 minutes.

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant changes noted at this examination compared to the last visit?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of the module which contains the visit (or visit interval) at which the patient withdrew or after Visit 10, if applicable.*

LABORATORY TESTS

If abnormal laboratory results were reported at the previous visit, 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 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.

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes', please record the findings and/or diagnosis in the Adverse Experiences section at the back of the module which contains the visit (or visit interval) at which the patient withdrew or after Visit 10, if applicable. (If a re-test is necessary, please use the Repeat Lab page at the end of this book)*

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Safety Follow-Up
207499/156		[redacted]			

PREGNANCY TEST

Is the patient a female of child-bearing potential?

☐ No

☐ Yes → *If 'Yes' please perform a urine pregnancy test locally.*

Urine Sample Date ☐☐ ☐☐☐ ☐☐ (Day Month Yr)

Is the patient pregnant?

☐ No

☐ Yes → *If the pregnancy test is positive, complete the Serious Adverse Experiences form and forward it to SB within 24 hours.*

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

If any abnormalities were noted at the last visit, please perform a physical examination (including respiratory examination).

Were any clinically significant changes noted at this examination compared to the last visit?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of the module which contains the visit (or visit interval) at which the patient withdrew or after Visit 10, if applicable.*

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 confirm that the pulmonary function tests were performed

[1] ☐ Not Performed

[2] ☐ Performed

PATIENT ACTIVITY POSTCARD

Please complete the patient activity postcard for ***Safety Follow-Up Visit*** located in the postcard section of this CRF. Detach the postcard and mail promptly. Postage has been prepaid.

STUDY CONCLUSION

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

CONC3

Please do not split modules

Module : **Study Conclusion**

CRF Pages **298**

Unprocessed Forms : **Within this module the following occur which will generate attachments that need to be brought in-house.**

None

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

STUDY CONCLUSION

Did the patient complete the double-blind phase of the study as planned?

☐ Yes

☐ No → *If 'No' please mark the **PRIMARY** cause of withdrawal. (Mark one box only).*

[1] ☐ Adverse experience (complete AE form)

[2] ☐ Insufficient therapeutic effect

[3] ☐ Protocol deviation (including non-compliance)

[4] ☐ Lost to follow-up

[7] ☐ Other - specify: _____

Date of Final Visit ☐☐ ☐☐☐ ☐☐ Day Month Yr

Date of Final Dose ☐☐ ☐☐☐ ☐☐ Day Month Yr

INVESTIGATOR SIGNATURE

I certify that I have reviewed the data on this case report form, 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	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

SAE3

Please do not split modules

Module : Serious Adverse Experiences

CRF Pages 299 - 301

Unprocessed Forms : Within this module the following occur which will generate attachments that need to be brought in-house.

None

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	SB Receipt Date
207499/156		[redacted]		Day Month Year

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

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 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 hospitalization (excluding elective surgery or routine clinical procedures)
[5] ☐ hospitalization 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 _____

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 randomization code broken at investigational site? ☐ No ☐ Yes

Randomization 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 _____

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials
207499/156	[redacted]	

SERIOUS ADVERSE EXPERIENCE (Cont.)
PHARMACOKINETIC EVALUATION

If the patient presents to the clinic within 24 hours of the onset of a serious adverse experience (SAE) or with an ongoing SAE, please collect a blood sample (5mL) for pharmacokinetic evaluation.

Was a pharmacokinetic sample taken?

☐ No

☐ Yes → *If 'Yes',* 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 taken prior to the onset of the serious adverse experience

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 serious adverse experience?

☐ No

☐ Yes → *If 'Yes',* record date and time of last dose of study medication taken prior to collection of the pharmacokinetic sample.

Day Month Yr 24hr:min

Was this dose taken with food?

☐ No

☐ Yes

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

FORMD3

Please do not split modules

Module: Form D

CRF Pages: 302

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

FORM D

Certified Cause of Death _____

Date of Death Day Month Yr → *Please complete Serious Adverse Experience section.*

Was a post-mortem examination carried out?

☐ No

☐ Yes → *If 'Yes' please summarize findings (include diagnosis):*

_____

_____

_____

_____

Reporting Physician's Signature _____ Date Day Month Yr

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		OPTIONAL Repeat Lab
207499/156		[redacted]			

RPLAB3

Please do not split modules

Module: Repeat Lab

CRF Pages: 303

Unprocessed Forms: Within this module, the following tests / procedures occur which may generate attachments.

None

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		OPTIONAL Repeat Lab
207499/156		[redacted]			

REPEAT 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, complete the Early Withdrawal between Scheduled Visits 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.*

REPEAT 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, complete the Early Withdrawal between Scheduled Visits 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	Center Number	Patient Number	Patient Initials	Investigator
207499/156		[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	
MOD5	V8, V9, AE, CM, MPro, COPD, RU	197 - 240	☐	☐	
MOD6	V10, AE, CM, Med Pro, COPD, RU	241 - 280	☐	☐	
EW2	Early Withdrawal	281 - 291	☐	☐	
SFU2	Safety Follow-Up	292 - 297	☐	☐	
CONC3	Conclusion	298	☐	☐	
SAE3	Serious Adverse Experiences	299 - 301	☐	☐	
FORMD3	Form D	302	☐	☐	
RPLAB3	Repeat Labs	303	☐	☐	

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	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

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

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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) which cause concern or interfere with usual activity (including eating and sleeping) at any time during the study.

Report this gastrointestinal symptom(s) to the SB Medical Monitor by telephone within 24 hours of the first assessment and fax the completed Supplemental Gastrointestinal Adverse Experience Report within 24 hours of the first assessment.

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.

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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 on page 3) specify: _____

☐ Back

☐ Groin

☐ Shoulder tip

☐ Other, specify: _____ _____

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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	☐	☐
Abdominal masses	☐	☐
Peritoneal signs	☐	☐

Other clinically significant GI physical examination findings, please specify: _____

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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: _____

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: _____

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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

_____ Day Month Yr 24hr:min

_____ Day Month Yr 24hr:min

_____ Day Month Yr 24hr:min

Investigator's Signature: _____

Telephone Number: ( ) ___-_____

Please PRINT name: _____

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Investigator
207499/156		[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

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

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

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[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:				
	☐	☐	☐	☐
	☐	☐	☐	☐
	☐	☐	☐	☐

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[redacted]			

SUPPLEMENTAL REPORT FOR GASTROINTESTINAL ADVERSE EXPERIENCE - FOLLOW UP

PHYSICAL EXAMINATION (*continued*)

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

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[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: _____

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: _____

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[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.

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Investigator
207499/156		[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)

_____

_____

_____

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_____

_____

Site Monitor's Signature _____ Date Submitted ☐☐ Day ☐☐ Month ☐☐ Yr

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number
207499/156	

PATIENT ASSIGNMENT SHEET

Investigator _____

For SB Date Day Month Yr

Directions: *Do not enter the patient on this form until he/she is randomized (starts double-blind medication).*

Final Status: C = *Completed study*
W = *Withdrawn from study*

	Patient Initials	Patient Number	Randomization Number	Date of Randomization Day Mth Yr	Status (C/W)	Ad Referral (for SB) Yes	No
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							
16							
17							
18							

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number				
207499/156					

PATIENT LOG

Investigator _____

Directions: *Enter **all** patients who have been considered for the study and who have been interviewed. Indicate if the patient was referred for the study through a study advertisement. For patients not entering the trial, note the reason for exclusion in the designated column.*

Patient Initials	Interview Date Day Mth Yr	Ad Referral		Reason for Exclusion
		Yes	No	

SB 207499/156

SB

SmithKline Beecham

Pharmaceuticals

PATIENT DIARY

This diary is a **very important** part of the study.

Remember:

- Complete the diary card if you feel different since starting the study medication.
- All visits should be in the morning between 10am and 12 noon, therefore on the day of your next visit do NOT take your morning dose of study medication before attending the clinic. In the exceptional case that your appointment has to be in the afternoon, please contact your doctor for instructions regarding your morning dose of study medication.
- DO NOT use your inhaler during the 4 hours before your next appointment unless you really have to.
- DO NOT smoke 2 hours before your next appointment.
- Bring all empty study medication bottles, any unused study medication, and the study inhaler and spacer to your next appointment.
- Bring this diary with you to your next appointment.
- At your next appointment, you will be asked to recall the time at which you took your study medication on the day before the visit.
- If you experience gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhea, or vomiting) that interfere with your usual activities (including eating and sleeping) or cause concern, please telephone the number below as soon as possible.

In an emergency, telephone:

_____
name

at:_____
phone number

Date and time of next appointment | | | | | | | | | | |
Day Month Yr 24hr:min

If you feel different since starting the study medication, please write in the space below and include the date:

Date

Date

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

QU1

Please do not split modules

Module QU1 : **SGRQ Withdrawal**

CRF Pages **SG1 - SG5**

Unprocessed Forms : **Within this module the following occur which will generate attachments that need to be brought in-house.**

None

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)
207499/156		[redacted]		

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. US version adapted and modified with permission by Judith Barr, Sc.D., Northeastern Univ., Boston, MA.

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Investigator
207499/156		[redacted]		_____

CRF TRACKING/REVIEW FORM

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- *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	
QU1	SGRQ Withdrawal	SG1 - SG5	☐	☐	_____

If multiple modules are submitted together, please ensure they are sorted according to the order above

Site Monitor's Comments (e.g. protocol violations or deviations)

_____

_____

_____

_____

_____

_____

Site Monitor's Signature _____ Date Submitted ☐☐ ☐☐ ☐☐
Day Month Yr

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

CONFIDENTIAL

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PROTOCOL 207499/156

BOOK 1 : SCREENING TO RANDOMIZATION

A RANDOMIZED, 24-WEEK, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY, SAFETY AND TOLERABILITY OF ARIFLO™ (15 MG BID) IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

GENERAL INSTRUCTIONS

- *Write clearly in capital letters using a ball point pen.*
- *Do not write in shaded areas*
- *Answer ALL questions on every page*
- *Enter "N/A" if information requested is not available*
- *Initial and date all changes, additions or deletions. Use a single pen stroke to remove an incorrect entry*
- *Enter the patient initials on all pages on which information has been entered and the patient number and center number where required*

DATE

Please use the following three-letter abbreviations for the months

January	JAN
February	FEB
March	MAR
April	APR
May	MAY
June	JUN
July	JUL
August	AUG
September	SEP
October	OCT
November	NOV
December	DEC

e.g. | 0 1 | J A N | 0 0 | = *1st January 2000*

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

PATIENT INITIALS

Please use the following format:

e.g. [redacted]

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*

STUDY PROCEDURES CHART 207499/156

Visit	1	2	3	3a	4	5	6	7	8	9	10		
	Screen		Baseline								End Double-blind	Early Withdrawal[1]	Final Safety Follow-up
Time relative to baseline (weeks)	-4	-2	0	+1	+2	+4	+8	+12	+16	+20	+24		+25
Signed written informed consent	x												
Medical & surgical history	x												
Physical examination[2]	x		x								x	x	x[3]
Pulmonary history & symptoms	x												
Postero-anterior chest radiograph[4]	x												
Exacerbation assessment/resource use	x	x	x	x	x	x	x	x	x	x	x	x	x
Medication history	x												
Overall breathlessness (modified Borg)	x	x	x		x	x	x	x	x	x	x		
Resting 12-lead ECG	x		x	x	x	x	x	x	x	x	x	x	x[3]
Vital signs (BP, HR)	x[5]	x	x[5]	x	x	x	x	x	x	x	x[5]	x[5]	x
Exercise Tolerance (6-Minute walk)	x	x	x			x	x	x	x	x	x	x	
Post-exercise SaO2 & breathlessness	x	x	x			x	x	x	x	x	x	x	
CO Diffusing Capacity (DLCO)[6]	x												
Albuterol reversibility[7]	x												
Laboratory tests	x		x[8]	x	x	x	x	x	x[9]	x[9]	x[8]	x[8]	x[3,9]
Dispense single-blind medication	x	x											
Albuterol Use		x	x	x	x	x	x	x	x	x	x		
Concomitant medication/medical procedures		x	x	x	x	x	x	x	x	x	x	x	x
PFTs (in absence of albuterol)[10]		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	
Baseline signs and symptoms/AEs[11]		x	x	x	x	x	x	x	x	x	x	x	x
Health status assessment: SGRQ			x					x			x	x	
Quality of life assessment: SF-36			x								x	x	
Cough and sputum assessments			x					x			x	x	
Pharmacokinetic evaluations[12]			x			x		x			x		
Arterial blood gas/SaO2[13]			x								x		
Hourly PFTs for 4 hrs post first/last dose [14]			x								x		
Dispense double-blind medication			x	x	x	x	x	x	x	x			
Investigator/Patient global assessment											x	x	
Study conclusion record												x	x

1 Patients who stop taking study medication between clinic visits will attend the clinic within 24 hours for an early withdrawal visit.

2 To include a respiratory examination.

3 If abnormalities at previous visit for patients who complete Visit 10 or withdraw from the study.

4 Postero-anterior chest X-ray must be performed at Visit 1 unless the film from a chest X-ray within the 12 weeks prior to Visit 1 is available to the Investigator.

5 Including Orthostatic vital signs.

6 DLCO should be done between Visit 1 and Visit 3 if not performed during the previous 24 weeks or if the results are unavailable.

7 Before and 15 to 30 (± 5) minutes after administration of 180 mcg albuterol via a MDI with a spacer to determine % predicted FEV_1, FVC, FEF_{25-75}, PEFR, and FEV_1: FVC.

8 In addition to usual laboratory tests, three fecal occult blood tests will be performed between Visits 1 and 3, between Visits 9 and 10, and at early withdrawal; amylase will be measured at Visit 3.

9 Urinary beta-HCG tests will be performed in females of childbearing potential. No other laboratory samples will be collected at Visits 8 and 9.

10 Includes FEV_1, FVC, FEF_{25-75}, PEFR, and FEV_1:FVC measured by centralized spirometry by the same person at each visit.

11 A diary will be used to record if patients feel different since starting study medication.

12 Visit 3: 3 hours post-dose. Visit 5: trough and 0.5-3 hours post-dose. Visit 7: trough and 3-10 hours post-dose. Visit 10: trough only.

13 In patients with <40% of predicted FEV_1 at Visit 1 and resting SaO_2 <88% or if the patient lives at a high altitude.

14 Pulmonary function tests 30 (± 5) minutes after albuterol followed by 4-hour post-double-blind drug assessments at Visits 3 and 10.

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Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

MOD1

Please do not split modules

Module 1 : **Visit 1 Screening**

CRF Pages **1 - 18**

Unprocessed Forms : **Within this module the following occur which will generate attachments that need to be brought in-house.**

None

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Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	
207499/156		[redacted]			Visit 1 Screening

PRESENTATION TO CLINIC

Record time of presentation to clinic ☐☐ 24hr:min

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?

☐ NA → Patient is not using beta$_2$ agonist.

☐ 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?

☐ NA → Patient is not using anticholinergic.

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: ☐☐ ☐☐ ☐☐ Day Month Yr ☐☐ 24hr:min

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.

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:* ☐☐

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes

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Protocol		Patient Number	Patient Initials		Visit 1 Screening
207499/156		[redacted]			

CONSENT

Date of signed informed consent to participate in this study ☐☐ ☐☐ ☐☐ Day Month Yr

DEMOGRAPHY

Date of Birth ☐☐ ☐☐ ☐☐ Day Month Year

Gender
[M] ☐ Male
[F] ☐ Female

Race
[1] ☐ White
[2] ☐ Black
[3] ☐ Oriental
[4] ☐ Other → *specify:* _____

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Protocol		Patient Number	Patient Initials		Visit 1 Screening
207499/156		[redacted]			

SIGNIFICANT MEDICAL/SURGICAL HISTORY AND PHYSICAL EXAMINATION
(INCLUDING RESPIRATORY EXAMINATION)

Is the patient suffering from or has he/she ever suffered from any **significant** medical or surgical condition, including any significant medical conditions detected during the physical examination?

☐ No

☑ Yes ⟶ *If 'Yes' please list below one diagnosis per line.*

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	[1] Past	[2] Ongoing
CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)		☐	☑
For SB			
		☐	☐
For SB			
		☐	☐
For SB			
		☐	☐
For SB			
		☐	☐
For SB			
		☐	☐
For SB			
		☐	☐
For SB			
		☐	☐
For SB			
		☐	☐
For SB			

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Protocol		Patient Number	Patient Initials		Visit 1 Screening
207499/156		[redacted]			

SIGNIFICANT MEDICAL/SURGICAL HISTORY AND PHYSICAL EXAMINATION (cont)

Diagnosis	Year of first diagnosis	[1] Past	[2] Ongoing
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			

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®
Selected short-acting inhaled beta$_2$-agonists	All **except** Ventolin®
Long-acting inhaled beta$_2$-agonists	Serevent®
Oral beta$_2$-agonists	Proventil®, Ventolin®, Volmax®, Brethine®
Nebulized beta$_2$-agonists	albuterol, metaproterenol, Alupent®, Isuprel®, Proventil®, Tornalate®, Ventolin®
Nebulized anticholinergics	Atrovent®
Inhaled cromolyn sodium	Intal®
Inhaled nedocromil	Tilade®
Oral xanthines	Slo-Bid®, Theo-Dur®
Leukotriene modifiers	Accolate®, Zyflo®, Singulair®
Mucolytics*	Mucomyst®, Mucosal®
Long-term oxygen therapy (LTOT)**	N/A

* Mucolytic administration should not be started during the study. Stable doses taken prior to study start may continue.

** 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. bid, prn)	**Route***	**Medical Illness/ Diagnosis** (or symptom in absence of a diagnosis)	**Start Date** (be as precise as possible) Day Mth Yr	**End Date** (or if Continuing mark box) Day Mth Yr	
TRADE NAME HERE	***200mcg***	***bid***	***IH***	***COPD***	15 JUN 00		✓
For SB							
							☐
For SB							

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Protocol	Patient Number	Patient Initials	Visit 1 Screening
207499/156	[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.*

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. 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							
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For SB							

** For Route, see general instructions for acceptable abbreviations.*

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Protocol		Patient Number	Patient Initials		Visit 1 Screening
207499/156		[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. 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 SB							
For SB							

** For Route, see general instructions for acceptable abbreviations.*

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Protocol		Patient Number	Patient Initials		Visit 1 Screening
207499/156		[redacted]			

AVERAGE ALCOHOL INTAKE

Number of units per week ☐☐

Note : A unit of alcohol is defined as 8 oz. (250 mL, half a pint) of beer, 4 oz. (125 mL, a medium-sized glass) of wine or 1 oz. (24mL, a measure) of spirits.

CHEST X-RAY

Perform a postero-anterior (PA) chest X-ray (unless one has been performed in the previous 12 weeks 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.*

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Protocol		Patient Number	Patient Initials		Visit 1 Screening
207499/156		[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 or antibiotics, that required treatment to be prescribed by a physician, or for which the patient was hospitalized?

   ☐ No

   ☐ Yes → *If 'Yes' please withdraw the patient and complete the Study Continuation / Withdrawal page at the back of this book.*

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Protocol		Patient Number	Patient Initials		Visit 1 Screening
207499/156		[redacted]			

HEALTHCARE RESOURCE UTILIZATION

1. COPD-related emergency department visits

   How many times did the patient go to the emergency room / Urgent Care Center for COPD treatment during the past year?

   [0] ☐ 0
   [1] ☐ 1
   [2] ☐ 2
   [3] ☐ 3 - 4
   [4] ☐ 5 or more

2. COPD-related hospitalization

   How many times was the patient admitted to the hospital for COPD treatment during the past year?

   [0] ☐ 0
   [1] ☐ 1
   [2] ☐ 2
   [3] ☐ 3 - 4
   [4] ☐ 5 or more

INDIRECT COST

Does the patient perform work for which they are paid?

☐ No

☐ Yes → *If 'Yes', on average, how many hours per **week** does the patient work?*

☐☐.☐ Hours

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Protocol		Patient Number	Patient Initials		Visit 1 Screening
207499/156		[redacted]			

OVERALL BREATHLESSNESS ASSESSMENT

Give the patient a copy of the following scale when assessing breathlessness.

Please ask the patient the following question and record the answer below.

"Generally speaking, how has your breathlessness been during the previous week when you carried out tasks that usually cause you to be short of breath (e.g. walking, carrying shopping, climbing stairs, etc)?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Overall breathlessness score ☐☐.☐

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Protocol		Patient Number	Patient Initials		Visit 1 Screening
207499/156		[redacted]			

INVESTIGATOR INSTRUCTIONS

The following procedures (Vital Signs, ECG, and Exercise Tolerance Test) must be performed greater than 4 hours after the patient's last albuterol administration.

VITAL SIGNS

Height	Weight (light clothes, no shoes)	After Sitting for 5 Minutes	
		Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
☐ cm ☐ in	☐ kg ☐ lb	☐☐☐ / ☐☐☐	☐☐☐

Were any clinically significant abnormalities noted?

☐ No

☐ Yes → *Record on the Significant Medical/Surgical History and Physical Examination page*

VITAL SIGNS - ORTHOSTATIC CHANGE

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)
☐☐☐ / ☐☐☐	☐☐☐	☐☐☐ / ☐☐☐	☐☐☐

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 ≥10 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'.*

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Protocol		Patient Number	Patient Initials		Visit 1 Screening
207499/156		[redacted]			

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant abnormalities noted at this examination?

☐ No

☐ Yes → *If 'Yes', enter details on the Significant Medical/Surgical History and Physical Examination page.*

EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted? The distance walked should be entered even if the patient did not walk for 6 minutes.

☐ No

☐ Yes → *If 'Yes', Distance walked* ☐☐☐ [M] Meters ☐

[YD] Yards ☐

Record any adverse experiences which occur during the exercise tolerance test in the Baseline Signs and Symptoms section.

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Protocol		Patient Number	Patient Initials		Visit 1 Screening
207499/156		[redacted]			

POST-EXERCISE ASSESSMENTS *(Immediately after the patient completes the exercise tolerance)*

Heart Rate ☐☐☐ beats/min

SaO_2 ☐☐☐ %

Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

"How short of breath do you feel right now?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Post-exercise breathlessness score ☐☐.☐

INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise test (rest for at least 10 minutes) before performing the pulmonary function tests.

CARBON MONOXIDE DIFFUSING CAPACITY (DLCO)

A carbon monoxide diffusing capacity test (DLCO) should be done if one has not been performed within the previous 24 weeks or the results are not available. DLCO assessments may be scheduled between Visits 1 and 3.

Date of DLCO test ☐☐☐ Day Month Yr

Mean DLCO ☐☐.☐☐

Units *(Mark appropriate)*

☐ $mL.min^{-1}.mmHg^{-1}$

☐ $mmol.min^{-1}.kPa^{-1}$

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 1 Screening
207499/156		[redacted]			

PRE-ALBUTEROL 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 confirm that the pulmonary function tests were performed

[1] ☐ Not performed

[2] ☐ Performed

Is the patient's pre-albuterol 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-albuterol Pulmonary Function Tests.*

POST-ALBUTEROL PULMONARY FUNCTION TESTS

Provide the patient with an albuterol MDI and spacer. Administer 180 mcg (2 puffs) of albuterol via MDI with a spacer. Remind the patient to use this inhaler (with or without the spacer), rather than any albuterol inhaler they may have at home, for "as required" rescue-medication use during the study. ***Record the start date for this prn albuterol use in the Prior and Concomitant medication section.***

Record the time of albuterol inhalation ☐☐:☐☐ 24hr:min

Wait 15 - 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 confirm that the pulmonary function tests were performed

[1] ☐ Not performed

[2] ☐ Performed

Does the patient have a ≤ 15% and/or ≤ 200 ml increase in FEV_1 after administration of albuterol?

☐ 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-albuterol 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

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Protocol		Patient Number	Patient Initials		Visit 1 Screening
207499/156		[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)*

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Protocol		Patient Number	Patient Initials		Visit 1 Screening
207499/156		[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. Patients with a clinical diagnosis of COPD, as defined by American Thoracic Society Guidelines (see Appendix G of the protocol).	☐	☐
3. Patients with a cigarette smoking history of ≥10 pack years (1 pack year = 20 cigarettes smoked per day for 1 year or the equivalent). Both current smokers and ex-smokers are eligible.	☐	☐
4. Patients with a pre-albuterol FEV_1 to FVC ratio (FEV_1:FVC) ≤ 0.7 at Visit 1 (Screening).	☐	☐
5. Patients with fixed airway obstruction, defined by ≤ 15% **or** ≤ 200 ml (or both) increase in FEV_1 after the administration of albuterol 180 mcg via MDI with a spacer at Visit 1 (Screening).	☐	☐
6. Patients with a post-albuterol FEV_1 between ≥30% and ≤ 70% of predicted normal for height, age and gender at Visit 1. Patients will be assessed 15 to 30 (± 5) minutes after receiving albuterol 180 mcg via MDI with a spacer.	☐	☐
7. Patients who give their signed written informed consent to participate.	☐	☐

Do not admit the patient to this study if any "NO" box has been marked.

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Protocol	Patient Number	Patient Initials	Visit 1 Screening
207499/156	[redacted]		

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. Patients with poorly controlled COPD, defined as the occurrence of any of the following in the 2 weeks prior to Visit 1: acute worsening of COPD that is managed by the patient at home by self-treatment with corticosteroids or antibiotics, that requires treatment prescribed by a physician, or for which the patient is hospitalized.	☐	☐
4. Patients with active tuberculosis, lung cancer, or clinically overt bronchiectasis.	☐	☐
5. Patients with clinically significant cardiovascular, neurological, renal, endocrine, or hematological abnormalities that are uncontrolled on permitted therapy.	☐	☐
6. Patients with clinically significant gastrointestinal or hepatic abnormalities.	☐	☐
7. Patients with clinically significant orthostatic changes in blood pressure or heart rate at Visit 1 (Protocol Section 5.4.2).	☐	☐
8. Patients with a history of hypersensitivity to PDE4 inhibitors.	☐	☐
9. Patients with a history (or suspected history) of alcohol misuse or any other recreational substance abuse.	☐	☐
10. Patients who require treatment with inhaled cromolyn sodium or nedocromil, inhaled long-acting $beta_2$-agonists, oral $beta_2$-agonists, nebulized $beta_2$-agonists, nebulized anticholinergics, xanthines, leukotriene modifiers or oral/inhaled corticosteroids beyond Visit 1. All COPD medications except anticholinergic medication or albuterol via MDI should be withdrawn prior to or at Visit 1 (Screening).	☐	☐
11. Patients receiving treatment with long term oxygen therapy (LTOT), patients who require supplemental oxygen more often than on an occasional (prn) basis, or patients who require nocturnal positive pressure for sleep apnea.	☐	☐
12. Patients who have participated in a Pulmonary Rehabilitation Program within 4 weeks prior to Visit 1 (Screening) or who will enter a Pulmonary Rehabilitation Program during the study.	☐	☐
13. Patients 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).	☐	☐
14. Patients who have previously participated in an Ariflo (SB 207499) study and who received randomized study medication.	☐	☐
15. Patients unable to comply with study procedures (including completion of the health status questionnaires).	☐	☐

Do not admit the patient to this study if any "YES" box has been marked.
Additional Exclusion Criteria will be evaluated at Visit 3.

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 1

- *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 a diary card and remind the patient to use the card to record if they feel differently since starting the study.*

    - *Issue the patient the fecal 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 10am + / - 2 hours.*

    - ***Remind the patient:***

        i *__not__ to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit (eg if study medication is taken at 08:00, the visit must be 16:00 or later).*

        ii *to refrain from using albuterol or anticholinergic agents during the **4 hours** immediately preceding the 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 albuterol inhaler and spacer, and the diary card.*

        v *to continue to take the anticholinergic medication, if prescribed, at a constant dose.*

        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, diarrhea, 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.*

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Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 1 Screening
207499/156		[redacted]			

STUDY MEDICATION LABEL

Register the patient with SB's Registration and Medication Ordering System (RAMOS) by calling 1-866-726-6760. Issue the patient 20 days supply of **single-blind study medication** (2 bottles). The first 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.

Attach the tear-off labels from the study medication bottles 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

Attach label here

Date and time visit dose was taken ____ ____ ____ (Day Month Yr) ____ ____ (24hr:min)

PATIENT ACTIVITY POSTCARD

Please complete the patient activity postcard for ***Visit 1 Screening*** located in the postcard section of this CRF. Detach the postcard and mail promptly. Postage has been prepaid.

VISIT 2, WEEK -2
SINGLE-BLIND RUN-IN

SmithKline Beecham
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Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

MOD2

Please do not split modules

Module 2 : **Visit 2, Visit 3 (Pre-Randomization), Baseline Signs and Symptoms, Concomitant Medications, Medical Procedures, COPD Exacerbations, Resource Utilization**

CRF Pages **19 - 63**

Unprocessed Forms : **Within this module the following occur which will generate attachments that need to be brought in-house.**

None

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Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	Visit 2 Single-blind Run-in Week -2
207499/156		[redacted]			

PRESENTATION TO CLINIC

Record time of presentation to clinic ☐☐ 24hr:min

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?

☐ NA → Patient is not using beta$_2$ agonist.

☐ 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?

☐ NA → Patient is not using anticholinergic.

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: ☐☐☐ 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 : ☐☐

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 2 Single-blind Run-in Week -2
207499/156		[redacted]			

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes ⟶ If 'Yes' please record details below.

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

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

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

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of excerbation (maximum level)	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1
	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2
	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3

If a patient experienced a COPD exacerbation that was treated with corticosteroids or antibiotics, 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.

RESOURCE UTILIZATION

If the patient has received any COPD exacerbation-related medical care since the last visit, record details in the Resource Utilization section at the back of this module.

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Protocol		Patient Number	Patient Initials		Visit 2 Single-blind Run-in Week -2
207499/156		[redacted]			

INDIRECT COST

Does the patient work?

☐ No

☐ Yes → *If 'Yes', has the patient missed work due to COPD-related symptoms, excluding scheduled protocol visits, since the last visit?*

☐ No

☐ Yes → *If 'Yes', please record lost work days below:*

Start Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence

How many days since your last visit have you been restricted in performing your leisure activities, due to your COPD-related symptoms? *(please enter number of days below, if not restricted, enter 0)*

☐☐ Days

Since your last visit, how many hours per week did you require paid or unpaid assistance by a relative, friend or professional with your daily activities such as dressing, bathing, cooking, etc., due to your COPD-related symptoms? *(please enter number of hours below, if no paid or unpaid assistance, enter 0 in each instance)*

☐☐☐ Hours per week of **paid** assistance

☐☐☐ Hours per week of **unpaid** assistance

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 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.

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 2 Single-blind Run-in Week -2
207499/156		[redacted]			

"AS NEEDED" ALBUTEROL USE

Record the patient's evaluation of their 'as needed' albuterol use since the last visit.

[1] ☐ Much less than usual
[2] ☐ Less than usual
[3] ☐ About the same as usual
[4] ☐ More than usual
[5] ☐ Much more than usual

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.

FECAL OCCULT BLOOD TEST

The fecal 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 fecal 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'.

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Protocol		Patient Number	Patient Initials		Visit 2 Single-blind Run-in Week -2
207499/156		[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. bid)

Date and time of last dose of study medication prior to the study visit ☐☐☐☐☐☐ Day Month Yr ☐☐☐☐ 24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
40	☐☐	☐☐	☐☐	☐☐	☐☐☐

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance ≥ 80% and ≤120%?

☐ No → *If 'No' please remind the patient of the importance of taking the medication according to the protocol.*

☐ Yes

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Protocol		Patient Number	Patient Initials		Visit 2 Single-blind Run-in Week -2
207499/156		[redacted]			

OVERALL BREATHLESSNESS ASSESSMENT

Give the patient a copy of the following scale when assessing breathlessness.

Please ask the patient the following question and record the answer below.

"Generally speaking, how has your breathlessness been during the previous week when you carried out tasks that usually cause you to be short of breath (e.g. walking, carrying shopping, climbing stairs, etc)?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Overall breathlessness score ☐☐.☐

PULMONARY REHABILITATION PROGRAM

Has the patient entered a Pulmonary Rehabilitation Program since the last visit?

☐ No

☐ Yes

INVESTIGATOR INSTRUCTIONS

The following procedures (Vital Signs and Exercise Tolerance Test) must be performed more than 4 hours after the patient's last albuterol administration.

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Protocol		Patient Number	Patient Initials		Visit 2 Single-blind Run-in Week -2
207499/156		[redacted]			

VITAL SIGNS

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 module.*

EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted? The distance walked should be entered even if the patient did not walk for 6 minutes.

☐ No

☐ Yes → *If 'Yes', Distance walked* ☐☐☐ Meters ☐

Yards ☐

Record any adverse experiences which occur during the exercise tolerance test in the Baseline Signs and Symptoms section.

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Protocol		Patient Number	Patient Initials		Visit 2 Single-blind Run-in Week -2
207499/156		[redacted]			

POST-EXERCISE ASSESSMENTS *(Immediately after the patient completes the exercise tolerance)*

Heart Rate ☐☐☐ beats/min

SaO_2 ☐☐☐ %

Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

"How short of breath do you feel right now?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Post-exercise breathlessness score ☐☐.☐

INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise tolerance test (rest for at least 10 minutes) before performing the pulmonary function tests.

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Protocol		Patient Number	Patient Initials		Visit 2 Single-blind Run-in Week -2
207499/156		[redacted]			

PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed at least 4 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 confirm that the pulmonary function tests were performed

[1] ☐ Not performed

[2] ☐ Performed

Has the patient's absolute value of FEV$_1$ increased or decreased by > 20% between Visits 1 and 2?

☐ No

☐ Yes ⟶ *If 'Yes please withdraw the patient and complete the Study Continuation/Withdrawal page at the back of this book.*

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 2

- *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 a new diary card and remind the patient to use the card to record if they feel differently since starting the study.*

    - *Ask the patient to return for the next visit in 14 +/- 3 days at 10:00 +/- 2 hours.*

    - ***Remind the patient:***

        i *__not__ to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).*

        ii *to refrain from using albuterol or anticholinergic agents during the **4 hours** immediately preceding the 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 albuterol inhaler and spacer, and the diary card.*

        v *to continue to take the anticholinergic medication, if prescribed, at a constant dose.*

        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, diarrhea, 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 fecal occult blood test(s) by the next visit if not already done.*

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Protocol		Patient Number	Patient Initials		Visit 2 Single-blind Run-in Week -2
207499/156		[redacted]			

STUDY MEDICATION LABEL

Issue the patient 20 days supply of **single-blind study medication** (2 bottles) and an albuterol MDI and spacer for 'as required' use if applicable (remind the patient to use this inhaler rather than any albuterol inhaler they may have at home). The first 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.

Attach the tear-off labels from the study medication bottles 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	Attach label here

Date and time visit dose was taken ____ ____ ____ (Day Month Yr) ____ ____ (24hr:min)

PATIENT ACTIVITY POSTCARD

Please complete the patient activity postcard for ***Visit 2 Single Blind Run-In*** located in the postcard section of this CRF. Detach the postcard and mail promptly. Postage has been prepaid.

VISIT 3, DAY 1
BASELINE
(PRE-RANDOMIZATION)

(PRE-RANDOMIZATION)

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	Visit 3 Baseline Pre-randomization Day1
207499/156		[redacted]			

PRESENTATION TO CLINIC

Record time of presentation to clinic ☐☐ 24hr:min

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?

☐ NA → Patient is not using beta$_2$ agonist.

☐ 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?

☐ NA → Patient is not using anticholinergic.

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: ☐☐☐ 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 : ☐☐

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes

ST. GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

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

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Protocol		Patient Number	Patient Initials		Visit 3
207499/156		[redacted]			

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. US version adapted and modified with permission by Judith Barr, Sc.D., Northeastern Univ., Boston, MA.

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Protocol		Patient Number	Patient Initials		Visit 3
207499/156		[redacted]			

SF - 36 (HEALTH STATUS QUESTIONNAIRE) (Page 1 of 5)

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Protocol		Patient Number	Patient Initials		Visit 3 Baseline Pre-randomization Day1
207499/156		[redacted]			

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes ⟶ *If 'Yes' please record details below.*

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

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

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

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of excerbation (maximum level)	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1
	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2
	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3

If a patient experienced a COPD exacerbation that was treated with corticosteroids or antibiotics, 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.

RESOURCE UTILIZATION

Please complete the COPD Resource Utilization section at the back of this module.

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 3 Baseline Pre-randomization Day1
207499/156		[redacted]			

INDIRECT COST

Does the patient work?

☐ No

☐ Yes → *If 'Yes'*, has the patient missed work due to COPD-related symptoms, excluding scheduled protocol visits, since the last visit?

☐ No

☐ Yes → *If 'Yes', please record lost work days below:*

Start Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence

How many days since your last visit have you been restricted in performing your leisure activities, due to your COPD-related symptoms? *(please enter number of days below, if not restricted, enter 0)*

☐☐ Days

Since your last visit, how many hours per week did you require paid or unpaid assistance by a relative, friend or professional with your daily activities such as dressing, bathing, cooking, etc., due to your COPD-related symptoms? *(please enter number of hours below, if no paid or unpaid assistance, enter 0 in each instance)*

☐☐☐ Hours per week of **paid** assistance

☐☐☐ Hours per week of **unpaid** assistance

BASELINE SIGNS AND SYMPTOMS

Please complete the Baseline Signs and Symptoms 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 Baseline Signs and Symptoms section at the back of this module. The patient should refer to the notes in their diary when answering this question.

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Protocol		Patient Number	Patient Initials		Visit 3 Baseline Pre-randomization Day1
207499/156		[redacted]			

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.

"AS NEEDED" ALBUTEROL USE

Record the patient's evaluation of their 'as needed' albuterol use since the last visit.

[1] ☐ Much less than usual
[2] ☐ Less than usual
[3] ☐ About the same as usual
[4] ☐ More than usual
[5] ☐ Much more than usual

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.

FECAL OCCULT BLOOD TEST

If not completed previously, record results from the test(s) in the Fecal Occult Blood Test section in Visit 2.

Has the patient had a positive fecal 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 module.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 3 Baseline Pre-randomization Day1
207499/156		[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. bid)

Date and time of last dose of study medication prior to the study visit ☐☐☐☐☐☐ Day Month Yr ☐☐☐☐ 24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
40	☐☐	☐☐	☐☐	☐☐	☐☐☐

Note: If this is a morning visit, patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance ≥ 80% and ≤120%?

☐ No → *If 'No' please withdraw the patient and complete the Study Continuation/Withdrawal page at the back of this book.*

☐ Yes

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Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 3 Baseline Pre-randomization Day1
207499/156		[redacted]			

OVERALL BREATHLESSNESS ASSESSMENT

Give the patient a copy of the following scale when assessing breathlessness.

Please ask the patient the following question and record the answer below.

"Generally speaking, how short of breath have you been during the previous week when you carried out tasks that usually cause you to be short of breath (e.g. walking, carrying shopping, climbing stairs, etc)?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Overall breathlessness score [ ][ ].[ ]

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 3 Baseline Pre-randomization Day1
207499/156		[redacted]			

COUGH AND SPUTUM PRODUCTION ASSESSMENTS

*Please ask the patient the following questions and record the answers below (Mark **one** box per section only.)*

COUGH

How troubled have you been by cough today?

[0] ☐ No symptoms at all

[1] ☐ Some symptoms, but hardly noticeable

[2] ☐ Symptoms noticeable and a little uncomfortable

[3] ☐ Symptoms definitely noticeable and uncomfortable

[4] ☐ Symptoms very bad and extremely uncomfortable

SPUTUM PRODUCTION

How much sputum have you produced today?

[0] ☐ No sputum at all

[1] ☐ Some sputum, but not as much as usual

[2] ☐ As much as usual

[3] ☐ More than usual

[4] ☐ A lot more than usual

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 Exercise Tolerance Test) must be performed greater than 4 hours after the patient's last albuterol administration.

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 3 Baseline Pre-randomization Day1
207499/156		[redacted]			

VITAL SIGNS

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 module.*

VITAL SIGNS - ORTHOSTATIC CHANGE

1st Measurement: After 5 Minutes Supine

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
☐☐☐/☐☐☐	☐☐☐

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
☐☐☐/☐☐☐	☐☐☐

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 ≥ 10 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	Patient Initials		Visit 3 Baseline Pre-randomization Day1
207499/156		[redacted]			

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant changes noted at this examination compared to Screening?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Baseline Signs and Symptoms section at the back of this module.*

RESTING SaO_2

Measure Resting SaO_2 by pulse oximetry for all patients with an FEV_1 < 40% of predicted for age, height and gender at Visit 1.

[1] ☐ Measurement not required (patient's FEV_1 at Visit 1 ≥ 40% of predicted)

[2] ☐ Measurement required but not performed

[3] ☐ Measurement taken, *please record value below:*

Resting SaO_2 ☐☐☐ %

EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted? The distance walked should be entered even if the patient did not walk for 6 minutes.

☐ No

☐ Yes → *If 'Yes', Distance walked* ☐☐☐ Meters [M] ☐

Yards [YD] ☐

Record any adverse experiences which occur during the exercise tolerance test in the Baseline Signs and Symptoms section at the back of this module.

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 3 Baseline Pre-randomization Day1
207499/156		[redacted]			

POST-EXERCISE ASSESSMENTS *(Immediately after the patient completes the exercise tolerance test)*

Heart Rate ☐☐☐ beats/min

SaO_2 ☐☐☐ %

Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

"How short of breath do you feel right now?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Post-exercise breathlessness score ☐☐.☐

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 3 Baseline Pre-randomization Day1
207499/156		[redacted]			

INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise tolerance test (rest for at least 10 minutes) before performing the pulmonary function tests.

PULMONARY FUNCTION TESTS - PRE-ALBUTEROL

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 randomized, additional pulmonary function tests will be performed after a dose of study albuterol is given in the clinic (Book 2) AND prior to the first dose of randomized 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 confirm that the pulmonary function tests were performed

[1] ☐ Not performed

[2] ☐ Performed

RANDOMIZATION CRITERION

Has the patient's absolute value of FEV$_1$ increased or decreased by > 20% between Visits 1 and 3?

☐ Yes → *If 'Yes' please withdraw the patient and complete the Study Continuation/Withdrawal page at the back of this book.*

☐ No

ADDITIONAL EXCLUSION CRITERIA

Complete the following exclusion criteria.	**Yes**	**No**
1. The patient has had a positive fecal occult blood test result between Visit 1 and 3.	☐	☐
2. The patient has a clinically significant orthostatic change in blood pressure or heart rate at Visit 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.

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 is 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 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 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

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[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)

If no baseline events prior to randomization into study please mark this box ☐

Baseline Event *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***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 randomization	[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 Concomitant Medication and/or Medical Procedures section if appropriate*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific event?	☐ Yes ☐ No	☐ Yes ☐ No

SmithKline Beecham Pharmaceuticals

Protocol	Patient Number	Patient Initials
207499/156	[redacted]	

BASELINE SIGNS AND SYMPTOMS (or events, or diagnoses) - Continued

*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)

If no baseline events prior to randomization into study please mark this box ☐

Baseline Event *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***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 randomization	[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 Concomitant Medication and/or Medical Procedures section if appropriate*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific event?	☐ Yes ☐ No	☐ Yes ☐ No

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		
207499/156		[redacted]			

BASELINE SIGNS AND SYMPTOMS (or events, or diagnoses) - Continued

*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)

If no baseline events prior to randomization into study please mark this box ☐

Baseline Event *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***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 randomization	[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 Concomitant Medication and/or Medical Procedures section if appropriate*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific event?	☐ Yes ☐ No	☐ Yes ☐ No

CONCOMITANT MEDICATION
excluding treatment for COPD Exacerbations
(These are recorded in the COPD Exacerbations section)

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 (albuterol) 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 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 Route, see General Instructions for acceptable abbreviations.*

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 (albuterol) 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 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.*

MEDICAL PROCEDURES
excluding treatment for COPD Exacerbations
(These are recorded in the COPD Exacerbations section)

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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			
For SB			

COPD EXACERBATION SECTION

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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***

If no COPD Exacerbations prior to randomization please mark this box. ☐

Baseline Event	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***If patient died, STOP: go to SAE COPD Exacerbation pages.***	[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) *See definitions page for Baseline Signs & Symptoms form.*	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Relationship to study procedures performed prior to randomization	[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 on the COPD Medications or Procedures page*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific event prior to randomization?	☐ Yes ☐ No	☐ Yes ☐ No

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

DETAILS OF COPD EXACERBATIONS - CONTINUED

*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***

If no COPD Exacerbations prior to randomization please mark this box. ☐

Baseline Event	**COPD EXACERBATION**	**COPD EXACERBATION**
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***If patient died, STOP: go to SAE COPD Exacerbation pages.***	[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) *See definitions page for Baseline Signs & Symptoms form.*	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Relationship to study procedures performed prior to randomization	[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 on the COPD Medications or Procedures page*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific event prior to randomization?	☐ Yes ☐ No	☐ Yes ☐ No

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 minimize 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	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation

Person Reporting SAE _____
(Please print clearly)

AEGIS Number

Serious Adverse Experience	**COPD Exacerbation** → *Specify reason(s) for considering this a serious AE. Mark all that apply.*
For SmithKline Beecham	
Onset Date and Time	Day 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

[1] ☐ fatal
[2] ☐ life threatening
[3] ☐ disabling/incapacitating
[4] ☐ results in hospitalization (excluding elective surgery or routine clinical procedures)
[5] ☐ hospitalization 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 _____

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 randomization code broken at investigational site? ☐ No ☐ Yes

Randomization 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

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible) Day Mth Yr	End Date (or if Continuing mark box) Day Mth Yr	
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							

* *For Route, see General Instructions for acceptable abbreviations.*

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			

RESOURCE UTILIZATION

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

RESOURCE UTILIZATION

Has the patient utilized any COPD Exacerbation-related medical care between Visits 1 and 3?

☐ No

☐ Yes → *If 'Yes', please record details below*

Has the patient had any **Physician Visits** (COPD care excluding scheduled protocol visits) between Visits 1 and 3?

☐ No

☐ Yes → *If 'Yes', please record details below*

Date of Visit Day Mth Yr	Reason for Visit

Has the patient had any **Emergency Room (ER)/Urgent Care Visits/Procedures (i.e., lung surgery)** between Visits 1 and 3?

☐ No

☐ Yes → *If 'Yes', please record details below*

Date of Visit Day Mth Yr	Reason for Visit	Patient Admitted from ER? Yes	No
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

RESOURCE UTILIZATION - (cont)

Has the patient had any **Hospitalizations** between Visits 1 and 3?

☐ No

☐ Yes → *If 'Yes', please record details below* ***(also record details of any hospitalization in the Serious Adverse Experience - COPD Exacerbation section)***

Name of Hospital & City	Date of Admission Day Mth Yr	Date of Discharge Day Mth Yr	Reason for Admission

Has the patient had any **Intensive Care Unit (ICU) stays** ***(did the patient stay in the ICU during any of the above hospitalizations?)*** between Visits 1 and 3?

☐ 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

STUDY CONTINUATION / WITHDRAWAL

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

CONC1

Please do not split modules

Module: Study Continuation / Withdrawal

CRF Pages: 64

Unprocessed Forms: Within this module, the following occur which will generate attachments that need to be brought in-house.

None

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

STUDY CONTINUATION/WITHDRAWAL

Is the patient continuing into the double-blind treatment phase of the study?

☐ Yes → *If 'Yes' please sign in the appropriate space below and continue immediately to Book 2.*

☐ No → *If 'No' please mark the **PRIMARY** cause of withdrawal and sign the box below.*

[1] ☐ Baseline sign/symptom (complete BS&S form)

[10] ☐ Does not meet inclusion/exclusion criteria

[3] ☐ Protocol deviation (including non-compliance)

[4] ☐ Lost to follow-up

[5] ☐ Other - specify: _____

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

PATIENT ACTIVITY POSTCARD

Please complete the patient activity postcard for ***Visit 3 Pre-randomization***, located in the postcard section of this CRF. Detach the postcard and mail promptly. Postage has been prepaid.

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	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

SAE1

Please do not split modules

Module: Serious Adverse Experiences

CRF Pages: 65 - 66

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	SB Receipt Date (Day Month Year)
207499/156		[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 hospitalization (excluding elective surgery or routine clinical procedures)
[5] ☐ hospitalization 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 section →
☐ Yes ☐ No

Was patient withdrawn due to this specific SAE ?
☐ Yes ☐ No

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[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 randomization code broken at investigational site? ☐ No ☐ Yes

Randomization 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 _____

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

FORMD1

Please do not split modules

Module: **Form D**

CRF Pages: **67**

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

FORM D

Certified Cause of Death _____

Date of Death Day Month Yr → *Please complete Serious Adverse Experience section.*

Was a post-mortem examination carried out?

☐ No

☐ Yes → *If 'Yes' please summarize findings (include diagnosis):*

_____

_____

_____

_____

Reporting Physician's Signature _____ Date Day Month Yr

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		OPTIONAL Repeat Lab
207499/156		[redacted]			

RPLAB1

Please do not split modules

Module: Repeat Lab

CRF Pages: 68

Unprocessed Forms: Within this module, the following tests / procedures occur which may generate attachments.

None

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		OPTIONAL Repeat Lab
207499/156		[redacted]			

REPEAT 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.*

REPEAT 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.

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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	Center Number	Patient Number	Patient Initials	Investigator
207499/156		[redacted]		

CRF TRACKING/REVIEW FORM

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 - 18	☐	☐	_____
MOD2	V2, V3, BSS, CM, MP, COPD, RU	19 - 63	☐	☐	_____
CONC1	Continuation/Withdrawal	64	☐	☐	_____
SAE1	Serious Adverse Experiences	65 - 66	☐	☐	_____
FORMD1	Form D	67	☐	☐	_____
RPLAB1	Repeat Labs	68	☐	☐	_____

If multiple modules are submitted together, please ensure they are sorted according to the order above

Site Monitor's Comments (e.g. protocol violations or deviations)

_____

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Site Monitor's Signature _____ Date Submitted ☐☐ Day ☐☐ Month ☐☐ Yr

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Investigator
207499/156		[redacted]		

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Site Monitor's Signature _____ Date Submitted ☐☐ Day ☐☐ Month ☐☐ Yr

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Investigator
207499/156		[redacted]		

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Site Monitor's Comments (e.g. protocol violations or deviations)

Site Monitor's Signature _____ Date Submitted ☐☐ ☐☐ ☐☐
Day Month Yr

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Investigator
207499/156		[redacted]		

CRF TRACKING/REVIEW FORM

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Site Monitor's Comments (e.g. protocol violations or deviations)

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Site Monitor's Signature _____ Date Submitted ☐☐ Day ☐☐ Month ☐☐ Yr

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Investigator
207499/156		[redacted]		

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Site Monitor's Comments (e.g. protocol violations or deviations)

Site Monitor's Signature _____ Date Submitted ☐☐ Day ☐☐ Month ☐☐ Yr

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Investigator
207499/156		[redacted]		

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Site Monitor's Signature _____ Date Submitted ☐☐ Day ☐☐ Month ☐☐ Yr

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

CONFIDENTIAL

SmithKline Beecham
Pharmaceuticals

PROTOCOL 207499/156

BOOK 2 : RANDOMIZATION TO VISIT 7

A RANDOMIZED, 24-WEEK, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY, SAFETY AND TOLERABILITY OF ARIFLO™ (15 MG BID) IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

Attach pharmacokinetic sampling group identification label here

GENERAL INSTRUCTIONS

- *Write clearly in capital letters using a black ball point pen and press firmly so that all copies are legible*
- *Do not write in shaded areas*
- *Answer ALL questions on every page*
- *Enter "N/A" if information requested is not available*
- *Initial and date all changes, additions or deletions. Use a single pen stroke to remove an incorrect entry*
- *Enter the patient initials on all pages on which information has been entered and the patient number and center number where required*

Do not enter additional data/information after the set of CRF pages has been split/separated

The cover flap or plastic writing board should be used to divide each set of pages before writing on them with a ball point pen

DATE

Please use the following three-letter abbreviations for the months

January	JAN
February	FEB
March	MAR
April	APR
May	MAY
June	JUN
July	JUL
August	AUG
September	SEP
October	OCT
November	NOV
December	DEC

e.g. | 0 1 | J A N | 0 0 | = *1st January 2000*

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

PATIENT INITIALS

Please use the following format:

e.g. [redacted]

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*

STUDY PROCEDURES CHART 207499/156

Visit	1	2	3	3a	4	5	6	7	8	9	10		
	Screen		Baseline								End Double-blind	Early Withdrawal[1]	Final Safety Follow-up
Time relative to baseline (weeks)	-4	-2	0	+1	+2	+4	+8	+12	+16	+20	+24		+25
Signed written informed consent	x												
Medical & surgical history	x												
Physical examination[2]	x		x								x	x	x[3]
Pulmonary history & symptoms	x												
Postero-anterior chest radiograph[4]	x												
Exacerbation assessment/resource use	x	x	x	x	x	x	x	x	x	x	x	x	x
Medication history	x												
Overall breathlessness (modified Borg)	x	x	x		x	x	x	x	x	x	x		
Resting 12-lead ECG	x		x	x	x	x	x	x	x	x	x	x	x[3]
Vital signs (BP, HR)	x[5]	x	x[5]	x	x	x	x	x	x	x	x[5]	x[5]	x
Exercise Tolerance (6-Minute walk)	x	x	x			x	x	x	x	x	x	x	
Post-exercise SaO2 & breathlessness	x	x	x			x	x	x	x	x	x	x	
CO Diffusing Capacity (DLCO)[6]	x												
Albuterol reversibility[7]	x												
Laboratory tests	x		x[8]	x	x	x	x	x	x[9]	x[9]	x[8]	x[8]	x[3,9]
Dispense single-blind medication	x	x											
Albuterol Use		x	x	x	x	x	x	x	x	x	x		
Concomitant medication/medical procedures		x	x	x	x	x	x	x	x	x	x	x	x
PFTs (in absence of albuterol)[10]		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	
Baseline signs and symptoms/AEs[11]		x	x	x	x	x	x	x	x	x	x	x	x
Health status assessment: SGRQ			x					x			x	x	
Quality of life assessment: SF-36			x								x	x	
Cough and sputum assessments			x					x			x	x	
Pharmacokinetic evaluations[12]			x			x		x			x		
Arterial blood gas/SaO2[13]			x								x		
Hourly PFTs for 4 hrs post first/last dose [14]			x								x		
Dispense double-blind medication			x	x	x	x	x	x	x	x			
Investigator/Patient global assessment											x	x	
Study conclusion record												x	x

1 Patients who stop taking study medication between clinic visits will attend the clinic within 24 hours for an early withdrawal visit.

2 To include a respiratory examination.

3 If abnormalities at previous visit for patients who complete Visit 10 or withdraw from the study.

4 Postero-anterior chest X-ray must be performed at Visit 1 unless the film from a chest X-ray within the 12 weeks prior to Visit 1 is available to the Investigator.

5 Including Orthostatic vital signs.

6 DLCO should be done between Visit 1 and Visit 3 if not performed during the previous 24 weeks or if the results are unavailable.

7 Before and 15 to 30 (± 5) minutes after administration of 180 mcg albuterol via a MDI with a spacer to determine % predicted FEV_1, FVC, FEF_{25-75}, PEFR, and FEV_1: FVC.

8 In addition to usual laboratory tests, three fecal occult blood tests will be performed between Visits 1 and 3, between Visits 9 and 10, and at early withdrawal; amylase will be measured at Visit 3.

9 Urinary beta-HCG tests will be performed in females of childbearing potential. No other laboratory samples will be collected at Visits 8 and 9.

10 Includes FEV_1, FVC, FEF_{25-75}, PEFR, and FEV_1:FVC measured by centralized spirometry by the same person at each visit.

11 A diary will be used to record if patients feel different since starting study medication.

12 Visit 3: 3 hours post-dose. Visit 5: trough and 0.5-3 hours post-dose. Visit 7: trough and 3-10 hours post-dose. Visit 10: trough only.

13 In patients with <40% of predicted FEV_1 at Visit 1 and resting SaO_2 <88% or if the patient lives at a high altitude.

14 Pulmonary function tests 30 (± 5) minutes after albuterol followed by 4-hour post-double-blind drug assessments at Visits 3 and 10.

VISIT 3, DAY 1
POST-RANDOMIZATION

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Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

MOD3

Please do not split modules

Module 3 : Visit 3 (Post-Randomization), Visit 3A, Visit 4, Visit 5, Adverse Experiences, Concomitant Medication, Medical Procedures, COPD Exacerbations, Resource Utilization

CRF Pages 69 - 126

Unprocessed Forms : Within this module the following occur which will generate attachments that need to be brought in-house.

None

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Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	Visit 3 Post-randomization Day 1
207499/156		[redacted]			

LABORATORY TESTS

Please take blood samples for hematology, 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. If the pregnancy test is positive, please withdraw the patient from the study, complete the Serious Adverse Experiences form and forward it to SB within 24 hours. Complete the Visit for Early Withdrawal between Scheduled Visits and the Study Continuation/ Withdrawal section at the back of this book.

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 (If a re-test is necessary, please use the Repeat Lab page at the end of this book)*

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Protocol		Patient Number	Patient Initials		Visit 3 Post-randomization Day 1
207499/156		[redacted]			

ARTERIAL BLOOD GASES

If a resting SaO2 test was required at this visit AND the patient's resting SaO2 < 88% OR the patient lives at a high altitude, please take an arterial blood gas sample for analysis if feasible. The patient should be rested (5 to 10 minute rest) after pulmonary function tests.

☐ Not required

☐ Sample required but not taken

PO_2 (mmHg)	PCO_2 (mmHg)	HCO_3- (mEq/L)	pH	SaO_2 %
☐☐☐	☐☐	☐☐	☐.☐☐	☐☐☐

POST-ALBUTEROL PULMONARY FUNCTION TESTS

Issue the patient an albuterol inhaler for 'as-required' use and retrieve their old inhaler.
Administer 180mcg (2 puffs) of albuterol via MDI with a spacer.

Record the time of albuterol inhalation ☐☐ 24hr:min

Wait 30 minutes *(+/-5 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 manuals)****. For each set of three* FEV_1 *measurements, one* FEV_1 *must be within 10% of the highest.*

Please confirm that the pulmonary function tests were performed

[1] ☐ Not Performed

[2] ☐ Performed

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Protocol		Patient Number	Patient Initials		Visit 3 Post-randomization Day 1
207499/156		[redacted]			

PATIENT RANDOMIZATION

Following completion of all preceding assessments contact RAMOS (1-866-726-6760) to obtain the container and randomization numbers assigned to the patient.

Please enter the 5-digit Randomization 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

Enter 6-digit Code as it appears on the study medication label ☐☐☐☐☐☐

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

The patient should remain in the clinic for the next 4 hours, during which time the patient will be observed and will undergo hourly pulmonary function testing (to be recorded on the following pages).

PHARMACOKINETIC EVALUATION

Assign the patient to the 'Early' or 'Late' group for pharmacokinetic sampling.

[1] ☐ Early

[2] ☐ Late

Select the appropriate label ('early' or 'late') from those supplied and affix it to the cover of this book.

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Protocol		Patient Number	Patient Initials		Visit 3 Post-randomization Day 1
207499/156		[redacted]			

POST-DOSE PULMONARY FUNCTION TESTS

Pulmonary function tests will be completed every hour in the 4-hour period following administration of the first dose of study medication.

Ask the patient to avoid using additional albuterol or anticholinergic medication and to refrain from smoking if at all possible.

If the patient uses their albuterol or anticholinergic medication during this period, the tests should be abandoned.

Time post-dose	Completed? Yes	No
1 Hour	☐	☐
2 Hours	☐	☐
Perform ECG and Pharmacokinetic Evaluation		
3 Hours	☐	☐
4 Hours	☐	☐

ADVERSE EXPERIENCES

Record any adverse experiences which occur during the pulmonary function tests in the Adverse Experience section at the back of this module.

12 LEAD ELECTROCARDIOGRAM - 3 HOURS POST DOSE

The ECG should be performed before the 3-hour post-dose pulmonary function test and after the patient has been semi-supine for 5 minutes.

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant changes noted at this examination compared to Baseline?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of this module.*

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Protocol		Patient Number	Patient Initials		Visit 3 Post-randomization Day 1
207499/156		[redacted]			

PHARMACOKINETIC EVALUATIONS - 3 HOURS POST DOSE

Collect a blood sample (5mL) 3 hours post dose (after the ECG and before the 3-hour post-dose pulmonary function test) for pharmacokinetic evaluation.

Was a pharmacokinetic sample taken?

☐ No

☐ Yes → *If 'Yes'*, 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)

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 3

- *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 a diary card and remind the patient to use the card to record if they feel differently since starting the study.*

    - *Ask the patient to return for Visit 3A in 7 +/- 2 days and for Visit 4 in 14 +/- 3 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. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).*

        iii *to refrain from using albuterol or anticholinergic agents during the **4 hours** immediately preceding the 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 albuterol inhaler and spacer, and the diary card.*

        vi *to continue to take the anticholinergic medication, if prescribed, at a constant dose.*

        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, diarrhea, 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.*

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Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	
207499/156		[redacted]			Visit 3A Week 1

PRESENTATION TO CLINIC

Record time of presentation to clinic ☐☐ 24hr:min

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?

☐ NA → Patient is not using beta$_2$ agonist.

☐ 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?

☐ NA → Patient is not using anticholinergic.

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: ☐☐☐ 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 : ☐☐

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes

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Protocol		Patient Number	Patient Initials		Visit 3A Week 1
207499/156		[redacted]			

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes → *If 'Yes' please record details below. If the patient has had more than three Level 2 or 3 exacerbations since the start of double-blind medication, patient may be withdrawn after consultation with the Medical Monitor. If withdrawing, complete the assessments scheduled at this visit and the Assessments for Patients Withdrawing at Visit 3A. The SGRQ and SF-36 should be completed before any additional assessments.*

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

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

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

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of excerbation (maximum level)	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1
	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2
	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations, including an increase in usual COPD medications, must be recorded in the COPD Medications or Procedures pages.

RESOURCE UTILIZATION

If the patient has received any COPD exacerbation-related medical care since the last visit, record details in the Resource Utilization section at the back of this module.

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Protocol		Patient Number	Patient Initials		Visit 3A Week 1
207499/156		[redacted]			

INDIRECT COST

Does the patient work?

☐ No

☐ Yes → *If 'Yes'*, has the patient missed work due to COPD-related symptoms, excluding scheduled protocol visits, since the last visit?

☐ No

☐ Yes → *If 'Yes', please record lost work days below:*

Start Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence

How many days since your last visit have you been restricted in performing your leisure activities, due to your COPD-related symptoms? *(please enter number of days below, if not restricted, enter 0)*

☐☐ Days

Since your last visit, how many hours per week did you require paid or unpaid assistance by a relative, friend or professional with your daily activities such as dressing, bathing, cooking, etc., due to your COPD-related symptoms? *(please enter number of hours below, if no paid or unpaid assistance, enter 0 in each instance)*

☐☐☐ Hours per week of **paid** assistance

☐☐☐ Hours per week of **unpaid** assistance

ADVERSE EXPERIENCES

If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

CONCOMITANT MEDICATION

If there has been any change in the patient's concomitant medication excluding treatment for COPD exacerbations (this is recorded in the COPD Exacerbations section) since the last visit, please record details in the Concomitant Medication section at the back of this module.

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Protocol		Patient Number	Patient Initials		Visit 3A Week 1
207499/156		[redacted]			

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.

"AS NEEDED" ALBUTEROL USE

Record the patient's evaluation of their 'as needed' albuterol use since the last visit.

[1] ☐ Much less than usual
[2] ☐ Less than usual
[3] ☐ About the same as usual
[4] ☐ More than usual
[5] ☐ Much more than usual

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Protocol		Patient Number	Patient Initials		Visit 3A Week 1
207499/156		[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. bid)

Date and time of last dose of study medication prior to the study visit ☐☐☐☐ Day Month Yr ☐☐ 24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
20	☐☐	☐☐	☐☐	☐☐	☐☐☐

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance ≥ 80% and ≤120%?

☐ No → *If 'No' please remind the patient of the importance of taking the medication according to the protocol.*

☐ Yes

PULMONARY REHABILITATION PROGRAM

Has the patient entered a Pulmonary Rehabilitation Program since the last visit?

☐ No

☐ Yes

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Protocol		Patient Number	Patient Initials		Visit 3A Week 1
207499/156		[redacted]			

INVESTIGATOR INSTRUCTIONS

The following procedures (Vital Signs and ECG) must be performed greater than 4 hours after the patient's last albuterol administration.

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
☐☐☐/☐☐☐	☐☐☐

Are there any **clinically significant worsenings** since Baseline?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes.

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant changes noted at this examination compared to Baseline?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of this module.*

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Protocol		Patient Number	Patient Initials		Visit 3A Week 1
207499/156		[redacted]			

LABORATORY TESTS

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 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.

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes', please record the findings and/or diagnosis in the Adverse Experiences section (If a re-test is necessary, please use the Repeat Lab page at the end of this book)*

STUDY MEDICATION LABEL

Issue the patient a 10 day supply of study medication (20 tablets).

Attach the tear-off label from the study medication bottle dispensed at this visit in the space below. Record the start date in the Study Medication Record section in the next visit.

Attach label here

Enter 6-digit Code as it appears on the study medication label ☐☐☐☐☐☐

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

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 3A

- *If the patient **is not continuing** in the study, please complete the assessments for Visit 3A and Assessments for Patients Withdrawing at Visit 3A.*
- *If the patient **is continuing** in the study, please:*
    - *Issue the patient a diary card and remind the patient to use the card to record if they feel differently since starting the study.*
    - *Ask the patient to return to the clinic for Visit 4 as previously scheduled.*
    - ***Remind the patient:***

        i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after breakfast.*

        ii ***not** to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).*

        iii *to refrain from using albuterol or anticholinergic agents during the **4 hours** immediately preceding the 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 albuterol inhaler and spacer, and the diary card.*

        vi *to continue to take the anticholinergic medication, if prescribed, at a constant dose.*

        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, diarrhea, 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.*

PATIENT ACTIVITY POSTCARD

Please complete the patient activity postcard for ***Visit 3A*** located in the postcard section of this CRF. Detach the postcard and mail promptly. Postage has been prepaid.

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Protocol		Patient Number	Patient Initials		Withdrawal at Visit 3A Week 1
207499/156		[redacted]			

ASSESSMENTS FOR PATIENTS WITHDRAWING AT VISIT 3A

Complete the assessments below only for patients who are withdrawing from the study.

ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

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

COUGH AND SPUTUM PRODUCTION ASSESSMENTS

*Please ask the patient the following questions and record the answers below (Mark **one** box per section only.)*

COUGH

How troubled have you been by cough today?

[0] ☐ No symptoms at all

[1] ☐ Some symptoms, but hardly noticeable

[2] ☐ Symptoms noticeable and a little uncomfortable

[3] ☐ Symptoms definitely noticeable and uncomfortable

[4] ☐ Symptoms very bad and extremely uncomfortable

SPUTUM PRODUCTION

How much sputum have you produced today?

[0] ☐ No sputum at all

[1] ☐ Some sputum, but not as much as usual

[2] ☐ As much as usual

[3] ☐ More than usual

[4] ☐ A lot more than usual

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Protocol		Patient Number	Patient Initials		Withdrawal at Visit 3A Week 1
207499/156		[redacted]			

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a **clinically significant worsening** in the patient's physical condition since the previous examination?

☐ No

☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of this module.*

EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted? The distance walked should be entered even if the patient did not walk for 6 minutes.

☐ No

☐ Yes → *If 'Yes', Distance walked* ☐☐☐ Meters ☐

Yards ☐

Record any adverse experiences which occur during the exercise tolerance test in the Adverse Experience section at the back of this module.

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Protocol		Patient Number	Patient Initials		Withdrawal at Visit 3A Week 1
207499/156		[redacted]			

POST-EXERCISE ASSESSMENTS *(Immediately after the patient completes the exercise tolerance)*

Heart Rate ☐☐☐ beats/min

SaO_2 ☐☐☐ %

Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

"How short of breath do you feel right now?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Post-exercise breathlessness score ☐☐.☐

INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise test (rest for at least 10 minutes) before performing the pulmonary function tests.

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Protocol		Patient Number	Patient Initials		Withdrawal at Visit 3A Week 1
207499/156		[redacted]			

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 confirm that the pulmonary function tests were performed

[1] ☐ Not performed

[2] ☐ Performed

FECAL OCCULT BLOOD TEST

Issue the patient the fecal 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. Samples should be collected on three consecutive bowel movements or three bowel movements closely spaced in time and returned to the clinic as soon as possible.

Did the patient follow the instructions provided with the kit?

☐ No → *If 'No', please specify:* _____

☐ Yes

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

Are these findings clinically significant?

☐ No

☐ Yes → *If 'Yes' please record the details in the Adverse Experience section at the back of this module.*

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Protocol		Patient Number	Patient Initials		Withdrawal at Visit 3A Week 1
207499/156		[redacted]			

VITAL SIGNS - ORTHOSTATIC CHANGE

1st Measurement: After 5 Minutes Supine

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
___ / ___	___

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
___ / ___	___

Are there any **clincially significant worsenings** since Baseline?

☐ No

☐ Yes → *If 'Yes' please record details in the Adverse Experience section at the back of this module.*

INVESTIGATOR GLOBAL ASSESSMENT

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

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Protocol		Patient Number	Patient Initials		Withdrawal at Visit 3A Week 1
207499/156		[redacted]			

PATIENT GLOBAL ASSESSMENT

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

INVESTIGATOR INSTRUCTIONS

Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return for the Safety Follow-Up Visit in 7 +/- 3 days.

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Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	
207499/156		[redacted]			Visit 4 Week 2

PRESENTATION TO CLINIC

Record time of presentation to clinic ☐☐ 24hr:min

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?

☐ NA → Patient is not using beta$_2$ agonist.

☐ 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?

☐ NA → Patient is not using anticholinergic.

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: ☐☐☐ 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 : ☐☐

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 4 Week 2
207499/156		[redacted]			

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes ⟶ *If 'Yes' please record details below. If the patient has had more than three Level 2 or 3 exacerbations since the start of double-blind medication, patient may be withdrawn after consultation with the Medical Monitor. If withdrawing, complete the assessments scheduled at this visit and the Assessments for Patients Withdrawing at Visit 4. The SGRQ and SF-36 should be completed before any additional assessments.*

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

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

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

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of excerbation (maximum level)	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1
	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2
	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations, including an increase in usual COPD medications, must be recorded in the COPD Medications or Procedures pages.

RESOURCE UTILIZATION

If the patient has received any COPD exacerbation-related medical care since the last visit, record details in the Resource Utilization section at the back of this module.

SmithKline Beecham Pharmaceuticals

Protocol	Patient Number	Patient Initials	Visit 4 Week 2
207499/156	[redacted]		

INDIRECT COST

Does the patient work?

☐ No

☐ Yes → *If 'Yes', has the patient missed work due to COPD-related symptoms, excluding scheduled protocol visits, since the last visit?*

☐ No

☐ Yes → *If 'Yes', please record lost work days below:*

Start Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence

How many days since your last visit have you been restricted in performing your leisure activities, due to your COPD-related symptoms? *(please enter number of days below, if not restricted, enter 0)*

☐☐ Days

Since your last visit, how many hours per week did you require paid or unpaid assistance by a relative, friend or professional with your daily activities such as dressing, bathing, cooking, etc., due to your COPD-related symptoms? *(please enter number of hours below, if no paid or unpaid assistance, enter 0 in each instance)*

☐☐☐ Hours per week of **paid** assistance

☐☐☐ Hours per week of **unpaid** assistance

ADVERSE EXPERIENCES

If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

CONCOMITANT MEDICATION

If there has been any change in the patient's concomitant medication excluding treatment for COPD exacerbations (this is recorded in the COPD Exacerbations section) since the last visit, please record details in the Concomitant Medication section at the back of this module.

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 4 Week 2
207499/156		[redacted]			

"AS NEEDED" ALBUTEROL USE

Record the patient's evaluation of their 'as needed' albuterol use since the last visit.

[1] ☐ Much less than usual
[2] ☐ Less than usual
[3] ☐ About the same as usual
[4] ☐ More than usual
[5] ☐ Much more than usual

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	Patient Initials		Visit 4 Week 2
207499/156		[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. bid)

Date and time of last dose of study medication prior to the study visit ____ Day Month Yr ____ 24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
20					

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance < 80% or >120%?

☐ No

☐ Yes → *If 'Yes' please check the percent compliance at the previous visit. If compliance was <80% or >120% at the last visit, please contact the Medical Monitor to discuss patient withdrawal. If the patient is to be withdrawn from the study, complete the assessments scheduled at this visit and the Assessments for Patients Withdrawing at Visit 4. The SGRQ and SF-36 should be completed before any additional assessments.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 4 Week 2
207499/156		[redacted]			

OVERALL BREATHLESSNESS ASSESSMENT

Give the patient a copy of the following scale when assessing breathlessness.

Please ask the patient the following question and record the answer below.

"Generally speaking, how has your breathlessness been during the previous week when you carried out tasks that usually cause you to be short of breath (e.g. walking, carrying shopping, climbing stairs, etc)?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Overall breathlessness score ☐☐.☐

PULMONARY REHABILITATION PROGRAM

Has the patient entered a Pulmonary Rehabilitation Program since the last visit?

☐ No

☐ Yes

INVESTIGATOR INSTRUCTIONS

The following procedures (Vital Signs and ECG) must be performed greater than 4 hours after the patient's last albuterol administration.

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 4 Week 2
207499/156		[redacted]			

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
☐☐☐/☐☐☐	☐☐☐

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes.

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant changes noted at this examination compared to the last visit?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of this module.*

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 confirm that the pulmonary function tests were performed

[1] ☐ Not Performed

[2] ☐ Performed

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials	Visit 4 Week 2
207499/156	[redacted]		

LABORATORY TESTS

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 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.

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes', please record the findings and/or diagnosis in the Adverse Experiences section (If a re-test is necessary, please use the Repeat Lab page at the end of this book)*

STUDY MEDICATION LABEL

Issue the patient a 20 day supply of study medication (2 bottles, 20 tablets per bottle). Attach the tear-off label from each of the study medication bottles 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

Attach study medication label here

Enter 6-digit Code as it appears on the study medication label ☐☐☐☐☐☐

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

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 4

- *If the patient **is not continuing** in the study, please complete the assessments for Visit 4 and the Assessments for Patients Withdrawing at Visit 4.*
- *If the patient **is continuing** in the study, please:*
    - *Issue the patient a diary card and and remind the patient to use the card to record if they feel differently since starting the study.*
    - *Ask the patient to return for the next visit in 14 +/- 3 days at 10:00 (+/-2 hours). Visit 5 must be performed in the morning.*
    - ***Remind the patient:***
        - i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after breakfast.*
        - ii ***not** to take the morning dose of study medication at home on the day of the next clinic visit.*
        - iii *to refrain from using albuterol or anticholinergic agents during the **4 hours** immediately preceding the 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 albuterol inhaler and spacer, and the diary card.*
        - vi *to continue to take the anticholinergic medication, if prescribed, at a constant dose.*
        - 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, diarrhea, 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.*

PHARMACOKINETIC EVALUATION REMINDER

Check the label on the front cover of this book to find out which sampling group (Early or Late) the patient was assigned to at Randomization (switching between groups is not permitted). Remind the patient that they will be having 2 blood samples drawn at the following visit and that the samples will be taken up to 2 hours post-dose for those in the Early group and up to 3 hours post-dose for those in the Late group.

PATIENT ACTIVITY POSTCARD

Please complete the patient activity postcard for ***Visit 4*** located in the postcard section of this CRF. Detach the postcard and mail promptly. Postage has been prepaid.

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Pharmaceuticals

Protocol		Patient Number	Patient Initials		Withdrawal at Visit 4 Week 2
207499/156		[redacted]			

ASSESSMENTS FOR PATIENTS WITHDRAWING AT VISIT 4

Complete the assessments below only for patients who are withdrawing from the study.

ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

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

INVESTIGATOR GLOBAL ASSESSMENT

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

PATIENT GLOBAL ASSESSMENT

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

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Protocol		Patient Number	Patient Initials		Withdrawal at Visit 4 Week 2
207499/156		[redacted]			

COUGH AND SPUTUM PRODUCTION ASSESSMENTS

*Please ask the patient the following questions and record the answers below (Mark **one** box per section only.)*

COUGH

How troubled have you been by cough today?

[0] ☐ No symptoms at all

[1] ☐ Some symptoms, but hardly noticeable

[2] ☐ Symptoms noticeable and a little uncomfortable

[3] ☐ Symptoms definitely noticeable and uncomfortable

[4] ☐ Symptoms very bad and extremely uncomfortable

SPUTUM PRODUCTION

How much sputum have you produced today?

[0] ☐ No sputum at all

[1] ☐ Some sputum, but not as much as usual

[2] ☐ As much as usual

[3] ☐ More than usual

[4] ☐ A lot more than usual

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a **clinically significant worsening** in the patient's physical condition since the previous examination?

☐ No

☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of this module.*

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Withdrawal at Visit 4 Week 2
207499/156		[redacted]			

FECAL OCCULT BLOOD TEST

Issue the patient the fecal 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. Samples should be collected on three consecutive bowel movements or three bowel movements closely spaced in time and returned to the clinic as soon as possible.

Did the patient follow the instructions provided with the kit?

☐ No → *If 'No', please specify:* _____

☐ Yes

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

Are these findings clinically significant?

☐ No

☐ Yes → *If 'Yes' please record the details in the Adverse Experience section at the back of this module.*

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Protocol		Patient Number	Patient Initials		Withdrawal at Visit 4 Week 2
207499/156		[redacted]			

VITAL SIGNS - ORTHOSTATIC CHANGE

1st Measurement: After 5 Minutes Supine

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
☐☐☐ / ☐☐☐	☐☐☐

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
☐☐☐ / ☐☐☐	☐☐☐

Are there any **clinically significant worsenings** since Baseline?

☐ No

☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of this module.*

INVESTIGATOR INSTRUCTIONS

Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return for the Safety Follow-Up Visit in 7 +/- 3 days.

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Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	Visit 5 Week 4
207499/156		[redacted]			

PRESENTATION TO CLINIC

Record time of presentation to clinic ☐☐ 24hr:min

Visit 5 must be performed in the morning at 10:00 (± 2 hours).

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?

☐ NA ⟶ Patient is not using beta$_2$ agonist.

☐ 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?

☐ NA ⟶ Patient is not using anticholinergic.

☐ No

☐ Yes ⟶ Record date and time of patient's last dose of anticholinergic: ☐☐☐ 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 : ☐☐

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 5 Week 4
207499/156		[redacted]			

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes → *If 'Yes' please record details below. If the patient has had more than three Level 2 or 3 exacerbations since the start of double-blind medication, patient maybe withdrawn after consultation with the Medical Monitor. If withdrawing, complete the assessments scheduled at this visit (except for the post-dose pharmacokinetic blood sample) and the Assessments for Patients Withdrawing at Visit 5. The SGRQ and SF-36 should be completed before any additional assessments.*

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

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

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

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of excerbation (maximum level)	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1
	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2
	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations, including an increase in usual COPD medications, must be recorded in the COPD Medications or Procedures pages.

RESOURCE UTILIZATION

Please complete the Resource Utilization section at the back of this module. If the patient has received any COPD exacerbation-related medical care since the last visit, record details in the Resource Utilization section at the back of this module.

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials	Visit 5 Week 4
207499/156	[redacted]		

INDIRECT COST

Does the patient work?

☐ No

☐ Yes → *If 'Yes'*, has the patient missed work due to COPD-related symptoms, excluding scheduled protocol visits, since the last visit?

☐ No

☐ Yes → *If 'Yes', please record lost work days below:*

Start Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence

How many days since your last visit have you been restricted in performing your leisure activities, due to your COPD-related symptoms? *(please enter number of days below, if not restricted, enter 0)*

☐☐ Days

Since your last visit, how many hours per week did you require paid or unpaid assistance by a relative, friend or professional with your daily activities such as dressing, bathing, cooking, etc., due to your COPD-related symptoms? *(please enter number of hours below, if no paid or unpaid assistance, enter 0 in each instance)*

☐☐☐ Hours per week of **paid** assistance

☐☐☐ Hours per week of **unpaid** assistance

ADVERSE EXPERIENCES

Please complete the Adverse Experience section at the back of this module. If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

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Protocol		Patient Number	Patient Initials		Visit 5 Week 4
207499/156		[redacted]			

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.

"AS NEEDED" ALBUTEROL USE

Record the patient's evaluation of their 'as needed' albuterol use since the last visit.

[1] ☐ Much less than usual
[2] ☐ Less than usual
[3] ☐ About the same as usual
[4] ☐ More than usual
[5] ☐ Much more than usual

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	Patient Initials		Visit 5 Week 4
207499/156		[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. bid)

Date and time of last dose of study medication prior to the study visit ☐☐☐☐ Day Month Yr ☐☐ 24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
40	☐☐	☐☐	☐☐	☐☐	☐☐☐

Note: Patients should not have taken the morning dose of study medication prior to this visit.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance < 80% or >120%?

☐ No

☐ Yes → *If 'Yes' please check the percent compliance at the previous visit. If compliance was <80% or >120% at the last visit, please contact the Medical Monitor to discuss patient withdrawal. If the patient is to be withdrawn, complete the assessments scheduled at this visit (except for the post-dose pharmacokinetics blood sample) and the Assessments for Patients Withdrawing at Visit 5. The SGRQ and SF-36 should be completed before any additional assessments.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 5 Week 4
207499/156		[redacted]			

OVERALL BREATHLESSNESS ASSESSMENT

Give the patient a copy of the following scale when assessing breathlessness.

Please ask the patient the following question and record the answer below.

"Generally speaking, how has your breathlessness been during the previous week when you carried out tasks that usually cause you to be short of breath (e.g. walking, carrying shopping, climbing stairs, etc)?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Overall breathlessness score ☐☐.☐

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 Exercise Tolerance Test) must be performed greater than 4 hours after the patient's last albuterol administration.

SmithKline Beecham
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Protocol		Patient Number	Patient Initials		Visit 5 Week 4
207499/156		[redacted]			

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
☐☐☐/☐☐☐	☐☐☐

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes.

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant changes noted at this examination compared to the last visit?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of this module.*

EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted? The distance walked should be entered even if the patient did not walk for 6 minutes.

☐ No

☐ Yes → *If 'Yes', Distance walked* ☐☐☐ [M] Meters ☐

[YD] Yards ☐

Record any adverse experiences which occur during the exercise tolerance test in the Adverse Experience section at the back of this module.

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Protocol		Patient Number	Patient Initials		Visit 5 Week 4
207499/156		[redacted]			

POST-EXERCISE ASSESSMENTS *(Immediately after the patient completes the exercise tolerance)*

Heart Rate ☐☐☐ beats/min

SaO_2 ☐☐☐ %

Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

"How short of breath do you feel right now?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Post-exercise breathlessness score ☐☐.☐

INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise test (rest for at least 10 minutes) before performing the pulmonary function tests.

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Protocol		Patient Number	Patient Initials		Visit 5 Week 4
207499/156		[redacted]			

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 confirm that the pulmonary function tests were performed

[1] ☐ Not Performed

[2] ☐ Performed

LABORATORY TESTS

Please take blood samples for hematology, 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. If the pregnancy test is positive, please withdraw the patient from the study, complete the Serious Adverse Experiences form and forward it to SB within 24 hours. Complete the Visit for Early Withdrawal Between Scheduled Visits and the Study Continuation/ Withdrawal section at the back of this book.

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes', please record the findings and/or diagnosis in the Adverse Experiences section (If a re-test is necessary, please use the Repeat Lab page at the end of this book)*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 5 Week 4
207499/156		[redacted]			

PHARMACOKINETIC EVALUATIONS - PRE-DOSE BLOOD SAMPLE

Record the date and time of the previous two doses of study medication.

Study Medication Taken	Date Day Mth Yr	Time 24hr:min	Did the patient take this dose with food ?	
Yesterday's Morning Dose			☐ Yes	☐ No
Yesterday's Evening Dose			☐ Yes	☐ No

Collect a pre-dose blood sample (5mL) for pharmacokinetic evaluation.

Was a pharmacokinetic sample taken?

☐ No

☐ Yes → *If 'Yes',* 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)

Did the patient accidentally take this morning's dose prior to attending the clinic?

☐ No

☐ Yes → *If 'Yes', check that the Study Medication Record for this visit is recorded correctly.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 5 Week 4
207499/156		[redacted]			

STUDY MEDICATION LABEL

Issue the patient a 35 day supply of study medication (1 bottle, 70 tablets). Attach the tear-off label from the study medication bottle dispensed at this visit in the space below. Record the start date in the Study Medication Record section in the next visit section. Issue the patient an albuterol inhaler and retrieve their old inhaler for 'as-required' use.

Attach study medication label here

Enter 6-digit Code as it appears on the study medication label ☐☐☐☐☐☐

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

Reminder: The patient's evening dose of study medication must not be taken until the post-dose pharmacokinetic sample has been taken.

PHARMACOKINETIC EVALUATIONS - POST-DOSE BLOOD SAMPLE

A blood sample is to be collected for pharmacokinetic evaluation, but not immediately. Please read the instructions below carefully before proceeding and refer to the label on the front cover of this book for which group (Early or Late) the patient was assigned to. 'Early' sample is to be collected between 0.5 and 2 hours post dose at this visit. 'Late' sample is to be collected between 1.5 and 3 hours post dose at this visit. ***Note: it is very important that samples from different patients are obtained over a broad range of times within each of these pre-defined sampling "windows" to prevent data-bunching at the extremes of each window (e.g. do not routinely collect samples at 0.5 hours in every "Early" group patient, instead collect samples at random times between 0.5 and 2 hours in different patients in this group. The same applies for the other sampling window).***

Collect a blood sample (5mL) for pharmacokinetic evaluation.

Was a pharmacokinetic sample taken?

☐ No

☐ Yes → *If 'Yes'*, 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)

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 5

- *If the patient **is not continuing** in the study, please complete the assessments for Visit 5 (except the post-dose pharmacokinetics blood sample) and the Assessments for Patients Withdrawing at Visit 5.*
- *If the patient **is continuing** in the study, please:*
  - *Issue the patient a diary card and and remind the patient to use the card to record if they feel differently since starting the study.*
  - *Ask the patient to return for the next visit in 28 +/- 6 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 breakfast.*

    ii ***not** to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).*

    iii *to refrain from using albuterol or anticholinergic agents during the **4 hours** immediately preceding the 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 albuterol inhaler and spacer, and the diary card.*

    vi *to continue to take the anticholinergic medication, if prescribed, at a constant dose.*

    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, diarrhea, 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.*

PATIENT ACTIVITY POSTCARD

Please complete the patient activity postcard for ***Visit 5*** located in the postcard section of this CRF. Detach the postcard and mail promptly. Postage has been prepaid.

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Withdrawal at Visit 5 Week 4
207499/156		[redacted]			

ASSESSMENTS FOR PATIENTS WITHDRAWING AT VISIT 5

Complete the assessments below only for patients who are withdrawing from the study.

ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

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

INVESTIGATOR GLOBAL ASSESSMENT

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

PATIENT GLOBAL ASSESSMENT

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	Patient Initials		Withdrawal at Visit 5 Week 4
207499/156		[redacted]			

COUGH AND SPUTUM PRODUCTION ASSESSMENTS

*Please ask the patient the following questions and record the answers below (Mark **one** box per section only.)*

COUGH

How troubled have you been by cough today?

[0] ☐ No symptoms at all

[1] ☐ Some symptoms, but hardly noticeable

[2] ☐ Symptoms noticeable and a little uncomfortable

[3] ☐ Symptoms definitely noticeable and uncomfortable

[4] ☐ Symptoms very bad and extremely uncomfortable

SPUTUM PRODUCTION

How much sputum have you produced today?

[0] ☐ No sputum at all

[1] ☐ Some sputum, but not as much as usual

[2] ☐ As much as usual

[3] ☐ More than usual

[4] ☐ A lot more than usual

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a **clinically significant worsening** in the patient's physical condition since the previous examination?

☐ No

☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of this module.*

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Withdrawal at Visit 5 Week 4
207499/156		[redacted]			

FECAL OCCULT BLOOD TEST

Issue the patient the fecal 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. Samples should be collected on three consecutive bowel movements or three bowel movements closely spaced in time and returned to the clinic as soon as possible.

Did the patient follow the instructions provided with the kit?

☐ No → *If 'No', please specify:* _____

☐ Yes

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

Are these findings clinically significant?

☐ No

☐ Yes → *If 'Yes' please record the details in the Adverse Experience section at the back of this module.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Withdrawal at Visit 5 Week 4
207499/156		[redacted]			

VITAL SIGNS - ORTHOSTATIC CHANGE

1st Measurement: After 5 Minutes Supine

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
___ / ___	___

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
___ / ___	___

Are there any **clinically significant worsenings** since Baseline?

☐ No

☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of this module.*

INVESTIGATOR INSTRUCTIONS

Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return for the Safety Follow-Up Visit in 7 +/- 3 days.

ADVERSE EXPERIENCES (Non-serious)

DEFINITIONS

INTENSITY (Maximum)

MILD	*Adverse experience which is easily tolerated*
MODERATE	*Adverse experience sufficiently discomforting to interfere with daily activities*
SEVERE	*Adverse experience which prevents normal everyday activities*

RELATIONSHIP TO INVESTIGATIONAL DRUG

NOT RELATED	*The adverse experience is definitely not related to the test drug*
UNLIKELY	*There are other more likely causes and the drug is not suspected as a cause*
SUSPECTED (REASONABLE POSSIBILITY)	*A direct cause and effect relationship between the drug and the adverse experience has not been demonstrated but there is a reasonable possibility that the experience was caused by the drug*
PROBABLE	*There probably is a direct cause and effect relationship between the adverse experience and the study drug*

SERIOUS ADVERSE EXPERIENCE (SAE)

An SAE is any 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	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

ADVERSE EXPERIENCES (Non-serious)

*Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Have you felt different in any way since starting the treatment or since the 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).

If no adverse experiences occured since Randomization, please mark this box. ☐

Adverse Experience *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***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) *See definitions page for Adverse Experience*	[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 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	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

ADVERSE EXPERIENCES (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

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the Serious Adverse Experience (SAE) section (See opposite for definitions of an SAE).

If no adverse experiences occured since Randomization, please mark this box. ☐

Adverse Experience *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***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) *See definitions page for Adverse Experience*	[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 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	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

ADVERSE EXPERIENCES (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

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the Serious Adverse Experience (SAE) section (See opposite for definitions of an SAE).

If no adverse experiences occured since Randomization, please mark this box. ☐

Adverse Experience *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***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) *See definitions page for Adverse Experience*	[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 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)

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

CONCOMITANT MEDICATION

Record any changes in concomitant medication taken since Randomization. (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 (albuterol) use, using the date the study inhaler was returned.

☐ No concomitant medication changes since Randomization

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 Route, see General Instructions for acceptable abbreviations.*

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 (albuterol) 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 Route, see General Instructions for acceptable abbreviations.*

MEDICAL PROCEDURES
excluding treatment for COPD Exacerbations
(These are recorded in the COPD Exacerbations section)

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 Randomization?

☐ 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			

COPD EXACERBATION SECTION

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 Randomization should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages***

If no COPD Exacerbations since randomization, please mark this box. ☐

Adverse Experience	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***If patient died, STOP: go to SAE COPD Exacerbation pages.***	[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) *See definitions page for Adverse Experience*	[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 COPD Medication and/or Medical Procedures section*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

DETAILS OF COPD EXACERBATIONS - CONTINUED

*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 Randomization should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages***

If no COPD Exacerbations since randomization, please mark this box. ☐

Adverse Experience	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***If patient died, STOP: go to SAE COPD Exacerbation pages.***	[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) *See definitions page for Adverse Experience*	[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 COPD Medication and/or Medical Procedures section*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No

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	Center Number	Patient Number	Patient Initials	SB Receipt Date (Day Month Year)
207499/156		[redacted]		

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation

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

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 Medication and Medical Procedures 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 hospitalization (excluding elective surgery or routine clinical procedures)
[5] hospitalization 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 _____

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation (cont)

Relevant Laboratory Data
Please provide relevant abnormal laboratory data below

Test	Date	Value	Units	Normal Range
	Day Month Yr			
	Day Month Yr			
	Day Month Yr			
	Day Month Yr			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomization code broken at investigational site? ☐ No ☐ Yes

Randomization 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 _____

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

SERIOUS ADVERSE EXPERIENCE - COPD EXACERBATION (Cont.) PHARMACOKINETIC EVALUATION

If the patient presents to the clinic within 24 hours of the onset of a serious adverse experience (SAE) COPD Exacerbation or with an ongoing SAE COPD Exacerbation, please collect a blood sample (5mL) for pharmacokinetic evaluation.

Was a pharmacokinetic sample taken?

☐ No

☐ Yes → *If 'Yes',* 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 taken prior to the onset of the serious adverse experience - COPD exacerbation

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 serious adverse experience - COPD exacerbation?

☐ No

☐ Yes → *If 'Yes',* record date and time of last dose of study medication taken prior to collection of the pharmacokinetic sample.

Day Month Yr 24hr:min

Was this dose taken with food?

☐ No

☐ Yes

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

MEDICATION FOR COPD EXACERBATIONS

Has the patient taken any medication for COPD exacerbations since Randomization?

☐ No

☐ Yes → *If 'Yes', please record details below*

Drug Name (Trade Name Preferred)	Unit Dose (eg 500mg)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible) Day Mth Yr	End Date (or if Continuing mark box) Day Mth Yr	
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							

* *For Route, see General Instructions for acceptable abbreviations.*

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Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

MEDICAL PROCEDURES FOR COPD EXACERBATIONS

Have any non-medication, therapeutic, diagnostic or surgical procedures been performed for COPD exacerbations since Randomization?

☐ 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		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
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For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			

RESOURCE UTILIZATION

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Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

RESOURCE UTILIZATION

Has the patient utilized any COPD Exacerbation-related medical care since Randomization?

☐ No

☐ Yes → *If 'Yes', please record details below*

Has the patient had any **Physician Visits** (COPD care excluding scheduled protocol visits) since Randomization?

☐ No

☐ Yes → *If 'Yes', please record details below*

Date of Visit Day Mth Yr	Reason for Visit

Has the patient had any **Emergency Room (ER)/Urgent Care Visits/Procedures (i.e., lung surgery)** since Randomization?

☐ No

☐ Yes → *If 'Yes', please record details below*

Date of Visit Day Mth Yr	Reason for Visit	Patient Admitted from ER? Yes	No
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐

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Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

RESOURCE UTILIZATION - (cont)

Has the patient had any **Hospitalizations** since Randomization?

☐ No

☐ Yes → *If 'Yes', please record details below* ***(also record details of any hospitalization in the Serious Adverse Experience - COPD Exacerbation section)***

Name of Hospital & City	Date of Admission Day Mth Yr	Date of Discharge Day Mth Yr	Reason for Admission

Has the patient had any **Intensive Care Unit (ICU) stays** ***(did the patient stay in the ICU during any of the above hospitalizations?)*** since Randomization?

☐ 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

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Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

MOD4

Please do not split modules

Module 4 : **Visit 6, Visit 7, Adverse Experiences, Concomitant Medication, Medical Procedures, COPD Exacerbations, Resource Utilization**

CRF Pages **127 - 173**

Unprocessed Forms : **Within this module the following occur which will generate attachments that need to be brought in-house.**

None

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Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	
207499/156		[redacted]			Visit 6 Week 8

PRESENTATION TO CLINIC

Record time of presentation to clinic ☐☐ 24hr:min

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?

☐ NA → Patient is not using beta$_2$ agonist.

☐ 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?

☐ NA → Patient is not using anticholinergic.

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: ☐☐☐ 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 : ☐☐

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 6 Week 8
207499/156		[redacted]			

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes → *If 'Yes' please record details below. If the patient has had more than three Level 2 or 3 exacerbations since the start of double-blind medication, patient may be withdrawn after consultation with the Medical Monitor. If withdrawing, complete the assessments scheduled at this visit and the Assessments for Patients Withdrawing at Visit 6. The SGRQ and SF-36 should be completed before any additional assessments.*

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

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

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

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of excerbation (maximum level)	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1
	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2
	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations, including an increase in usual COPD medications, must be recorded in the COPD Medications or Procedures pages.

RESOURCE UTILIZATION

If the patient has received any COPD exacerbation-related medical care since the last visit, record details in the Resource Utilization section at the back of this module.

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Protocol		Patient Number	Patient Initials		Visit 6 Week 8
207499/156		[redacted]			

INDIRECT COST

Does the patient work?

☐ No

☐ Yes → *If 'Yes'*, has the patient missed work due to COPD-related symptoms, excluding scheduled protocol visits, since the last visit?

☐ No

☐ Yes → *If 'Yes', please record lost work days below:*

Start Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence

How many days since your last visit have you been restricted in performing your leisure activities, due to your COPD-related symptoms? *(please enter number of days below, if not restricted, enter 0)*

☐☐ Days

Since your last visit, how many hours per week did you require paid or unpaid assistance by a relative, friend or professional with your daily activities such as dressing, bathing, cooking, etc., due to your COPD-related symptoms? *(please enter number of hours below, if no paid or unpaid assistance, enter 0 in each instance)*

☐☐☐ Hours per week of **paid** assistance

☐☐☐ Hours per week of **unpaid** assistance

ADVERSE EXPERIENCES

If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

CONCOMITANT MEDICATION

If there has been any change in the patient's concomitant medication excluding treatment for COPD exacerbations (this is recorded in the COPD Exacerbations section) since the last visit, please record details in the Concomitant Medication section at the back of this module.

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Protocol		Patient Number	Patient Initials		Visit 6 Week 8
207499/156		[redacted]			

"AS NEEDED" ALBUTEROL USE

Record the patient's evaluation of their 'as needed' albuterol use since the last visit.

[1] ☐ Much less than usual
[2] ☐ Less than usual
[3] ☐ About the same as usual
[4] ☐ More than usual
[5] ☐ Much more than usual

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	Patient Initials		Visit 6 Week 8
207499/156		[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. bid)

Date and time of last dose of study medication prior to the study visit ☐☐☐☐ Day Month Yr ☐☐ 24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
70	☐☐	☐☐	☐☐	☐☐	☐☐☐

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance < 80% or >120%?

☐ No

☐ Yes → *If 'Yes' please check the percent compliance at the previous visit. If compliance was <80% or >120% at the last visit, please contact the Medical Monitor to discuss patient withdrawal. If the patient is to be withdrawn, complete the assessments scheduled at this visit and the Assessments for Patients Withdrawing at Visit 6. The SGRQ and SF-36 should be completed before any additional assessments.*

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Protocol		Patient Number	Patient Initials		Visit 6 Week 8
207499/156		[redacted]			

OVERALL BREATHLESSNESS ASSESSMENT

Give the patient a copy of the following scale when assessing breathlessness.

Please ask the patient the following question and record the answer below.

"Generally speaking, how has your breathlessness been during the previous week when you carried out tasks that usually cause you to be short of breath (e.g. walking, carrying shopping, climbing stairs, etc)?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Overall breathlessness score ☐☐.☐

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 Exercise Tolerance Test) must be performed greater than 4 hours after the patient's last albuterol administration.

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Protocol	Patient Number	Patient Initials	Visit 6 Week 8
207499/156	[redacted]		

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
☐☐☐/☐☐☐	☐☐☐

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes.

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant changes noted at this examination compared to the last visit?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of this module.*

EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted? The distance walked should be entered even if the patient did not walk for 6 minutes.

☐ No

☐ Yes → *If 'Yes', Distance walked* ☐☐☐ [M] Meters ☐

[YD] Yards ☐

Record any adverse experiences which occur during the exercise tolerance test in the Adverse Experience section at the back of this module.

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Protocol		Patient Number	Patient Initials		Visit 6 Week 8
207499/156		[redacted]			

POST-EXERCISE ASSESSMENTS *(Immediately after the patient completes the exercise tolerance)*

Heart Rate ☐☐☐ beats/min

SaO_2 ☐☐☐ %

Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

"How short of breath do you feel right now?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Post-exercise breathlessness score ☐☐.☐

INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise test (rest for at least 10 minutes) before performing the pulmonary function tests.

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Protocol		Patient Number	Patient Initials		Visit 6 Week 8
207499/156		[redacted]			

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 confirm that the pulmonary function tests were performed

[1] ☐ Not Performed

[2] ☐ Performed

LABORATORY TESTS

Please take blood samples for hematology, 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. If the pregnancy test is positive, please withdraw the patient from the study, complete the Serious Adverse Experiences form and forward it to SB within 24 hours. Complete the Visit for Early Withdrawal between Scheduled Visits and the Study Continuation/ Withdrawal section at the back of this book.

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes', please record the findings and/or diagnosis in the Adverse Experiences section (If a re-test is necessary, please use the Repeat Lab page at the end of this book)*

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Protocol		Patient Number	Patient Initials		Visit 6 Week 8
207499/156		[redacted]			

STUDY MEDICATION LABEL

Issue the patient a 35 day supply of study medication (1 bottle, 70 tablets). Attach the tear-off label from the study medication bottle dispensed at this visit in the space below. Record the start date in the Study Medication Record section in the next visit section. Issue the patient an albuterol inhaler and retrieve their old inhaler for 'as-required' use.

Attach study medication label here

Enter 6-digit Code as it appears on the study medication label | | | | | | |

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

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 6

- *If the patient **is not continuing** in the study, please complete the assessments for Visit 6 and the Assessments for Patients Withdrawing at Visit 6.*
- *If the patient **is continuing** in the study, please:*
  - *Issue the patient a diary card and and remind the patient to use the card to record if they feel differently since starting the study.*
  - *Ask the patient to return for the next visit in 28 +/- 6 days at 10:00 (+/- 2 hours). Visit 7 must be performed in the morning.*
  - ***Remind the patient:***
    - i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after breakfast.*
    - ii ***not** to take the morning dose of study medication at home on the day of the next clinic visit.*
    - iii *to refrain from using albuterol or anticholinergic agents during the **4 hours** immediately preceding the 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 albuterol inhaler and spacer, and the diary card.*
    - vi *to continue to take the anticholinergic medication, if prescribed, at a constant dose.*
    - 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, diarrhea, 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.*

PHARMACOKINETIC EVALUATION REMINDER

Check the label on the front cover of this book to find out which sampling group (Early or Late) the patient was assigned to at Randomization (switching between groups is not permitted). Remind the patient that they will be having 2 blood samples drawn at the following visit and that the samples will be taken up to 6 hours post-dose for those in the Early group and up to 10 hours post-dose for those in the Late group. If the patient expresses unwillingness to stay in the clinic for so long at Visit 7, then the patient has the option of going home and coming back the same day.

PATIENT ACTIVITY POSTCARD

Please complete the patient activity postcard for ***Visit 6*** located in the postcard section of this CRF. Detach the postcard and mail promptly. Postage has been prepaid.

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Withdrawal at Visit 6 Week 8
207499/156		[redacted]			

ASSESSMENTS FOR PATIENTS WITHDRAWING AT VISIT 6

Complete the assessments below only for patients who are withdrawing from the study.

ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

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

INVESTIGATOR GLOBAL ASSESSMENT

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

PATIENT GLOBAL ASSESSMENT

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

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Protocol		Patient Number	Patient Initials		Withdrawal at Visit 6 Week 8
207499/156		[redacted]			

COUGH AND SPUTUM PRODUCTION ASSESSMENTS

*Please ask the patient the following questions and record the answers below (Mark **one** box per section only.)*

COUGH

How troubled have you been by cough today?

[0] ☐ No symptoms at all

[1] ☐ Some symptoms, but hardly noticeable

[2] ☐ Symptoms noticeable and a little uncomfortable

[3] ☐ Symptoms definitely noticeable and uncomfortable

[4] ☐ Symptoms very bad and extremely uncomfortable

SPUTUM PRODUCTION

How much sputum have you produced today?

[0] ☐ No sputum at all

[1] ☐ Some sputum, but not as much as usual

[2] ☐ As much as usual

[3] ☐ More than usual

[4] ☐ A lot more than usual

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a **clinically significant worsening** in the patient's physical condition since the previous examination?

☐ No

☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of this module.*

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Withdrawal at Visit 6 Week 8
207499/156		[redacted]			

FECAL OCCULT BLOOD TEST

Issue the patient the fecal 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. Samples should be collected on three consecutive bowel movements or three bowel movements closely spaced in time and returned to the clinic as soon as possible.

Did the patient follow the instructions provided with the kit?

☐ No → *If 'No', please specify:* _____

☐ Yes

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

Are these findings clinically significant?

☐ No

☐ Yes → *If 'Yes' please record the details in the Adverse Experience section at the back of this module.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Withdrawal at Visit 6 Week 8
207499/156		[redacted]			

VITAL SIGNS - ORTHOSTATIC CHANGE

1st Measurement: After 5 Minutes Supine

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
___ / ___	___

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
___ / ___	___

Are there any **clinically significant worsenings** since Baseline?

☐ No

☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of this module.*

INVESTIGATOR INSTRUCTIONS

Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return for the Safety Follow-Up Visit in 7 +/- 3 days.

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Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	
207499/156		[redacted]			Visit 7 Week 12

PRESENTATION TO CLINIC

Record time of presentation to clinic ☐☐ 24hr:min

Visit 7 must be performed in the morning at 10:00 (± 2 hours).

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?

☐ NA → Patient is not using beta$_2$ agonist.

☐ 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?

☐ NA → Patient is not using anticholinergic.

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: ☐☐☐ 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 : ☐☐

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes

ST. GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE

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

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Protocol		Patient Number	Patient Initials		Visit 7 Week 12
207499/156		[redacted]			

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. US version adapted and modified with permission by Judith Barr, Sc.D., Northeastern Univ., Boston, MA.

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Protocol		Patient Number	Patient Initials		Visit 7 Week 12
207499/156		[redacted]			

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes → *If 'Yes' please record details below. If the patient has had more than three Level 2 or 3 exacerbations since the start of double-blind medication, patient may be withdrawn after consultation with the Medical Monitor. If withdrawing, complete the assessments scheduled at this visit (except for the post-dose pharmacokinetic blood sample) and the Assessments for Patients Withdrawing at Visit 7. The SGRQ and SF-36 should be completed before any additional assessments.*

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

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

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

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of excerbation (maximum level)	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1
	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2
	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations, including an increase in usual COPD medications, must be recorded in the COPD Medications or Procedures pages.

RESOURCE UTILIZATION

Please complete the Resource Utilization section at the back of this module. If the patient has received any COPD exacerbation related medical care since the previous visit, please complete the COPD Resource Utilization section at the back of this module.

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Protocol		Patient Number	Patient Initials		Visit 7 Week 12
207499/156		[redacted]			

INDIRECT COST

Does the patient work?

☐ No

☐ Yes → *If 'Yes'*, has the patient missed work due to COPD-related symptoms, excluding scheduled protocol visits, since the last visit?

☐ No

☐ Yes → *If 'Yes', please record lost work days below:*

Start Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence

How many days since your last visit have you been restricted in performing your leisure activities, due to your COPD-related symptoms? *(please enter number of days below, if not restricted, enter 0)*

☐☐ Days

Since your last visit, how many hours per week did you require paid or unpaid assistance by a relative, friend or professional with your daily activities such as dressing, bathing, cooking, etc., due to your COPD-related symptoms? *(please enter number of hours below, if no paid or unpaid assistance, enter 0 in each instance)*

☐☐☐ Hours per week of **paid** assistance

☐☐☐ Hours per week of **unpaid** assistance

ADVERSE EXPERIENCES

Please complete the Adverse Experience section at the back of this module. If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

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Protocol		Patient Number	Patient Initials		Visit 7 Week 12
207499/156		[redacted]			

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.

"AS NEEDED" ALBUTEROL USE

Record the patient's evaluation of their 'as needed' albuterol use since the last visit.

[1] ☐ Much less than usual
[2] ☐ Less than usual
[3] ☐ About the same as usual
[4] ☐ More than usual
[5] ☐ Much more than usual

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	Patient Initials		Visit 7 Week 12
207499/156		[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. bid)

Date and time of last dose of study medication prior to the study visit ____ ____ ____ (Day Month Yr) ____ ____ (24hr:min)

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
70					

Note: Patients should not have taken the morning dose of study medication prior to this visit.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance < 80% or >120%?

☐ No

☐ Yes → *If 'Yes' please check the percent compliance at the previous visit. If compliance was <80% or >120% at the last visit, please contact the Medical Monitor to discuss patient withdrawal. If the patient is to be withdrawn, complete the assessments scheduled at this visit (except for the post-dose pharmacokinetics blood sample) and the Assessments for Patients Withdrawing at Visit 7. The SF-36 should be completed before any additional assessments.*

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Protocol		Patient Number	Patient Initials		Visit 7 Week 12
207499/156		[redacted]			

OVERALL BREATHLESSNESS ASSESSMENT

Give the patient a copy of the following scale when assessing breathlessness.

Please ask the patient the following question and record the answer below.

"Generally speaking, how has your breathlessness been during the previous week when you carried out tasks that usually cause you to be short of breath (e.g. walking, carrying shopping, climbing stairs, etc)?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Overall breathlessness score ☐☐.☐

PULMONARY REHABILITATION PROGRAM

Has the patient entered a Pulmonary Rehabilitation Program since the last visit?

☐ No

☐ Yes

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 7 Week 12
207499/156		[redacted]			

COUGH AND SPUTUM PRODUCTION ASSESSMENTS

*Please ask the patient the following questions and record the answers below (Mark **one** box per section only.)*

COUGH

How troubled have you been by cough today?

[0] ☐ No symptoms at all

[1] ☐ Some symptoms, but hardly noticeable

[2] ☐ Symptoms noticeable and a little uncomfortable

[3] ☐ Symptoms definitely noticeable and uncomfortable

[4] ☐ Symptoms very bad and extremely uncomfortable

SPUTUM PRODUCTION

How much sputum have you produced today?

[0] ☐ No sputum at all

[1] ☐ Some sputum, but not as much as usual

[2] ☐ As much as usual

[3] ☐ More than usual

[4] ☐ A lot more than usual

INVESTIGATOR INSTRUCTIONS

The following procedures (Vital Signs, ECG, and Exercise Tolerance Test) must be performed greater than 4 hours after the patient's last albuterol administration.

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
☐☐☐/☐☐☐	☐☐☐

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

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Protocol		Patient Number	Patient Initials		Visit 7 Week 12
207499/156		[redacted]			

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes.

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant changes noted at this examination compared to the last visit?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of this module.*

EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted? The distance walked should be entered even if the patient did not walk for 6 minutes.

☐ No

☐ Yes → *If 'Yes', Distance walked* ☐☐☐ [M] Meters ☐

[YD] Yards ☐

Record any adverse experiences which occur during the exercise tolerance test in the Adverse Experience section at the back of this module.

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Protocol		Patient Number	Patient Initials		Visit 7 Week 12
207499/156		[redacted]			

POST-EXERCISE ASSESSMENTS *(Immediately after the patient completes the exercise tolerance)*

Heart Rate ☐☐☐ beats/min

SaO_2 ☐☐☐ %

Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

"How short of breath do you feel right now?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Post-exercise breathlessness score ☐☐.☐

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 7 Week 12
207499/156		[redacted]			

INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise tolerance test (rest for at least 10 minutes) before performing the pulmonary function tests.

PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed 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 confirm that the pulmonary function tests were performed

[1] ☐ Not Performed

[2] ☐ Performed

LABORATORY TESTS

Please take blood samples for hematology, 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. If the pregnancy test is positive, please withdraw the patient from the study, complete the Serious Adverse Experiences form and forward it to SB within 24 hours. Complete the Visit for Early Withdrawal Between Scheduled Visits and the Study Continuation/ Withdrawal section at the back of this book.

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes', please record the findings and/or diagnosis in the Adverse Experiences section (If a re-test is necessary, please use the Repeat Lab page at the end of this book)*

SmithKline Beecham
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Protocol		Patient Number	Patient Initials		Visit 7 Week 12
207499/156		[redacted]			

PHARMACOKINETIC EVALUATIONS - PRE-DOSE BLOOD SAMPLE

Record the date and time of the previous two doses of study medication.

Study Medication Taken	Date Day Mth Yr	Time 24hr:min	Did the patient take this dose with food ?	
Yesterday's Morning Dose			☐ Yes	☐ No
Yesterday's Evening Dose			☐ Yes	☐ No

Collect a pre-dose blood sample (5mL) for pharmacokinetic evaluation.

Was a pharmacokinetic sample taken?

☐ No

☐ Yes → *If 'Yes'*, 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)

Did the patient accidentally take this morning's dose prior to attending the clinic?

☐ No

☐ Yes → *If 'Yes', check that the Study Medication Record for this visit is recorded correctly.*

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Protocol		Patient Number	Patient Initials		Visit 7 Week 12
207499/156		[redacted]			

STUDY MEDICATION LABEL

Issue the patient a 35 day supply of study medication (1 bottle, 70 tablets). Attach the tear-off label from the study medication bottle dispensed at this visit in the space below. Record the start date in the Study Medication Record section in the next visit section. Issue the patient an albuterol inhaler and retrieve their old inhaler for 'as-required' use.

Attach study medication label here

Enter 6-digit Code as it appears on the study medication label ☐☐☐☐☐☐

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

Reminder: The patient's evening dose of study medication must not be taken until the post-dose pharmacokinetic sample has been taken.

PHARMACOKINETIC EVALUATIONS - POST-DOSE BLOOD SAMPLE

A blood sample is to be collected for pharmacokinetic evaluation, but not immediately. Please read the instructions below carefully before proceeding and refer to the label on the front cover of this book for which group (Early or Late) the patient was assigned to. 'Early' sample is to be collected between 3 and 6 hours post dose at this visit. 'Late' sample is to be collected between 5 and 10 hours post dose at this visit. ***Note: it is very important that samples from different patients are obtained over a broad range of times within each of these pre-defined sampling "windows" to prevent data-bunching at the extremes of each window (e.g. do not routinely collect samples at 3 hours in every "Early" group patient, instead collect samples at random times between 3 and 6 hours in different patients in this group. The same applies for the other sampling window).***

Collect a blood sample (5mL) for pharmacokinetic evaluation.

Was a pharmacokinetic sample taken?

☐ No

☐ Yes → *If 'Yes'*, 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)

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 7

- *If the patient **is not continuing** in the study, please complete the assessments for Visit 7 (except the post-dose pharmacokinetics blood sample) and the Assessments for Patients Withdrawing at Visit 7.*
- *If the patient **is continuing** in the study, please:*
  - *Issue the patient a diary card and and remind the patient to use the card to record if they feel differently since starting the study.*
  - *Ask the patient to return for the next visit in 28 +/- 6 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. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).*

    iii *to refrain from using albuterol or anticholinergic agents during the **4 hours** immediately preceding the 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 albuterol inhaler and spacer, and the diary card.*

    vi *to continue to take the anticholinergic medication, if prescribed, at a constant dose.*

    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, diarrhea, 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.*

PATIENT ACTIVITY POSTCARD

Please complete the patient activity postcard for ***Visit 7*** located in the postcard section of this CRF. Detach the postcard and mail promptly. Postage has been prepaid.

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Withdrawal at Visit 7 Week 12
207499/156		[redacted]			

ASSESSMENTS FOR PATIENTS WITHDRAWING AT VISIT 7

Complete the assessments below only for patients who are withdrawing from the study.

SF-36 QUESTIONNAIRE

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

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a **clinically significant worsening** in the patient's physical condition since the previous examination?

☐ No

☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of this module.*

INVESTIGATOR GLOBAL ASSESSMENT

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

PATIENT GLOBAL ASSESSMENT

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

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Protocol		Patient Number	Patient Initials		Withdrawal at Visit 7 Week 12
207499/156		[redacted]			

FECAL OCCULT BLOOD TEST

Issue the patient the fecal 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. Samples should be collected on three consecutive bowel movements or three bowel movements closely spaced in time and returned to the clinic as soon as possible.

Did the patient follow the instructions provided with the kit?

☐ No → *If 'No', please specify:* _____

☐ Yes

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

Are these findings clinically significant?

☐ No

☐ Yes → *If 'Yes' please record the details in the Adverse Experience section at the back of this module.*

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Protocol		Patient Number	Patient Initials		Withdrawal at Visit 7 Week 12
207499/156		[redacted]			

VITAL SIGNS - ORTHOSTATIC CHANGE

1st Measurement: After 5 Minutes Supine

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
___ / ___	___

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
___ / ___	___

Are there any **clinically significant worsenings** since Baseline?

☐ No

☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of this module.*

INVESTIGATOR INSTRUCTIONS

Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return for the Safety Follow-Up Visit in 7 +/- 3 days.

ADVERSE EXPERIENCES (Non-serious)

DEFINITIONS

INTENSITY (Maximum)

MILD	*Adverse experience which is easily tolerated*
MODERATE	*Adverse experience sufficiently discomforting to interfere with daily activities*
SEVERE	*Adverse experience which prevents normal everyday activities*

RELATIONSHIP TO INVESTIGATIONAL DRUG

NOT RELATED	*The adverse experience is definitely not related to the test drug*
UNLIKELY	*There are other more likely causes and the drug is not suspected as a cause*
SUSPECTED (REASONABLE POSSIBILITY)	*A direct cause and effect relationship between the drug and the adverse experience has not been demonstrated but there is a reasonable possibility that the experience was caused by the drug*
PROBABLE	*There probably is a direct cause and effect relationship between the adverse experience and the study drug*

SERIOUS ADVERSE EXPERIENCE (SAE)

An SAE is any 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	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

ADVERSE EXPERIENCES (Non-serious)

*Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Have you felt different in any way since starting the treatment or since the 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).

If no adverse experiences occured since the previous module (i.e., since Visit 5), please mark this box. ☐

Adverse Experience *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***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) *See definitions page for Adverse Experience*	[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 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	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

ADVERSE EXPERIENCES (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

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the Serious Adverse Experience (SAE) section (See opposite for definitions of an SAE).

If no adverse experiences occured since the previous module (i.e., since Visit 5), please mark this box. ☐

Adverse Experience *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr ☐☐☐ 24hr:min ☐☐	Day Month Yr ☐☐☐ 24hr:min ☐☐
End Date and Time *(If ongoing please leave blank)*	Day Month Yr ☐☐☐ 24hr:min ☐☐	Day Month Yr ☐☐☐ 24hr:min ☐☐
Outcome ***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) *See definitions page for Adverse Experience*	[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 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	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

ADVERSE EXPERIENCES (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

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the Serious Adverse Experience (SAE) section (See opposite for definitions of an SAE).

If no adverse experiences occured since the previous module (i.e., since Visit 5), please mark this box. ☐

Adverse Experience *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***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) *See definitions page for Adverse Experience*	[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 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)

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

CONCOMITANT MEDICATION

Record any changes in concomitant medication taken since the previous module (i.e., since Visit 5). (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 (albuterol) use, using the date the study inhaler was returned.

☐ No concomitant medication changes since the previous module (i.e., since Visit 5)

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 Route, see General Instructions for acceptable abbreviations.*

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 (albuterol) 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 Route, see General Instructions for acceptable abbreviations.*

MEDICAL PROCEDURES
excluding treatment for COPD Exacerbations
(These are recorded in the COPD Exacerbations section)

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 (i.e., since Visit 5)?

☐ 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			

COPD EXACERBATION SECTION

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 Visit 5 should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages***

If no COPD Exacerbations since previous module (i.e., since Visit 5), please mark this box. ☐

Adverse Experience	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***If patient died, STOP: go to SAE COPD Exacerbation pages.***	[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) *See definitions page for Adverse Experience*	[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 COPD Medication 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	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

DETAILS OF COPD EXACERBATIONS - CONTINUED

*An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy.*
All exacerbations of COPD since the previous module (i.e., since Visit 5) should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). ***COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages***

If no COPD Exacerbations since previous module (i.e., since Visit 5), please mark this box. ☐

Adverse Experience	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***If patient died, STOP: go to SAE COPD Exacerbation pages.***	[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) *See definitions page for Adverse Experience*	[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 COPD Medication and/or Medical Procedures section if appropriate*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No

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	Center Number	Patient Number	Patient Initials	SB Receipt Date Day Month Year
207499/156		[redacted]		

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation

Person Reporting SAE _____ *(Please print clearly)*

AEGIS Number _____

Serious Adverse Experience *(Please print clearly)*: **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

Specify reason(s) for considering this a serious AE. Mark all that apply.

- [1] ☐ fatal
- [2] ☐ life threatening
- [3] ☐ disabling/incapacitating
- [4] ☐ results in hospitalization (excluding elective surgery or routine clinical procedures)
- [5] ☐ hospitalization 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 COPD Medication and/or Medical Procedures section*: ☐ Yes ☐ No

Was patient withdrawn due to this specific SAE ?: ☐ Yes ☐ No

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation (cont)

Relevant Laboratory Data
Please provide relevant abnormal laboratory data below

Test	Date	Value	Units	Normal Range
	Day Month Yr			
	Day Month Yr			
	Day Month Yr			
	Day Month Yr			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomization code broken at investigational site? ☐ No ☐ Yes

Randomization 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 _____

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

SERIOUS ADVERSE EXPERIENCE - COPD EXACERBATION (Cont.) PHARMACOKINETIC EVALUATION

If the patient presents to the clinic within 24 hours of the onset of a serious adverse experience (SAE) COPD Exacerbation or with an ongoing SAE COPD Exacerbation, please collect a blood sample (5mL) for pharmacokinetic evaluation.

Was a pharmacokinetic sample taken?

☐ No

☐ Yes → *If 'Yes',* 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 taken prior to the onset of the serious adverse experience - COPD exacerbation

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 serious adverse experience - COPD exacerbation?

☐ No

☐ Yes → *If 'Yes',* record date and time of last dose of study medication taken prior to collection of the pharmacokinetic sample.

Day Month Yr 24hr:min

Was this dose taken with food?

☐ No

☐ Yes

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

MEDICATION FOR COPD EXACERBATIONS

Has the patient taken any medication for COPD exacerbations since the previous module (i.e., since Visit 5)?

☐ No

☐ Yes → *If 'Yes', please record details below*

Drug Name (Trade Name Preferred)	Unit Dose (eg 500mg)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible) Day Mth Yr	End Date (or if Continuing mark box) Day Mth Yr	
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							

** For Route, see General Instructions for acceptable abbreviations.*

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

MEDICAL PROCEDURES FOR COPD EXACERBATIONS

Have any non-medication, therapeutic, diagnostic or surgical procedures been performed for COPD exacerbations since the previous module (i.e., since Visit 5)?

☐ 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		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			

RESOURCE UTILIZATION

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

RESOURCE UTILIZATION

Has the patient utilized any COPD Exacerbation-related medical care since the previous module (i.e., since Visit 5)?

☐ No

☐ Yes → *If 'Yes', please record details below*

Has the patient had any **Physician Visits** (COPD care excluding scheduled protocol visits) since the previous module (i.e., since Visit 5)?

☐ No

☐ Yes → *If 'Yes', please record details below*

Date of Visit Day Mth Yr	Reason for Visit

Has the patient had any **Emergency Room (ER)/Urgent Care Visits/Procedures (i.e., lung surgery)** since the previous module (i.e., since Visit 5)?

☐ No

☐ Yes → *If 'Yes', please record details below*

Date of Visit Day Mth Yr	Reason for Visit	Patient Admitted from ER? Yes	No
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

RESOURCE UTILIZATION - (cont)

Has the patient had any **Hospitalizations** since the previous module (i.e., since Visit 5)?

☐ No

☐ Yes → *If 'Yes', please record details below* ***(also record details of any hospitalization in the Serious Adverse Experience - COPD Exacerbation section)***

Name of Hospital & City	Date of Admission Day Mth Yr	Date of Discharge Day Mth Yr	Reason for Admission

Has the patient had any **Intensive Care Unit (ICU) stays** ***(did the patient stay in the ICU during any of the above hospitalizations?)*** since the previous module (i.e., since Visit 5)?

☐ 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

EARLY WITHDRAWAL BETWEEN SCHEDULED VISITS

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

EW1

Please do not split modules

Module: **Early Withdrawal between scheduled visits**

CRF Pages **174 - 184**

Unprocessed Forms : **Within this module the following occur which will generate attachments that need to be brought in-house.**

SGRQ Quality of Life Assessment
SF-36

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

Complete these assessments ONLY for patients who withdraw from the study between scheduled clinic visits. These assessments should be completed within 24 hours of stopping study medication.

PRESENTATION TO CLINIC

Record time of presentation to clinic ☐☐ 24hr:min

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?

☐ NA → Patient is not using beta$_2$ agonist.

☐ 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?

☐ NA → Patient is not using anticholinergic.

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: ☐☐ 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 : ☐☐

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

ST. GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

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

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes ⟶ *If 'Yes' please record details below.*

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

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

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

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of excerbation (maximum level)	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1
	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2
	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of the module that contains the visit (or visit interval) at which the patient withdrew, 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.

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

RESOURCE UTILIZATION

If the patient has received any COPD exacerbation related medical care since the previous visit, record details in the Resource Utilization section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.

INDIRECT COST

Does the patient work?

☐ No

☐ Yes → *If 'Yes'*, has the patient missed work due to COPD-related symptoms, excluding scheduled protocol visits, since the last visit?

☐ No

☐ Yes → *If 'Yes', please record lost work days below:*

Start Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence

How many days since your last visit have you been restricted in performing your leisure activities, due to your COPD-related symptoms? *(please enter number of days below, if not restricted, enter 0)*

☐☐ Days

Since your last visit, how many hours per week did you require paid or unpaid assistance by a relative, friend or professional with your daily activities such as dressing, bathing, cooking, etc., due to your COPD-related symptoms? *(please enter number of hours below, if no paid or unpaid assistance, enter 0 in each instance)*

☐☐☐ Hours per week of **paid** assistance

☐☐☐ Hours per week of **unpaid** assistance

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

ADVERSE EXPERIENCES

If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of the module which contains the visit (or visit interval) at which the patient withdrew. 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 the module which contains the visit (or visit interval) at which the patient withdrew.

"AS NEEDED" ALBUTEROL USE

Record the patient's evaluation of their 'as needed' albuterol use since the last visit.

[1] ☐ Much less than usual
[2] ☐ Less than usual
[3] ☐ About the same as usual
[4] ☐ More than usual
[5] ☐ Much more than usual

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 the module which contains the visit (or visit interval) at which the patient withdrew.

INVESTIGATOR GLOBAL ASSESSMENT

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	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

PATIENT GLOBAL ASSESSMENT

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

COUGH AND SPUTUM PRODUCTION ASSESSMENTS

*Please ask the patient the following questions and record the answers below (Mark **one** box per section only.)*

COUGH

How troubled have you been by cough today?

[0] ☐ No symptoms at all

[1] ☐ Some symptoms, but hardly noticeable

[2] ☐ Symptoms noticeable and a little uncomfortable

[3] ☐ Symptoms definitely noticeable and uncomfortable

[4] ☐ Symptoms very bad and extremely uncomfortable

SPUTUM PRODUCTION

How much sputum have you produced today?

[0] ☐ No sputum at all

[1] ☐ Some sputum, but not as much as usual

[2] ☐ As much as usual

[3] ☐ More than usual

[4] ☐ A lot more than usual

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a **clinically significant worsening** in the patient's physical condition since the previous examination?

☐ No

☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of this module.*

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

FECAL OCCULT BLOOD TEST

Issue the patient the fecal 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. Samples should be collected on three consecutive bowel movements or three bowel movements closely spaced in time and returned to the clinic as soon as possible.

Did the patient follow the instructions provided with the kit?

☐ No → *If 'No', please specify:* _____

☐ Yes

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

Are these findings clinically significant?

☐ No

☐ Yes → *If 'Yes' please record the details in the Adverse Experience section at the back of this module.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[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. bid)

Date and time of last dose of study medication prior to the study visit

Day Month Yr 24hr:min

Did the patient take their last dose with food?

☐ No

☐ Yes

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance

Note: If this is a morning visit, patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance ≥ 80% and ≤120%?

☐ No

☐ Yes

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[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 and ECG) must be performed greater than 4 hours after the patient's last albuterol administration.

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
☐☐☐/☐☐☐	☐☐☐

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

VITAL SIGNS - ORTHOSTATIC CHANGE

1st Measurement: After 5 Minutes Supine

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
☐☐☐ / ☐☐☐	☐☐☐

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
☐☐☐ / ☐☐☐	☐☐☐

Are there any clinically significant worsenings since Baseline?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes.

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant changes noted at this examination compared to the last visit?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.*

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Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted? The distance walked should be entered even if the patient did not walk for 6 minutes.

☐ No

☐ Yes → *If 'Yes', Distance walked* ☐☐☐ [M] Meters ☐

[YD] Yards ☐

Record any adverse experiences which occur during the exercise tolerance test in the Adverse Experience section at the back of the module which contains the visit (or visit interval) at which the patient withdrew).

POST-EXERCISE ASSESSMENTS *(Immediately after the patient completes the exercise tolerance)*

Heart Rate ☐☐☐ beats/min

SaO_2 ☐☐☐ %

Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

"How short of breath do you feel right now?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Post-exercise breathlessness score ☐☐.☐

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Pharmaceuticals

Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise test (rest for at least 10 minutes) before performing the pulmonary function tests.

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 confirm that the pulmonary function tests were performed

[1] ☐ Not performed

[2] ☐ Performed

LABORATORY TESTS

Please take blood samples for hematology, 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. If the pregnancy test is positive, please complete the Serious Adverse Experiences form and forward it to SB within 24 hours.

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes ⟶ *If 'Yes', please record the findings and/or diagnosis in the Adverse Experiences section (If a re-test is necessary, please use the Repeat Lab page at the end of this book)*

INSTRUCTION TO THE INVESTIGATOR

Please complete the Study Continuation / Withdrawal page at the end of Book 2.
Ask the patient to return for the Safety Follow-Up Visit in 7 +/- 3 days.

PATIENT ACTIVITY POSTCARD

Please complete the patient activity postcard for ***Early Withdrawal Between Scheduled Visits*** located in the postcard section of this CRF. Detach the postcard and mail promptly. Postage has been prepaid.

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

SFU1

Please do not split modules

Module: **Safety Follow-Up**

CRF Pages **185 - 190**

Unprocessed Forms : **Within this module the following occur which will generate attachments that need to be brought in-house.**

None

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	
207499/156		[redacted]			Safety Follow-Up

INVESTIGATOR INSTRUCTIONS

Complete these assessments only for those patients who have withdrawn from the study. These assessments should be completed within 7 +/- 3 days after discontinuation of study medication.

PRESENTATION TO CLINIC

Record time of presentation to clinic ☐☐ 24hr:min

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?

☐ NA → Patient is not using $beta_2$ agonist.

☐ 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?

☐ NA → Patient is not using anticholinergic.

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: ☐☐☐ 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 : ☐☐

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Safety Follow-Up
207499/156		[redacted]			

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes ⟶ *If 'Yes' please record details below.*

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

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

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

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of excerbation (maximum level)	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1
	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2
	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of the module which contains the visit (or the visit interval) at which the patient withdrew, 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 UTILIZATION

If the patient has received any COPD exacerbation related medical care since the previous visit, record details in the Resource Utilization section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials	Safety Follow-Up
207499/156	[redacted]		

INDIRECT COST

Does the patient work?

☐ No

☐ Yes → *If 'Yes'*, has the patient missed work due to COPD-related symptoms, excluding scheduled protocol visits, since the last visit?

☐ No

☐ Yes → *If 'Yes', please record lost work days below:*

Start Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence

How many days since your last visit have you been restricted in performing your leisure activities, due to your COPD-related symptoms? *(please enter number of days below, if not restricted, enter 0)*

☐☐ Days

Since your last visit, how many hours per week did you require paid or unpaid assistance by a relative, friend or professional with your daily activities such as dressing, bathing, cooking, etc., due to your COPD-related symptoms? *(please enter number of hours below, if no paid or unpaid assistance, enter 0 in each instance)*

☐☐☐ Hours per week of **paid** assistance

☐☐☐ Hours per week of **unpaid** assistance

ADVERSE EXPERIENCES

If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.

SmithKline Beecham
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Protocol		Patient Number	Patient Initials		Safety Follow-Up
207499/156		[redacted]			

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 the module which contains the visit (or visit interval) at which the patient withdrew. ***At the patient's final study visit, record the end date for prn study rescue medication (albuterol) use, using the date the study inhaler was returned.***

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 the module which contains the visit (or visit interval) at which the patient withdrew.

PULMONARY REHABILITATION PROGRAM

Has the patient entered a Pulmonary Rehabilitation Program since the last visit?

☐ No

☐ Yes

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
☐☐☐/☐☐☐	☐☐☐

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Safety Follow-Up
207499/156		[redacted]			

12 LEAD ELECTROCARDIOGRAM

If any abnormalities were observed at the last visit, please perform a 12-lead ECG. The ECG should be performed after the patient has been semi-supine for 5 minutes.

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant changes noted at this examination compared to the last visit?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.*

LABORATORY TESTS

If abnormal laboratory results were reported at the previous visit, 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 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.

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes', please record the findings and/or diagnosis in the Adverse Experiences section at the back of the module which contains the visit (or visit interval) at which the patient withdrew. (If a re-test is necessary, please use the Repeat Lab page at the end of this book)*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Safety Follow-Up
207499/156		[redacted]			

PREGNANCY TEST

Is the patient a female of child-bearing potential?

☐ No

☐ Yes → *If 'Yes' please perform a urine pregnancy test locally.*

Urine Sample Date ☐☐ ☐☐ ☐☐ (Day Month Yr)

Is the patient pregnant?

☐ No

☐ Yes → *If the pregnancy test is positive, complete the Serious Adverse Experiences form and forward it to SB within 24 hours.*

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

If any abnormalities were noted at the last visit, please perform a physical examination (including respiratory examination).

Were any clinically significant changes noted at this examination compared to the last visit?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.*

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 confirm that the pulmonary function tests were performed

[1] ☐ Not performed

[2] ☐ Performed

PATIENT ACTIVITY POSTCARD

Please complete the patient activity postcard for ***Safety Follow-Up Visit*** located in the postcard section of this CRF. Detach the postcard and mail promptly. Postage has been prepaid.

STUDY CONTINUATION / WITHDRAWAL

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

CONC2

Please do not split modules

Module: **Study Continuation / Withdrawal**

CRF Pages **191**

Unprocessed Forms : **Within this module the following occur which will generate attachments that need to be brought in-house.**

None

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

STUDY CONTINUATION/WITHDRAWAL

Is the patient continuing in the study?

☐ Yes → *If 'Yes' please continue in Book 3.*

☐ No → *If 'No' please mark the **PRIMARY** cause of withdrawal and record the date of final visit and date of final dose.*

[1] ☐ Adverse experience (complete AE form)

[2] ☐ Insufficient therapeutic effect

[3] ☐ Protocol deviation (including non-compliance)

[4] ☐ Lost to follow-up

[7] ☐ Other - specify: _____

Date of Final Visit ☐☐ ☐☐ ☐☐ Day Month Yr

Date of Final Dose ☐☐ ☐☐ ☐☐ Day Month Yr

INVESTIGATOR SIGNATURE

I certify that I have reviewed the data on this case report form, 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	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

SAE2

Please do not split modules

Module: Serious Adverse Experiences, Pharmacokinetic Evaluation for Serious Adverse Experiences

CRF Pages 192 - 194

Unprocessed Forms : Within this module the following occur which will generate attachments that need to be brought in-house.

None

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	SB Receipt Date Day Month Year
207499/156		[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 hospitalization (excluding elective surgery or routine clinical procedures)
[5] ☐ hospitalization 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 section* ☐ Yes ☐ No

Was patient withdrawn due to this specific SAE ? ☐ Yes ☐ No

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 randomization code broken at investigational site? ☐ No ☐ Yes

Randomization 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 _____

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials
207499/156	[redacted]	

SERIOUS ADVERSE EXPERIENCE (Cont.)
PHARMACOKINETIC EVALUATION

If the patient presents to the clinic within 24 hours of the onset of a serious adverse experience (SAE) or with an ongoing SAE, please collect a blood sample (5mL) for pharmacokinetic evaluation.

Was a pharmacokinetic sample taken?

☐ No

☐ Yes → *If 'Yes',* 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 taken prior to the onset of the serious adverse experience

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 serious adverse experience?

☐ No

☐ Yes → *If 'Yes',* record date and time of last dose of study medication taken prior to collection of the pharmacokinetic sample.

Day Month Yr 24hr:min

Was this dose taken with food?

☐ No

☐ Yes

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

FORMD2

Please do not split modules

Module: Form D

CRF Pages: 195

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

FORM D

Certified Cause of Death _____

Date of Death Day Month Yr → *Please complete Serious Adverse Experience section.*

Was a post-mortem examination carried out?

☐ No

☐ Yes → *If 'Yes' please summarize findings (include diagnosis):*

_____

_____

_____

_____

Reporting Physician's Signature _____ Date Day Month Yr

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		OPTIONAL Repeat Lab
207499/156		[redacted]			

RPLAB2

Please do not split modules

Module: Repeat Lab

CRF Pages: 196

Unprocessed Forms: Within this module, the following tests / procedures occur which may generate attachments.

None

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		OPTIONAL Repeat Lab
207499/156		[redacted]			

REPEAT 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, complete the Early Withdrawal between Scheduled Visits 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.*

REPEAT 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, complete the Early Withdrawal between Scheduled Visits 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.*

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Protocol	Center Number	Patient Number	Patient Initials	Investigator
207499/156		[redacted]		

CRF TRACKING/REVIEW FORM

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SAE2	Serious Adverse Experiences	192 - 194	☐	☐	
FORMD2	Form D	195	☐	☐	
RPLAB2	Repeat Lab	196	☐	☐	

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Site Monitor's Comments (e.g. protocol violations or deviations)

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Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

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PROTOCOL 207499/156

BOOK 3 : VISIT 8 TO STUDY CONCLUSION

A RANDOMIZED, 24-WEEK, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY, SAFETY AND TOLERABILITY OF ARIFLO™ (15 MG BID) IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

GENERAL INSTRUCTIONS

- *Write clearly in capital letters using a black ball point pen and press firmly so that all copies are legible*
- *Do not write in shaded areas*
- *Answer ALL questions on every page*
- *Enter "N/A" if information requested is not available*
- *Initial and date all changes, additions or deletions. Use a single pen stroke to remove an incorrect entry*
- *Enter the patient initials on all pages on which information has been entered and the patient number and center number where required*

Do not enter additional data/information after the set of CRF pages has been split/separated

The cover flap or plastic writing board should be used to divide each set of pages before writing on them with a ball point pen

DATE

Please use the following three-letter abbreviations for the months

January	JAN
February	FEB
March	MAR
April	APR
May	MAY
June	JUN
July	JUL
August	AUG
September	SEP
October	OCT
November	NOV
December	DEC

e.g. | 0 1 | J A N | 0 0 | = *1st January 2000*

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

PATIENT INITIALS

Please use the following format:

e.g. [redacted]

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*

STUDY PROCEDURES CHART 207499/156

Visit	1	2	3	3a	4	5	6	7	8	9	10		
	Screen		Baseline								End Double-blind	Early Withdrawal[1]	Final Safety Follow-up
Time relative to baseline (weeks)	-4	-2	0	+1	+2	+4	+8	+12	+16	+20	+24		+25
Signed written informed consent	x												
Medical & surgical history	x												
Physical examination[2]	x		x								x	x	x[3]
Pulmonary history & symptoms	x												
Postero-anterior chest radiograph[4]	x												
Exacerbation assessment/resource use	x	x	x	x	x	x	x	x	x	x	x	x	x
Medication history	x												
Overall breathlessness (modified Borg)	x	x	x		x	x	x	x	x	x	x		
Resting 12-lead ECG	x		x	x	x	x	x	x	x	x	x	x	x[3]
Vital signs (BP, HR)	x[5]	x	x[5]	x	x	x	x	x	x	x	x[5]	x[5]	x
Exercise Tolerance (6-Minute walk)	x	x	x			x	x	x	x	x	x	x	
Post-exercise SaO2 & breathlessness	x	x	x			x	x	x	x	x	x	x	
CO Diffusing Capacity (DLCO)[6]	x												
Albuterol reversibility[7]	x												
Laboratory tests	x		x[8]	x	x	x	x	x	x[9]	x[9]	x[8]	x[8]	x[3,9]
Dispense single-blind medication	x	x											
Albuterol Use		x	x	x	x	x	x	x	x	x	x		
Concomitant medication/medical procedures		x	x	x	x	x	x	x	x	x	x	x	x
PFTs (in absence of albuterol)[10]		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	
Baseline signs and symptoms/AEs[11]		x	x	x	x	x	x	x	x	x	x	x	x
Health status assessment: SGRQ			x					x			x	x	
Quality of life assessment: SF-36			x								x	x	
Cough and sputum assessments			x					x			x	x	
Pharmacokinetic evaluations[12]			x			x		x			x		
Arterial blood gas/SaO2[13]			x								x		
Hourly PFTs for 4 hrs post first/last dose [14]			x								x		
Dispense double-blind medication			x	x	x	x	x	x	x	x			
Investigator/Patient global assessment											x	x	
Study conclusion record												x	x

1 Patients who stop taking study medication between clinic visits will attend the clinic within 24 hours for an early withdrawal visit.

2 To include a respiratory examination.

3 If abnormalities at previous visit for patients who complete Visit 10 or withdraw from the study.

4 Postero-anterior chest X-ray must be performed at Visit 1 unless the film from a chest X-ray within the 12 weeks prior to Visit 1 is available to the Investigator.

5 Including Orthostatic vital signs.

6 DLCO should be done between Visit 1 and Visit 3 if not performed during the previous 24 weeks or if the results are unavailable.

7 Before and 15 to 30 (± 5) minutes after administration of 180 mcg albuterol via a MDI with a spacer to determine % predicted FEV_1, FVC, FEF_{25-75}, PEFR, and FEV_1: FVC.

8 In addition to usual laboratory tests, three fecal occult blood tests will be performed between Visits 1 and 3, between Visits 9 and 10, and at early withdrawal; amylase will be measured at Visit 3.

9 Urinary beta-HCG tests will be performed in females of childbearing potential. No other laboratory samples will be collected at Visits 8 and 9.

10 Includes FEV_1, FVC, FEF_{25-75}, PEFR, and FEV_1:FVC measured by centralized spirometry by the same person at each visit.

11 A diary will be used to record if patients feel different since starting study medication.

12 Visit 3: 3 hours post-dose. Visit 5: trough and 0.5-3 hours post-dose. Visit 7: trough and 3-10 hours post-dose. Visit 10: trough only.

13 In patients with <40% of predicted FEV_1 at Visit 1 and resting SaO_2 <88% or if the patient lives at a high altitude.

14 Pulmonary function tests 30 (± 5) minutes after albuterol followed by 4-hour post-double-blind drug assessments at Visits 3 and 10.

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Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

MOD5

Please do not split modules

Module 5 : **Visit 8, Visit 9, Adverse Experiences, Concomitant Medications, Medical Procedures, COPD Exacerbations, Resource Utilization**

CRF Pages **197 - 240**

Unprocessed Forms : **Within this module the following occur which will generate attachments that need to be brought in-house.**

None

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Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	
207499/156		[redacted]			Visit 8 Week 16

PRESENTATION TO CLINIC

Record time of presentation to clinic ☐☐ 24hr:min

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?

☐ NA → Patient is not using beta$_2$ agonist.

☐ 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?

☐ NA → Patient is not using anticholinergic.

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: ☐☐☐ 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 : ☐☐

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes

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Protocol		Patient Number	Patient Initials		Visit 8 Week 16
207499/156		[redacted]			

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes → *If 'Yes' please record details below. If the patient has had more than three Level 2 or 3 exacerbations since the start of double-blind medication, patient may be withdrawn after consultation with the Medical Monitor. If withdrawing, complete the assessments scheduled at this visit and the Assessments for Patients Withdrawing at Visit 8. The SGRQ and SF-36 should be completed before any additional assessments.*

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

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

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

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of excerbation (maximum level)	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1
	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2
	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations, including an increase in usual COPD medications, must be recorded in the COPD Medications or Procedures pages.

RESOURCE UTILIZATION

If the patient has received any COPD exacerbation-related medical care since the last visit, record details in the Resource Utilization section at the back of this module.

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Protocol		Patient Number	Patient Initials		Visit 8 Week 16
207499/156		[redacted]			

INDIRECT COST

Does the patient work?

☐ No

☐ Yes → *If 'Yes'*, has the patient missed work due to COPD-related symptoms, excluding scheduled protocol visits, since the last visit?

☐ No

☐ Yes → *If 'Yes', please record lost work days below:*

Start Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence

How many days since your last visit have you been restricted in performing your leisure activities, due to your COPD-related symptoms? *(please enter number of days below, if not restricted, enter 0)*

☐☐ Days

Since your last visit, how many hours per week did you require paid or unpaid assistance by a relative, friend or professional with your daily activities such as dressing, bathing, cooking, etc., due to your COPD-related symptoms? *(please enter number of hours below, if no paid or unpaid assistance, enter 0 in each instance)*

☐☐☐ Hours per week of **paid** assistance

☐☐☐ Hours per week of **unpaid** assistance

ADVERSE EXPERIENCES

If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

CONCOMITANT MEDICATION

If there has been any change in the patient's concomitant medication excluding treatment for COPD exacerbations (this is recorded in the COPD Exacerbations section) since the last visit, please record details in the Concomitant Medication section at the back of this module.

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Protocol		Patient Number	Patient Initials		Visit 8 Week 16
207499/156		[redacted]			

"AS NEEDED" ALBUTEROL USE

Record the patient's evaluation of their 'as needed' albuterol use since the last visit.

[1] ☐ Much less than usual
[2] ☐ Less than usual
[3] ☐ About the same as usual
[4] ☐ More than usual
[5] ☐ Much more than usual

MEDICAL PROCEDURES

If there have been any non-medication, therapeutic, diagnostic or surgical procedures excluding those for COPD exacerbations (these are recorded in the COPD Exacerbations section) performed since the last visit, please record details in the Medical Procedures section at the back of this module.

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Protocol		Patient Number	Patient Initials		Visit 8 Week 16
207499/156		[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. bid)

Date and time of last dose of study medication prior to the study visit ☐☐☐ Day Month Yr ☐☐ 24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
70	☐☐	☐☐	☐☐	☐☐	☐☐☐

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance < 80% or >120%?

☐ No

☐ Yes → *If 'Yes' please check the percent compliance at the previous visit. If compliance was <80% or >120% at the last visit, please contact the Medical Monitor to discuss patient withdrawal. If the patient is to be withdrawn, complete the assessments scheduled at this visit and the Assessments for Patients Withdrawing at Visit 8. The SGRQ and SF-36 should be completed before any additional assessments.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 8 Week 16
207499/156		[redacted]			

OVERALL BREATHLESSNESS ASSESSMENT

Give the patient a copy of the following scale when assessing breathlessness.

Please ask the patient the following question and record the answer below.

"Generally speaking, how has your breathlessness been during the previous week when you carried out tasks that usually cause you to be short of breath (e.g. walking, carrying shopping, climbing stairs, etc)?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Overall breathlessness score ☐☐.☐

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 Exercise Tolerance Test) must be performed greater than 4 hours after the patient's last albuterol administration.

SmithKline Beecham
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Protocol		Patient Number	Patient Initials		Visit 8 Week 16
207499/156		[redacted]			

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
☐☐☐/☐☐☐	☐☐☐

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes.

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant changes noted at this examination compared to the last visit?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of this module.*

EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted? The distance walked should be entered even if the patient did not walk for 6 minutes.

☐ No

☐ Yes → *If 'Yes', Distance walked* ☐☐☐ Meters ☐

Yards ☐

Record any adverse experiences which occur during the exercise tolerance test in the Adverse Experience section at the back of this module.

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 8 Week 16
207499/156		[redacted]			

POST-EXERCISE ASSESSMENTS *(Immediately after the patient completes the exercise tolerance)*

Heart Rate ☐☐☐ beats/min

SaO_2 ☐☐☐ %

Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

"How short of breath do you feel right now?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Post-exercise breathlessness score ☐☐.☐

INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise test (rest for at least 10 minutes) before performing the pulmonary function tests.

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials	Visit 8 Week 16
207499/156	[redacted]		

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 confirm that the pulmonary function tests were performed

[1] ☐ Not Performed

[2] ☐ Performed

PREGNANCY TEST

Is the patient a female of child-bearing potential?

☐ No

☐ Yes → *If 'Yes' please perform a urine pregnancy test locally.*

Urine Sample Date ☐☐ ☐☐☐ ☐☐
Day Month Yr

Is the patient pregnant?

☐ No

☐ Yes → *If 'Yes' please withdraw the patient from the study, complete the Serious Adverse Experiences form and forward it to SB within 24 hours. Complete the assessments scheduled at this visit and the Assessments for Patients Withdrawing at Visit 8. The SGRQ and SF-36 should be completed before any additional assessments.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 8 Week 16
207499/156		[redacted]			

STUDY MEDICATION LABEL

Issue the patient a 35 day supply of study medication (1 bottles, 70 tablets). Attach the tear-off label from the study medication bottle dispensed at this visit in the space below. Record the start date in the Study Medication Record section in the next visit section. Issue the patient an albuterol inhaler and retrieve their old inhaler for 'as-required' use.

Attach study medication label here

Enter 6-digit Code as it appears on the study medication label | | | | | | |

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

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 8

- *If the patient **is not continuing** in the study, please complete the assessments for Visit 8 and the Assessments for Patients Withdrawing at Visit 8.*
- *If the patient **is continuing** in the study, please:*
  - *Issue the patient a diary card and and remind the patient to use the card to record if they feel differently since starting the study.*
  - *Ask the patient to return for the next visit in 28 +/- 6 days at the same time of day as at Visit 3.*
  - ***Remind the patient:***

    i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after breakfast.*

    ii ***not** to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).*

    iii *to refrain from using albuterol or anticholinergic agents during the **4 hours** immediately preceding the 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 albuterol inhaler and spacer, and the diary card.*

    vi *to continue to take the anticholinergic medication, if prescribed, at a constant dose.*

    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, diarrhea, 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.*

PATIENT ACTIVITY POSTCARD

Please complete the patient activity postcard for ***Visit 8*** located in the postcard section of this CRF. Detach the postcard and mail promptly. Postage has been prepaid.

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Withdrawal at Visit 8 Week 16
207499/156		[redacted]			

ASSESSMENTS FOR PATIENTS WITHDRAWING AT VISIT 8

Complete the assessments below only for patients who are withdrawing from the study.

ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

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

INVESTIGATOR GLOBAL ASSESSMENT

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

PATIENT GLOBAL ASSESSMENT

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	Patient Initials		Withdrawal at Visit 8 Week 16
207499/156		[redacted]			

COUGH AND SPUTUM PRODUCTION ASSESSMENTS

*Please ask the patient the following questions and record the answers below (Mark **one** box per section only.)*

COUGH

How troubled have you been by cough today?

[0] ☐ No symptoms at all

[1] ☐ Some symptoms, but hardly noticeable

[2] ☐ Symptoms noticeable and a little uncomfortable

[3] ☐ Symptoms definitely noticeable and uncomfortable

[4] ☐ Symptoms very bad and extremely uncomfortable

SPUTUM PRODUCTION

How much sputum have you produced today?

[0] ☐ No sputum at all

[1] ☐ Some sputum, but not as much as usual

[2] ☐ As much as usual

[3] ☐ More than usual

[4] ☐ A lot more than usual

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a **clinically significant worsening** in the patient's physical condition since the previous examination?

☐ No

☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of this module.*

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Withdrawal at Visit 8 Week 16
207499/156		[redacted]			

LABORATORY TESTS

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 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.

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes', please record the findings and/or diagnosis in the Adverse Experiences section (If a re-test is necessary, please use the Repeat Lab page at the end of this book)*

FECAL OCCULT BLOOD TEST

Issue the patient the fecal 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. Samples should be collected on three consecutive bowel movements or three bowel movements closely spaced in time and returned to the clinic as soon as possible.

Did the patient follow the instructions provided with the kit?

☐ No → *If 'No', please specify:* _____

☐ Yes

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

Are these findings clinically significant?

☐ No

☐ Yes → *If 'Yes' please record the details in the Adverse Experience section at the back of this module.*

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Protocol		Patient Number	Patient Initials		Withdrawal at Visit 8 Week 16
207499/156		[redacted]			

VITAL SIGNS - ORTHOSTATIC CHANGE

1st Measurement: After 5 Minutes Supine

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
☐☐☐ / ☐☐☐	☐☐☐

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
☐☐☐ / ☐☐☐	☐☐☐

Are there any **clincially significant worsenings** since Baseline?

☐ No

☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of this module.*

INVESTIGATOR INSTRUCTIONS

Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return for the Safety Follow-Up Visit in 7 +/- 3 days.

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Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	Visit 9 Week 20
207499/156		[redacted]			

PRESENTATION TO CLINIC

Record time of presentation to clinic ☐☐ 24hr:min

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?

☐ NA → Patient is not using beta$_2$ agonist.

☐ 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?

☐ NA → Patient is not using anticholinergic.

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: ☐☐☐ 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 : ☐☐

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes

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Protocol		Patient Number	Patient Initials		Visit 9 Week 20
207499/156		[redacted]			

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes → *If 'Yes' please record details below. If the patient has had more than three Level 2 or 3 exacerbations since the start of double-blind medication, patient may be withdrawn after consultation with Medical Monitor. If withdrawing, complete the assessments scheduled at this visit and the Assessments for Patients Withdrawing at Visit 9. The SGRQ and SF-36 should be completed before any additional assessments.*

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

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

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

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of excerbation (maximum level)	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1
	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2
	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations, including an increase in usual COPD medications, must be recorded in the COPD Medications or Procedures pages.

RESOURCE UTILIZATION

Please complete the Resource Utilization section at the back of this module. If the patient has received any COPD exacerbation-related medical care since the last visit, record details in the Resource Utilization section at the back of this module.

SmithKline Beecham
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Protocol		Patient Number	Patient Initials		Visit 9 Week 20
207499/156		[redacted]			

INDIRECT COST

Does the patient work?

☐ No

☐ Yes → *If 'Yes', has the patient missed work due to COPD-related symptoms, excluding scheduled protocol visits, since the last visit?*

☐ No

☐ Yes → *If 'Yes', please record lost work days below:*

Start Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence

How many days since your last visit have you been restricted in performing your leisure activities, due to your COPD-related symptoms? *(please enter number of days below, if not restricted, enter 0)*

☐☐ Days

Since your last visit, how many hours per week did you require paid or unpaid assistance by a relative, friend or professional with your daily activities such as dressing, bathing, cooking, etc., due to your COPD-related symptoms? *(please enter number of hours below, if no paid or unpaid assistance, enter 0 in each instance)*

☐☐☐ Hours per week of **paid** assistance

☐☐☐ Hours per week of **unpaid** assistance

ADVERSE EXPERIENCES

Please complete the Adverse Experience section at the back of this module. If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

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Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 9 Week 20
207499/156		[redacted]			

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.

"AS NEEDED" ALBUTEROL USE

Record the patient's evaluation of their 'as needed' albuterol use since the last visit.

[1] ☐ Much less than usual
[2] ☐ Less than usual
[3] ☐ About the same as usual
[4] ☐ More than usual
[5] ☐ Much more than usual

MEDICAL PROCEDURES

If there have been any non-medication, therapeutic, diagnostic or surgical procedures excluding those for COPD exacerbations (these are recorded in the COPD Exacerbations section) performed since the last visit, please record details in the Medical Procedures section at the back of this module.

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Protocol		Patient Number	Patient Initials		Visit 9 Week 20
207499/156		[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. bid)

Date and time of last dose of study medication prior to the study visit ☐☐☐ Day Month Yr ☐☐ 24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
70	☐☐	☐☐	☐☐	☐☐	☐☐☐

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance < 80% or > 120%?

☐ No

☐ Yes → *If 'Yes' please check the percent compliance at the previous visit. If compliance was <80% or >120% at the last visit, please contact the Medical Monitor to discuss patient withdrawal. If the patient is to be withdrawn, complete the assessments scheduled at this visit and the Assessments for Patients Withdrawing at Visit 9. The SGRQ and SF-36 should be completed before any additional assessments.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 9 Week 20
207499/156		[redacted]			

OVERALL BREATHLESSNESS ASSESSMENT

Give the patient a copy of the following scale when assessing breathlessness.

Please ask the patient the following question and record the answer below.

"Generally speaking, how has your breathlessness been during the previous week when you carried out tasks that usually cause you to be short of breath (e.g. walking, carrying shopping, climbing stairs, etc)?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Overall breathlessness score ☐☐.☐

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 Exercise Tolerance Test) must be performed greater than 4 hours after the patient's last albuterol administration.

SmithKline Beecham Pharmaceuticals

Protocol	Patient Number	Patient Initials	Visit 9 Week 20
207499/156	[redacted]		

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
___ / ___	___

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes.

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant changes noted at this examination compared to the last visit?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of this module.*

EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted? The distance walked should be entered even if the patient did not walk for 6 minutes.

☐ No

☐ Yes → *If 'Yes', Distance walked* ___ Meters ☐

Yards ☐

Record any adverse experiences which occur during the exercise tolerance test in the Adverse Experience section at the back of this module.

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 9 Week 20
207499/156		[redacted]			

POST-EXERCISE ASSESSMENTS *(Immediately after the patient completes the exercise tolerance)*

Heart Rate ☐☐☐ beats/min

SaO_2 ☐☐☐ %

Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

"How short of breath do you feel right now?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Post-exercise breathlessness score ☐☐.☐

INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise test (rest for at least 10 minutes) before performing the pulmonary function tests.

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 9 Week 20
207499/156		[redacted]			

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 confirm that the pulmonary function tests were performed

[1] ☐ Not Performed

[2] ☐ Performed

PREGNANCY TEST

Is the patient a female of child-bearing potential?

☐ No

☐ Yes → *If 'Yes' please perform a urine pregnancy test locally.*

Urine Sample Date ☐☐ ☐☐☐ ☐☐
Day Month Yr

Is the patient pregnant?

☐ No

☐ Yes → *If 'Yes' please withdraw the patient from the study, complete the Serious Adverse Experiences form and forward it to SB within 24 hours. Complete the assessments scheduled at this visit and the Assessments for Patients Withdrawing at Visit 9. The SGRQ and SF-36 should be completed before any additional assessments.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 9 Week 20
207499/156		[redacted]			

STUDY MEDICATION LABEL

Issue the patient a 35 day supply of study medication (1 bottle, 70 tablets). Attach the tear-off label from the study medication bottle dispensed at this visit in the space below. Record the start date in the Study Medication Record section in the next visit section. Issue the patient an albuterol inhaler and retrieve their old inhaler for 'as-required' use.

Attach study medication label here

Enter 6-digit Code as it appears on the study medication label | | | | | | |

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

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 9

- *If the patient **is not continuing** in the study, please complete the assessments for Visit 9 and the Assessments for Patients Withdrawing at Visit 9.*
- *If the patient **is continuing** in the study, please:*
    - *Issue the patient a diary card and and remind the patient to use the card to record if they feel differently since starting the study.*
    - *Issue the patient the fecal 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.*
    - *Ask the patient to return for the next visit in 28 +/- 6 days at the same time of day as at Visit 3.*
    - ***Remind the patient:***

        i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after breakfast.*

        ii ***not** to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).*

        iii *to refrain from using albuterol or anticholinergic agents during the **4 hours** immediately preceding the 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 albuterol inhaler and spacer, and the diary card.*

        vi *to continue to take the anticholinergic medication, if prescribed, at a constant dose.*

        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, diarrhea, 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.*

PATIENT ACTIVITY POSTCARD

Please complete the patient activity postcard for ***Visit 9*** located in the postcard section of this CRF. Detach the postcard and mail promptly. Postage has been prepaid.

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Withdrawal at Visit 9 Week 20
207499/156		[redacted]			

ASSESSMENTS FOR PATIENTS WITHDRAWING AT VISIT 9

Complete the assessments below only for patients who are withdrawing from the study.

ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

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INVESTIGATOR GLOBAL ASSESSMENT

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PATIENT GLOBAL ASSESSMENT

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Protocol		Patient Number	Patient Initials		Withdrawal at Visit 9 Week 20
207499/156		[redacted]			

COUGH AND SPUTUM PRODUCTION ASSESSMENTS

*Please ask the patient the following questions and record the answers below (Mark **one** box per section only.)*

COUGH

How troubled have you been by cough today?

[0] ☐ No symptoms at all

[1] ☐ Some symptoms, but hardly noticeable

[2] ☐ Symptoms noticeable and a little uncomfortable

[3] ☐ Symptoms definitely noticeable and uncomfortable

[4] ☐ Symptoms very bad and extremely uncomfortable

SPUTUM PRODUCTION

How much sputum have you produced today?

[0] ☐ No sputum at all

[1] ☐ Some sputum, but not as much as usual

[2] ☐ As much as usual

[3] ☐ More than usual

[4] ☐ A lot more than usual

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a **clinically significant worsening** in the patient's physical condition since the previous examination?

☐ No

☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of this module.*

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Withdrawal at Visit 9 Week 20
207499/156		[redacted]			

LABORATORY TESTS

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 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.

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes', please record the findings and/or diagnosis in the Adverse Experiences section (If a re-test is necessary, please use the Repeat Lab page at the end of this book)*

FECAL OCCULT BLOOD TEST

Issue the patient the fecal 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. Samples should be collected on three consecutive bowel movements or three bowel movements closely spaced in time and returned to the clinic as soon as possible.

Did the patient follow the instructions provided with the kit?

☐ No → *If 'No', please specify:* _____

☐ Yes

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

Are these findings clinically significant?

☐ No

☐ Yes → *If 'Yes' please record the details in the Adverse Experience section at the back of this module.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Withdrawal at Visit 9 Week 20
207499/156		[redacted]			

VITAL SIGNS - ORTHOSTATIC CHANGE

1st Measurement: After 5 Minutes Supine

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
☐☐☐ / ☐☐☐	☐☐☐

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
☐☐☐ / ☐☐☐	☐☐☐

Are there any **clincially significant worsenings** since Baseline?

☐ No

☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of this module.*

INVESTIGATOR INSTRUCTIONS

Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return for the Safety Follow-Up Visit in 7 +/- 3 days.

ADVERSE EXPERIENCES (Non-serious)

DEFINITIONS

INTENSITY (Maximum)

MILD	*Adverse experience which is easily tolerated*
MODERATE	*Adverse experience sufficiently discomforting to interfere with daily activities*
SEVERE	*Adverse experience which prevents normal everyday activities*

RELATIONSHIP TO INVESTIGATIONAL DRUG

NOT RELATED	*The adverse experience is definitely not related to the test drug*
UNLIKELY	*There are other more likely causes and the drug is not suspected as a cause*
SUSPECTED (REASONABLE POSSIBILITY)	*A direct cause and effect relationship between the drug and the adverse experience has not been demonstrated but there is a reasonable possibility that the experience was caused by the drug*
PROBABLE	*There probably is a direct cause and effect relationship between the adverse experience and the study drug*

SERIOUS ADVERSE EXPERIENCE (SAE)

An SAE is any 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	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

ADVERSE EXPERIENCES (Non-serious)

*Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Have you felt different in any way since starting the treatment or since the previous 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).

If no adverse experiences occured since the previous module (i.e., since Visit 7), please mark this box. ☐

Adverse Experience *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***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) *See definitions page for Adverse Experience*	[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 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	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

ADVERSE EXPERIENCES (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 previous 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).

If no adverse experiences occured since the previous module (i.e., since Visit 7), please mark this box. ☐

Adverse Experience *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***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) *See definitions page for Adverse Experience*	[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 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	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

ADVERSE EXPERIENCES (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 previous 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).

If no adverse experiences occured since the previous module (i.e., since Visit 7), please mark this box. ☐

Adverse Experience *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***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) *See definitions page for Adverse Experience*	[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 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)

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

CONCOMITANT MEDICATION

Record any changes in concomitant medication taken since the previous module (i.e., since Visit 7). (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 (albuterol) use, using the date the study inhaler was returned.

☐ No concomitant medication changes since the previous module (i.e., since Visit 7)

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 Route, see General Instructions for acceptable abbreviations.*

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[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 (albuterol) 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 Route, see General Instructions for acceptable abbreviations.*

MEDICAL PROCEDURES
excluding treatment for COPD Exacerbations
(These are recorded in the COPD Exacerbations section)

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[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 (i.e., since Visit 7)?

☐ 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			

COPD EXACERBATION SECTION

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 previous module (i.e., since Visit 7) should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages***

If no COPD Exacerbations since previous module (i.e., since Visit 7), please mark this box. ☐

Adverse Experience	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***If patient died, STOP: go to SAE COPD Exacerbation pages.***	[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) *See definitions page for Adverse Experience form*	[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 COPD Medications and/or Medical Procedures page*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

DETAILS OF COPD EXACERBATIONS - CONTINUED

*An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy.*
*All exacerbations of COPD since the previous module (i.e., since Visit 7) should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages***

If no COPD Exacerbations since previous module (i.e., since Visit 7), please mark this box. ☐

Adverse Experience	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***If patient died, STOP: go to SAE COPD Exacerbation pages.***	[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) *See definitions page for Adverse Experience form*	[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 COPD Medications and/or Medical Procedures page*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

DETAILS OF COPD EXACERBATIONS - CONTINUED

*An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy.*
*All exacerbations of COPD since the previous module (i.e., since Visit 7) should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages***

If no COPD Exacerbations since previous module (i.e., since Visit 7), please mark this box. ☐

Adverse Experience	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***If patient died, STOP: go to SAE COPD Exacerbation pages.***	[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) *See definitions page for Adverse Experience form*	[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 COPD Medications and/or Medical Procedures page*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No

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	Center Number	Patient Number	Patient Initials	SB Receipt Date Day Month Year
207499/156		[redacted]		

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation

Person Reporting SAE _____ *(Please print clearly)*

AEGIS Number

Serious Adverse Experience *(Please print clearly)*: **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

Specify reason(s) for considering this a serious AE. Mark all that apply.

- [1] ☐ fatal
- [2] ☐ life threatening
- [3] ☐ disabling/incapacitating
- [4] ☐ results in hospitalization (excluding elective surgery or routine clinical procedures)
- [5] ☐ hospitalization 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 COPD Medication or Medical Procedures section*: ☐ Yes ☐ No

Was patient withdrawn due to this specific SAE ?: ☐ Yes ☐ No

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation (cont)

Relevant Laboratory Data
Please provide relevant abnormal laboratory data below

Test	Date	Value	Units	Normal Range
	Day Month Yr			
	Day Month Yr			
	Day Month Yr			
	Day Month Yr			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomization code broken at investigational site? ☐ No ☐ Yes

Randomization 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 _____

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Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

SERIOUS ADVERSE EXPERIENCE - COPD EXACERBATION (Cont.) PHARMACOKINETIC EVALUATION

If the patient presents to the clinic within 24 hours of the onset of a serious adverse experience (SAE) COPD Exacerbation or with an ongoing SAE COPD Exacerbation, please collect a blood sample (5mL) for pharmacokinetic evaluation.

Was a pharmacokinetic sample taken?

☐ No

☐ Yes → *If 'Yes',* 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 taken prior to the onset of the serious adverse experience - COPD exacerbation

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 serious adverse experience - COPD exacerbation?

☐ No

☐ Yes → *If 'Yes',* record date and time of last dose of study medication taken prior to collection of the pharmacokinetic sample.

Day Month Yr 24hr:min

Was this dose taken with food?

☐ No

☐ Yes

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Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

MEDICATION FOR COPD EXACERBATIONS

Has the patient taken any medication for COPD exacerbations since the previous module (i.e., since Visit 7)?

☐ No

☐ Yes → *If 'Yes', please record details below*

Drug Name (Trade Name Preferred)	Unit Dose (eg 500mg)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible) Day Mth Yr	End Date (or if Continuing mark box) Day Mth Yr	
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							

** For Route, see General Instructions for acceptable abbreviations.*

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Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

MEDICAL PROCEDURES FOR COPD EXACERBATIONS

Have any non-medication, therapeutic, diagnostic or surgical procedures been performed for COPD exacerbations since the previous module (i.e., since Visit 7)?

☐ 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		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			

RESOURCE UTILIZATION

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Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

RESOURCE UTILIZATION

Has the patient utilized any COPD Exacerbation-related medical care since the previous module (i.e., since Visit 7)?

☐ No

☐ Yes → *If 'Yes', please record details below*

Has the patient had any **Physician Visits** (COPD care excluding scheduled protocol visits) since the previous module (i.e., since Visit 7)?

☐ No

☐ Yes → *If 'Yes', please record details below*

Date of Visit Day Mth Yr	Reason for Visit

Has the patient had any **Emergency Room (ER)/Urgent Care Visits/Procedures (i.e., lung surgery)** between since the previous module (i.e., since Visit 7)?

☐ No

☐ Yes → *If 'Yes', please record details below*

Date of Visit Day Mth Yr	Reason for Visit	Patient Admitted from ER? Yes	No
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐

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Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

RESOURCE UTILIZATION - (cont)

Has the patient had any **Hospitalizations** since the previous module (i.e., since Visit 7)?

☐ No

☐ Yes → *If 'Yes', please record details below* ***(also record details of any hospitalization in the Serious Adverse Experience - COPD Exacerbation section)***

Name of Hospital & City	Date of Admission Day Mth Yr	Date of Discharge Day Mth Yr	Reason for Admission

Has the patient had any **Intensive Care Unit (ICU) stays** ***(did the patient stay in the ICU during any of the above hospitalizations?)*** since the previous module (i.e., since Visit 7)?

☐ 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

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Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

MOD6

Please do not split modules

Module 6 : **Visit 10, Adverse Experiences, Concomitant Medications, Medical Procedures, COPD Exacerbations, Resource Utilization**

CRF Pages **241 - 280**

Unprocessed Forms : **Within this module the following occur which will generate attachments that need to be brought in-house.**

None

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Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	
207499/156		[redacted]			Visit 10 Week 24

PRESENTATION TO CLINIC

Record time of presentation to clinic ☐☐ 24hr:min

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?

☐ NA → Patient is not using beta$_2$ agonist.

☐ 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?

☐ NA → Patient is not using anticholinergic.

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: ☐☐ ☐☐ ☐☐ 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 : ☐☐

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes

ST. GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

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

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Protocol		Patient Number	Patient Initials		Visit 10 Week 24
207499/156		[redacted]			

ST. GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE (PAGE 1 OF 5)

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Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day / Month / Year)	
207499/156		[redacted]			Visit 10 Week 24

SF - 36 (HEALTH STATUS QUESTIONNAIRE) (Page 1 of 5)

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Protocol		Patient Number	Patient Initials		Visit 10 Week 24
207499/156		[redacted]			

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes ⟶ *If 'Yes' please record details below.*

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

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

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

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of excerbation (maximum level)	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1
	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2
	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations, including an increase in usual COPD medications, must be recorded in the COPD Medications or Procedures pages.

RESOURCE UTILIZATION

Please complete the Resource Utilization section at the back of this module. If the patient has received any COPD exacerbation related medical care since the previous visit, please complete the COPD Resource Utilization section at the back of this module.

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Protocol		Patient Number	Patient Initials		Visit 10 Week 24
207499/156		[redacted]			

INDIRECT COST

Does the patient work?

☐ No

☐ Yes → *If 'Yes', has the patient missed work due to COPD-related symptoms, excluding scheduled protocol visits, since the last visit?*

☐ No

☐ Yes → *If 'Yes', please record lost work days below:*

Start Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence

How many days since your last visit have you been restricted in performing your leisure activities, due to your COPD-related symptoms? *(please enter number of days below, if not restricted, enter 0)*

☐☐ Days

Since your last visit, how many hours per week did you require paid or unpaid assistance by a relative, friend or professional with your daily activities such as dressing, bathing, cooking, etc., due to your COPD-related symptoms? *(please enter number of hours below, if no paid or unpaid assistance, enter 0 in each instance)*

☐☐☐ Hours per week of **paid** assistance

☐☐☐ Hours per week of **unpaid** assistance

ADVERSE EXPERIENCES

Please complete the Adverse Experience section at the back of this module. If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

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Protocol	Patient Number	Patient Initials	Visit 10 Week 24
207499/156	[redacted]		

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.

"AS NEEDED" ALBUTEROL USE

Record the patient's evaluation of their 'as needed' albuterol use since the last visit.

[1] ☐ Much less than usual
[2] ☐ Less than usual
[3] ☐ About the same as usual
[4] ☐ More than usual
[5] ☐ Much more than usual

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.

FECAL OCCULT BLOOD TEST

The fecal occult blood test should be performed on three consecutive bowel movements or on bowel movements closely spaced in time between Visits 9 and 10. 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 the instructions provided with the kit?

☐ No → *If 'No', please specify:* _____

☐ Yes

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

Are these findings clinically significant?

☐ No

☐ Yes → *If 'Yes' please record the details in the Adverse Experience section at the back of this module.*

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Protocol		Patient Number	Patient Initials		Visit 10 Week 24
207499/156		[redacted]			

INVESTIGATOR GLOBAL ASSESSMENT

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

PATIENT GLOBAL ASSESSMENT

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

COUGH AND SPUTUM PRODUCTION ASSESSMENTS

*Please ask the patient the following questions and record the answers below (Mark **one** box per section only.)*

COUGH

How troubled have you been by cough today?

[0] ☐ No symptoms at all

[1] ☐ Some symptoms, but hardly noticeable

[2] ☐ Symptoms noticeable and a little uncomfortable

[3] ☐ Symptoms definitely noticeable and uncomfortable

[4] ☐ Symptoms very bad and extremely uncomfortable

SPUTUM PRODUCTION

How much sputum have you produced today?

[0] ☐ No sputum at all

[1] ☐ Some sputum, but not as much as usual

[2] ☐ As much as usual

[3] ☐ More than usual

[4] ☐ A lot more than usual

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Protocol		Patient Number	Patient Initials		Visit 10 Week 24
207499/156		[redacted]			

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a **clinically significant worsening** in the patient's physical condition since the previous examination?

☐ No

☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of this module.*

OVERALL BREATHLESSNESS ASSESSMENT

Give the patient a copy of the following scale when assessing breathlessness.

Please ask the patient the following question and record the answer below.

"Generally speaking, how has your breathlessness been during the previous week when you carried out tasks that usually cause you to be short of breath (e.g. walking, carrying shopping, climbing stairs, etc)?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Overall breathlessness score ☐☐.☐

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 Exercise Tolerance Test) must be performed greater than 4 hours after the patient's last albuterol administration.

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Protocol		Patient Number	Patient Initials		Visit 10 Week 24
207499/156		[redacted]			

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
___ / ___	___

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

VITAL SIGNS - ORTHOSTATIC CHANGE

1st Measurement: After 5 Minutes Supine

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
___ / ___	___

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
___ / ___	___

Are there any clinically significant worsenings since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

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Protocol		Patient Number	Patient Initials		Visit 10 Week 24
207499/156		[redacted]			

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes.

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant changes noted at this examination compared to the last visit?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of this module.*

RESTING SaO_2

Measure Resting SaO_2 by pulse oximetry for all patients with an FEV_1 < 40% of predicted for age, height and gender at Visit 1.

[1] ☐ Measurement not required (patient's FEV_1 at Visit 1 ≥ 40% of predicted)

[2] ☐ Measurement required but not performed

[3] ☐ Measurement taken, *please record value below:*

Resting SaO_2 ☐☐☐ %

EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted? The distance walked should be entered even if the patient did not walk for 6 minutes.

☐ No

☐ Yes → *If 'Yes', Distance walked* ☐☐☐ [M] Meters ☐

[YD] Yards ☐

Record any adverse experiences which occur during the exercise tolerance test in the Adverse Experience section at the back of this module.

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Protocol		Patient Number	Patient Initials		Visit 10 Week 24
207499/156		[redacted]			

POST-EXERCISE ASSESSMENTS *(Immediately after the patient completes the exercise tolerance)*

Heart Rate ☐☐☐ beats/min

SaO_2 ☐☐☐ %

Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

"How short of breath do you feel right now?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Post-exercise breathlessness score ☐☐.☐

INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise tolerance test (rest for at least 10 minutes) before performing the pulmonary function tests.

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Protocol		Patient Number	Patient Initials		Visit 10 Week 24
207499/156		[redacted]			

PULMONARY FUNCTION TESTS (PRE-ALBUTEROL)

Pulmonary function tests will be assessed at least 4 hours after the last dose of inhaled beta-$_2$ agonist or anticholinergic agent.
NOTE: Additional pulmonary function tests will be performed after a dose of study albuterol is given in the clinic (see next page).

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 confirm that the pulmonary function tests were performed

[1] ☐ Not Performed

[2] ☐ Performed

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. If the pregnancy test is positive, complete the Serious Adverse Experiences form and forward it to SB within 24 hours.

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes', please record the findings and/or diagnosis in the Adverse Experiences section (If a re-test is necessary, please use the Repeat Lab page at the end of this book)*

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Protocol		Patient Number	Patient Initials		Visit 10 Week 24
207499/156		[redacted]			

ARTERIAL BLOOD GASES

If a resting SaO2 test was required at this visit AND the patient's resting SaO2 < 88% OR the patient lives at a high altitude, please take an arterial blood gas sample for analysis if feasible. The patient should be rested (5 to 10 minute rest) after pulmonary function tests.

☐ Not required

☐ Sample required but not taken

PO_2 (mmHg)	PCO_2 (mmHg)	HCO_3- (mEq/L)	pH	SaO_2 %
☐☐☐	☐☐	☐☐	☐.☐☐	☐☐☐

POST-ALBUTEROL PULMONARY FUNCTION TESTS

Administer 180mcg (2 puffs) of albuterol via MDI with a spacer using the study inhaler provided for "as required" rescue-medication use.

Record the time of albuterol inhalation ☐☐ 24hr:min

Wait 30 minutes *(+/-5 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 manuals).*** *For each set of three FEV_1 measurements, one FEV_1 must be within 10% of the highest.*

Please confirm that the pulmonary function tests were performed

[1] ☐ Not Performed

[2] ☐ Performed

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Protocol		Patient Number	Patient Initials		Visit 10 Week 24
207499/156		[redacted]			

PHARMACOKINETIC EVALUATIONS - PRE-DOSE BLOOD SAMPLE

Record the date and time of the previous two doses of study medication.

Study Medication Taken	Date Day Mth Yr	Time 24hr:min	Did the patient take this dose with food ?	
Yesterday's Morning Dose			☐ Yes	☐ No
Yesterday's Evening Dose			☐ Yes	☐ No

Collect a pre-dose blood sample (5mL) for pharmacokinetic evaluation.

Was a pharmacokinetic sample taken?

☐ No

☐ Yes → *If 'Yes',* 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)

Did the patient accidentally take this morning's dose prior to attending the clinic?

☐ No

☐ Yes → *If 'Yes', check that the Study Medication Record for this visit is recorded correctly.*

ADMINISTRATION OF STUDY MEDICATION

Give the patient their dose of study medication (from the bottle dispensed at Visit 9) with food and record the date and time of administration below.

Date and time of administration ☐☐ ☐☐ ☐☐ Day Month Yr ☐☐ 24hr:min

Note: If this is a morning visit, patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

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Protocol		Patient Number	Patient Initials		Visit 10 Week 24
207499/156		[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 (and should reflect the date of the dose given in the clinic at Visit 10). Record interruptions or changes in dose on separate lines.

Start Date Day Mth Yr	End Date Day Mth Yr	Number of tablets per dose	Frequency (e.g. bid)

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
70					

Note: Include the dose of study medication given to the patient at this visit.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance < 80% or > 120%?

☐ No

☐ Yes

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Protocol		Patient Number	Patient Initials		Visit 10 Week 24
207499/156		[redacted]			

POST-DOSE PULMONARY FUNCTION TESTS

Pulmonary function tests will be completed every hour in the 4-hour period following administration of the dose of study medication.

Ask the patient to avoid using their albuterol or anticholinergic medication and to refrain from smoking if at all possible.

If the patient uses their albuterol or anticholinergic medication during this period, the tests should be abandoned.

Time post-dose	Completed?	
	Yes	No
1 Hour	☐	☐
2 Hours	☐	☐
3 Hours	**Perform ECG**	
3 Hours	☐	☐
4 Hours	☐	☐

Record any adverse experiences which occur during the pulmonary function tests in the Adverse Experience section at the back of this module.

12 LEAD ELECTROCARDIOGRAM - 3 HOURS POST DOSE

The ECG should be performed before the 3-hour post-dose pulmonary function test and after the patient has been semi-supine for 5 minutes.

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant changes noted at this examination compared to the ECG performed earlier in this visit?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of this module.*

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 10

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 previous COPD medications as appropriate.*
- ***Remind the patient:***

  i *to refrain from using albuterol or anticholinergic agents during the **4 hours** immediately preceding the visit.*

  ii *to refrain from smoking for **2 hours** immediately preceding the visit.*

  iii *to bring the study albuterol inhaler and spacer to the visit.*

  iv *to call the investigator as soon as possible to report any gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhea, 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.*

PATIENT ACTIVITY POSTCARD

Please complete the patient activity postcard for ***Visit 10*** located in the postcard section of this CRF. Detach the postcard and mail promptly. Postage has been prepaid.

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	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

ADVERSE EXPERIENCES (Non-serious)

*Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Have you felt different in any way since starting the treatment or since the previous 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).

If no adverse experiences occured since the last visit, please mark this box. ☐

Adverse Experience *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***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) *See definitions page for Adverse Experience*	[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 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	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

ADVERSE EXPERIENCES (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 previous 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).

If no adverse experiences occured since the last visit, please mark this box. ☐

Adverse Experience *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***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) *See definitions page for Adverse Experience*	[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 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	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

ADVERSE EXPERIENCES (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 previous 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).

If no adverse experiences occured since the last visit, please mark this box. ☐

Adverse Experience *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***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) *See definitions page for Adverse Experience*	[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 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)

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

CONCOMITANT MEDICATION

Record any changes in concomitant medication taken since the last 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 (albuterol) use, using the date the study inhaler was returned.

☐ No concomitant medication changes since the last visit

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.*

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 (albuterol) 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 Route, see General Instructions for acceptable abbreviations.*

MEDICAL PROCEDURES
excluding treatment for COPD Exacerbations
(These are recorded in the COPD Exacerbations section)

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 visit?

☐ 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			

COPD EXACERBATION SECTION

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 visit should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages***

If no COPD Exacerbations since the last visit, please mark this box. ☐

Adverse Experience	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***If patient died, STOP: go to SAE COPD Exacerbation pages.***	[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) *See definitions page for Adverse Experience*	[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 COPD Medication 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	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

DETAILS OF COPD EXACERBATIONS - CONTINUED

*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 since the last visit should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages***

If no COPD Exacerbations since the last visit, please mark this box. ☐

Adverse Experience	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***If patient died, STOP: go to SAE COPD Exacerbation pages.***	[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) *See definitions page for Adverse Experience*	[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 COPD Medication 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	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

DETAILS OF COPD EXACERBATIONS - CONTINUED

*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 since the last visit should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages***

If no COPD Exacerbations since the last visit, please mark this box. ☐

Adverse Experience	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***If patient died, STOP: go to SAE COPD Exacerbation pages.***	[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) *See definitions page for Adverse Experience*	[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 COPD Medication and/or Medical Procedures section if appropriate*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No

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	Center Number	Patient Number	Patient Initials	SB Receipt Date Day Month Year
207499/156		[redacted]		

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation

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 hospitalization (excluding elective surgery or routine clinical procedures)
[5] hospitalization 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 COPD Medication or Medical Procedures section* Yes No

Was patient withdrawn due to this specific SAE ? Yes No

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation (cont)

Relevant Laboratory Data
Please provide relevant abnormal laboratory data below

Test	Date	Value	Units	Normal Range
	Day Month Yr			
	Day Month Yr			
	Day Month Yr			
	Day Month Yr			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomization code broken at investigational site? ☐ No ☐ Yes

Randomization 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

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

SERIOUS ADVERSE EXPERIENCE - COPD EXACERBATION (Cont.) PHARMACOKINETIC EVALUATION

If the patient presents to the clinic within 24 hours of the onset of a serious adverse experience (SAE) COPD Exacerbation or with an ongoing SAE COPD Exacerbation, please collect a blood sample (5mL) for pharmacokinetic evaluation.

Was a pharmacokinetic sample taken?

☐ No

☐ Yes → *If 'Yes',* 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 taken prior to the onset of the serious adverse experience - COPD exacerbation

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 serious adverse experience - COPD exacerbation?

☐ No

☐ Yes → *If 'Yes',* record date and time of last dose of study medication taken prior to collection of the pharmacokinetic sample.

Day Month Yr 24hr:min

Was this dose taken with food?

☐ No

☐ Yes

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

MEDICATION FOR COPD EXACERBATIONS

Has the patient taken any medication for COPD exacerbations since the previous visit?

☐ No

☐ Yes → *If 'Yes', please record details below*

Drug Name (Trade Name Preferred)	Unit Dose (eg 500mg)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible) Day Mth Yr	End Date (or if Continuing mark box) Day Mth Yr	
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							

** For Route, see General Instructions for acceptable abbreviations.*

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

MEDICAL PROCEDURES FOR COPD EXACERBATIONS

Have any non-medication, therapeutic, diagnostic or surgical procedures been performed for COPD exacerbations since the previous visit?

☐ 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		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			

RESOURCE UTILIZATION

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

RESOURCE UTILIZATION

Has the patient utilized any COPD Exacerbation-related medical care since the last visit?

☐ No

☐ Yes → *If 'Yes', please record details below*

Has the patient had any **Physician Visits** (COPD care excluding scheduled protocol visits) since the last visit?

☐ No

☐ Yes → *If 'Yes', please record details below*

Date of Visit Day Mth Yr	Reason for Visit

Has the patient had any **Emergency Room (ER)/Urgent Care Visits/Procedures (i.e., lung surgery)** since the last visit?

☐ No

☐ Yes → *If 'Yes', please record details below*

Date of Visit Day Mth Yr	Reason for Visit	Patient Admitted from ER? Yes	No
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

RESOURCE UTILIZATION - (cont)

Has the patient had any **Hospitalizations** since the last visit?

☐ No

☐ Yes → *If 'Yes', please record details below* ***(also record details of any hospitalization in the Serious Adverse Experience - COPD Exacerbation section)***

Name of Hospital & City	Date of Admission Day Mth Yr	Date of Discharge Day Mth Yr	Reason for Admission

Has the patient had any **Intensive Care Unit (ICU) stays** ***(did the patient stay in the ICU during any of the above hospitalizations?)*** since the last visit?

☐ 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

EARLY WITHDRAWAL BETWEEN SCHEDULED VISITS

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

EW2

Please do not split modules

Module : Early Withdrawal Between Scheduled Visits

CRF Pages 281 - 291

Unprocessed Forms : Within this module the following occur which will generate attachments that need to be brought in-house.

Early Withdrawal:
SGRQ Quality of Life Assessment
SF-36 Quality of Life Assessment

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Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

Complete these assessments ONLY for patients who withdraw from the study between scheduled clinic visits. These assessments should be completed within 24 hours of stopping study medication.

PRESENTATION TO CLINIC

Record time of presentation to clinic ☐☐ 24hr:min

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?

☐ NA ⟶ Patient is not using beta$_2$ agonist.

☐ 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?

☐ NA ⟶ Patient is not using anticholinergic.

☐ No

☐ Yes ⟶ Record date and time of patient's last dose of anticholinergic: ☐☐☐ 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 : ☐☐

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

ST. GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

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

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes ⟶ *If 'Yes' please record details below.*

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

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

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

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of excerbation (maximum level)	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1
	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2
	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of the module which contains the visit (or visit interval) at which the patient withdrew, 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 UTILIZATION

If the patient has received any COPD exacerbation related medical care since the previous visit, record details in the Resource Utilization section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

INDIRECT COST

Does the patient work?

☐ No

☐ Yes → *If 'Yes'*, has the patient missed work due to COPD-related symptoms, excluding scheduled protocol visits, since the last visit?

☐ No

☐ Yes → *If 'Yes', please record lost work days below:*

Start Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence

How many days since your last visit have you been restricted in performing your leisure activities, due to your COPD-related symptoms? *(please enter number of days below, if not restricted, enter 0)*

☐☐ Days

Since your last visit, how many hours per week did you require paid or unpaid assistance by a relative, friend or professional with your daily activities such as dressing, bathing, cooking, etc., due to your COPD-related symptoms? *(please enter number of hours below, if no paid or unpaid assistance, enter 0 in each instance)*

☐☐☐ Hours per week of **paid** assistance

☐☐☐ Hours per week of **unpaid** assistance

ADVERSE EXPERIENCES

If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of the module which contains the visit (or visit interval) at which the patient withdrew. The patient should refer to the notes in their diary when answering this question.

SmithKline Beecham
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Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

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 the module which contains the visit (or visit interval) at which the patient withdrew.

"AS NEEDED" ALBUTEROL USE

Record the patient's evaluation of their 'as needed' albuterol use since the last visit.

[1] ☐ Much less than usual
[2] ☐ Less than usual
[3] ☐ About the same as usual
[4] ☐ More than usual
[5] ☐ Much more than usual

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 the module which contains the visit (or visit interval) at which the patient withdrew.

INVESTIGATOR GLOBAL ASSESSMENT

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

PATIENT GLOBAL ASSESSMENT

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

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Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

COUGH AND SPUTUM PRODUCTION ASSESSMENTS

*Please ask the patient the following questions and record the answers below (Mark **one** box per section only.)*

COUGH

How troubled have you been by cough today?

- [0] ☐ No symptoms at all
- [1] ☐ Some symptoms, but hardly noticeable
- [2] ☐ Symptoms noticeable and a little uncomfortable
- [3] ☐ Symptoms definitely noticeable and uncomfortable
- [4] ☐ Symptoms very bad and extremely uncomfortable

SPUTUM PRODUCTION

How much sputum have you produced today?

- [0] ☐ No sputum at all
- [1] ☐ Some sputum, but not as much as usual
- [2] ☐ As much as usual
- [3] ☐ More than usual
- [4] ☐ A lot more than usual

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a **clinically significant worsening** in the patient's physical condition since the previous examination?

- ☐ No
- ☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.*

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Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

FECAL OCCULT BLOOD TEST

Issue the patient the fecal 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. Samples should be collected on three consecutive bowel movements or three bowel movements closely spaced in time and returned to the clinic as soon as possible.

Did the patient follow the instructions provided with the kit?

☐ No → *If 'No', please specify:* _____

☐ Yes

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

Are these findings clinically significant?

☐ No

☐ Yes → *If 'Yes' please record the details in the Adverse Experience section at the back of this module.*

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Pharmaceuticals

Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[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. bid)

Date and time of last dose of study medication prior to the study visit ☐☐☐ ☐☐ (Day Month Yr / 24hr:min)

Did the patient take their last dose with food?

☐ No

☐ Yes

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
☐☐	☐☐	☐☐	☐☐	☐☐	☐☐☐

Note: If this is a morning visit, patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance ≥ 80% and ≤120%?

☐ No

☐ Yes

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Pharmaceuticals

Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[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 and ECG) must be performed greater than 4 hours after the patient's last albuterol administration.

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
☐☐☐/☐☐☐	☐☐☐

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.*

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Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

VITAL SIGNS - ORTHOSTATIC CHANGE

1st Measurement: After 5 Minutes Supine

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
___ / ___	___

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
___ / ___	___

Are there any clinically significant worsenings since Baseline?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes.

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant changes noted at this examination compared to the last visit?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.*

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Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted? The distance walked should be entered even if the patient did not walk for 6 minutes.

☐ No

☐ Yes → *If 'Yes', Distance walked* ☐☐☐ [M] Meters ☐

[YD] Yards ☐

Record any adverse experiences which occur during the exercise tolerance test in the Adverse Experience section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.

POST-EXERCISE ASSESSMENTS *(Immediately after the patient completes the exercise tolerance)*

Heart Rate ☐☐☐ beats/min

SaO_2 ☐☐☐ %

Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

"How short of breath do you feel right now?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0 Nothing at all

1 Very, very slight (just noticeable)

2 Very slight

3 Moderate

4 Somewhat severe

5 Severe

6

7 Very severe

8

9 Very, very severe (almost maximal)

10 Maximal

Post-exercise breathlessness score ☐☐.☐

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise test (rest for at least 10 minutes) before performing the pulmonary function tests.

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 confirm that the pulmonary function tests were performed

[1] ☐ Not Performed

[2] ☐ Performed

LABORATORY TESTS

Please take blood samples for hematology, 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. If the pregnancy test is positive, please complete the Serious Adverse Experiences form and forward it to SB within 24 hours.

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes', please record the findings and/or diagnosis in the Adverse Experiences section (If a re-test is necessary, please use the Repeat Lab page at the end of this book)*

INSTRUCTION TO THE INVESTIGATOR

Please complete the Study Conclusion page at the end of this book.

Ask the patient to return for the Safety Follow-Up Visit in 7 +/- 3 days.

PATIENT ACTIVITY POSTCARD

Please complete the patient activity postcard for ***Early Withdrawal Between Scheduled Visits*** located in the postcard section of this CRF. Detach the postcard and mail promptly. Postage has been prepaid.

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

SFU2

Please do not split modules

Module : **Safety Follow-Up**

CRF Pages **292 - 297**

Unprocessed Forms : **Within this module the following occur which will generate attachments that need to be brought in-house.**

None

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Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	
207499/156		[redacted]			Safety Follow-Up

INVESTIGATOR INSTRUCTIONS

Complete these assessments for those patients who withdrew early from the study or for patients who have completed Visit 10. These assessments should be completed within 7 +/- 3 days after discontinuation of study medication.

PRESENTATION TO CLINIC

Record time of presentation to clinic ☐☐ 24hr:min

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?

☐ NA → Patient is not using beta$_2$ agonist.

☐ 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?

☐ NA → Patient is not using anticholinergic.

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: ☐☐☐ 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 : ☐☐

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Safety Follow-Up
207499/156		[redacted]			

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes ⟶ *If 'Yes' please record details below.*

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

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

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

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of excerbation (maximum level)	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1
	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2
	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of the module which contains the visit (or visit interval) at which the patient withdrew or after Visit 10, if applicable, 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 UTILIZATION

If the patient has received any COPD exacerbation related medical care since the previous visit, record details in the Resource Utilization section at the back of the module which contains the visit (or visit interval) at which the patient withdrew or after Visit 10, if applicable.

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Safety Follow-Up
207499/156		[redacted]			

INDIRECT COST

Does the patient work?

☐ No

☐ Yes → *If 'Yes'*, has the patient missed work due to COPD-related symptoms, excluding scheduled protocol visits, since the last visit?

☐ No

☐ Yes → *If 'Yes', please record lost work days below:*

Start Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence

How many days since your last visit have you been restricted in performing your leisure activities, due to your COPD-related symptoms? *(please enter number of days below, if not restricted, enter 0)*

☐☐ Days

Since your last visit, how many hours per week did you require paid or unpaid assistance by a relative, friend or professional with your daily activities such as dressing, bathing, cooking, etc., due to your COPD-related symptoms? *(please enter number of hours below, if no paid or unpaid assistance, enter 0 in each instance)*

☐☐☐ Hours per week of **paid** assistance

☐☐☐ Hours per week of **unpaid** assistance

ADVERSE EXPERIENCES

If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of the module which contains the visit (or visit interval) at which the patient withdrew or after Visit 10, if applicable.

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Safety Follow-Up
207499/156		[redacted]			

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 the module which contains the visit (or visit interval) at which the patient withdrew or after Visit 10, if applicable.
At the patient's final study visit, record the end date for prn study rescue medication (albuterol) use, using the date the study inhaler was returned.

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 the module which contains the visit (or visit interval) at which the patient withdrew or after Visit 10, if applicable.

PULMONARY REHABILITATION PROGRAM

Has the patient entered a Pulmonary Rehabilitation Program since the last visit?

☐ No

☐ Yes

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
☐☐☐/☐☐☐	☐☐☐

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of the module which contains the visit (or visit interval) at which the patient withdrew or after Visit 10, if applicable.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Safety Follow-Up
207499/156		[redacted]			

12 LEAD ELECTROCARDIOGRAM

If any abnormalities were observed at the last visit, please perform a 12-lead ECG. The ECG should be performed after the patient has been semi-supine for 5 minutes.

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant changes noted at this examination compared to the last visit?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of the module which contains the visit (or visit interval) at which the patient withdrew or after Visit 10, if applicable.*

LABORATORY TESTS

If abnormal laboratory results were reported at the previous visit, 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 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.

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes', please record the findings and/or diagnosis in the Adverse Experiences section at the back of the module which contains the visit (or visit interval) at which the patient withdrew or after Visit 10, if applicable. (If a re-test is necessary, please use the Repeat Lab page at the end of this book)*

SmithKline Beecham
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Protocol		Patient Number	Patient Initials		Safety Follow-Up
207499/156		[redacted]			

PREGNANCY TEST

Is the patient a female of child-bearing potential?

☐ No

☐ Yes → *If 'Yes' please perform a urine pregnancy test locally.*

Urine Sample Date ☐☐ ☐☐ ☐☐
Day Month Yr

Is the patient pregnant?

☐ No

☐ Yes → *If the pregnancy test is positive, complete the Serious Adverse Experiences form and forward it to SB within 24 hours.*

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

If any abnormalities were noted at the last visit, please perform a physical examination (including respiratory examination).

Were any clinically significant changes noted at this examination compared to the last visit?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of the module which contains the visit (or visit interval) at which the patient withdrew or after Visit 10, if applicable.*

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 confirm that the pulmonary function tests were performed

[1] ☐ Not Performed

[2] ☐ Performed

PATIENT ACTIVITY POSTCARD

Please complete the patient activity postcard for ***Safety Follow-Up Visit*** located in the postcard section of this CRF. Detach the postcard and mail promptly. Postage has been prepaid.

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

CONC3

Please do not split modules

Module : **Study Conclusion**

CRF Pages **298**

Unprocessed Forms : **Within this module the following occur which will generate attachments that need to be brought in-house.**

None

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

STUDY CONCLUSION

Did the patient complete the double-blind phase of the study as planned?

☐ Yes

☐ No → *If 'No' please mark the **PRIMARY** cause of withdrawal. (Mark one box only).*

[1] ☐ Adverse experience (complete AE form)

[2] ☐ Insufficient therapeutic effect

[3] ☐ Protocol deviation (including non-compliance)

[4] ☐ Lost to follow-up

[7] ☐ Other - specify: _____

Date of Final Visit ☐☐ ☐☐ ☐☐ Day Month Yr

Date of Final Dose ☐☐ ☐☐ ☐☐ Day Month Yr

INVESTIGATOR SIGNATURE

I certify that I have reviewed the data on this case report form, 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	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

SAE3

Please do not split modules

Module : **Serious Adverse Experiences**

CRF Pages **299 - 301**

Unprocessed Forms : **Within this module the following occur which will generate attachments that need to be brought in-house.**

None

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	SB Receipt Date Day Month Year
207499/156		[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 hospitalization (excluding elective surgery or routine clinical procedures)
[5] ☐ hospitalization 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 section
☐ Yes ☐ No

Was patient withdrawn due to this specific SAE ?
☐ Yes ☐ No

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 randomization code broken at investigational site? ☐ No ☐ Yes

Randomization 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 _____

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		
207499/156		[redacted]			

SERIOUS ADVERSE EXPERIENCE (Cont.)
PHARMACOKINETIC EVALUATION

If the patient presents to the clinic within 24 hours of the onset of a serious adverse experience (SAE) or with an ongoing SAE, please collect a blood sample (5mL) for pharmacokinetic evaluation.

Was a pharmacokinetic sample taken?

☐ No

☐ Yes → *If 'Yes',* 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 taken prior to the onset of the serious adverse experience

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 serious adverse experience?

☐ No

☐ Yes → *If 'Yes',* record date and time of last dose of study medication taken prior to collection of the pharmacokinetic sample.

Day Month Yr 24hr:min

Was this dose taken with food?

☐ No

☐ Yes

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

FORMD3

Please do not split modules

Module: **Form D**

CRF Pages: **302**

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

FORM D

Certified Cause of Death _____

Date of Death Day Month Yr → *Please complete Serious Adverse Experience section.*

Was a post-mortem examination carried out?

☐ No

☐ Yes → *If 'Yes' please summarize findings (include diagnosis):*

_____

_____

_____

_____

Reporting Physician's Signature _____ Date Day Month Yr

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		OPTIONAL Repeat Lab
207499/156		[redacted]			

RPLAB3

Please do not split modules

Module: Repeat Lab

CRF Pages: 303

Unprocessed Forms: Within this module, the following tests / procedures occur which may generate attachments.

None

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		OPTIONAL Repeat Lab
207499/156		[redacted]			

REPEAT 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, complete the Early Withdrawal between Scheduled Visits 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.*

REPEAT 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, complete the Early Withdrawal between Scheduled Visits and complete the Serious Adverse Experiences form and forward it to SB within 24 hours.

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☐ No

☐ Yes → *If 'Yes', please record the findings and/or diagnosis in the Adverse Experiences section.*

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Investigator
207499/156		[redacted]		

CRF TRACKING/REVIEW FORM

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- *Ensure all sections of the TRF are legible*

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SAE3	Serious Adverse Experiences	299 - 301	☐	☐	
FORMD3	Form D	302	☐	☐	
RPLAB3	Repeat Labs	303	☐	☐	

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Site Monitor's Comments (e.g. protocol violations or deviations)

Site Monitor's Signature _____ Date Submitted ☐☐ Day ☐☐ Month ☐☐ Yr

SmithKline Beecham
Pharmaceuticals

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207499/156		[redacted]		

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Day Month Yr

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Pharmaceuticals

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_____

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SmithKline Beecham
Pharmaceuticals

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Day Month Yr

SmithKline Beecham
Pharmaceuticals

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Site Monitor's Comments (e.g. protocol violations or deviations)

Site Monitor's Signature _____ Date Submitted ☐☐ Day ☐☐ Month ☐☐ Yr

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

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

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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) which cause concern or interfere with usual activity (including eating and sleeping) at any time during the study.

Report this gastrointestinal symptom(s) to the SB Medical Monitor by telephone within 24 hours of the first assessment and fax the completed Supplemental Gastrointestinal Adverse Experience Report within 24 hours of the first assessment.

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.

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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 on page 3) specify: _____

☐ Back

☐ Groin

☐ Shoulder tip

☐ Other, specify: _____ _____

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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 and questions. If the patient has been randomized, the patient must be referred to a gastroenterologist for a complete colonoscopy.*

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

If female, is bloody stool possibly menstrual or uterine in origin? ☐ No ☐ Yes ☐ Not applicable

Does the patient presently have hemorrhoids? ☐ No ☐ Yes

Is the patient taking NSAIDS/ASA? ☐ No ☐ Yes

PHYSICAL EXAMINATION

	Present	Absent
Abdominal tenderness	☐	☐
Abdominal masses	☐	☐
Peritoneal signs	☐	☐

Other clinically significant GI physical examination findings, please specify: _ _ _ _ _ _ _ _ _ _ _ _ _ _

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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.*

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[redacted]			

SUPPLEMENTAL REPORT FOR GASTROINTESTINAL ADVERSE EXPERIENCE

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

Was one of the tests positive?

☐ No

☐ Yes → *If 'Yes', and the patient has been randomized, please refer the patient to a gastroenterologist for a complete colonoscopy and answer the following questions.*

Has the patient had a nosebleed or bleeding gums in the 2 days prior to or during the fecal sample collection period?

☐ No

☐ Yes

If female, were the fecal samples collected during or within 3 days after a menstrual period?

☐ No

☐ Yes

☐ Not applicable

Does the patient have hemorrhoids?

☐ No

☐ Yes → If 'Yes', were the hemorrhoids bleeding when the fecal samples were collected?

☐ No

☐ Yes

Did the patient have blood in the urine when the fecal samples were collected?

☐ No

☐ Yes

Has the patient taken aspirin or other non-steroidal anti-inflammatory drugs within the 7 days prior to or during the sample collection?

☐ No

☐ Yes

Has the patient taken Vitamin C in excess of 250 mg from all sources, or eaten red meat including processed meats and liver, or eaten raw fruits and vegetables within the 72 hours prior to or during the sample collection period?

☐ No

☐ Yes

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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
☐ Colonoscopy
☐ Rectal/pelvic examination
☐ Stool for ova and parasites
☐ Ultrasound of the abdomen
☐ Other, specify: _____

(Note: Complete colonoscopy must be performed for all randomized patients with a GIAE of concern and melena or a positive fecal occult blood test.)

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 fax results as soon as available and record tests in the Medical Procedures page of the CRF.

Investigator's Remarks: _____

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Supplemental Report
207499/156		[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

_ _ _ _

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Investigator
207499/156		[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

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

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

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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) which cause concern or interfere with usual activity (including eating and sleeping) at any time during the study.

Report this gastrointestinal symptom(s) to the SB Medical Monitor by telephone within 24 hours of the first assessment and fax the completed Supplemental Gastrointestinal Adverse Experience Report within 24 hours of the first assessment.

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.

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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 on page 3) specify: _____

☐ Back

☐ Groin

☐ Shoulder tip

☐ Other, specify: _____ _____

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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 and questions. If the patient has been randomized, the patient must be referred to a gastroenterologist for a complete colonoscopy.*

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

If female, is bloody stool possibly menstrual or uterine in origin? ☐ No ☐ Yes ☐ Not applicable

Does the patient presently have hemorrhoids? ☐ No ☐ Yes

Is the patient taking NSAIDS/ASA? ☐ No ☐ Yes

PHYSICAL EXAMINATION

	Present	Absent
Abdominal tenderness	☐	☐
Abdominal masses	☐	☐
Peritoneal signs	☐	☐

Other clinically significant GI physical examination findings, please specify: _ _ _ _ _ _ _ _ _ _ _ _ _ _

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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.*

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[redacted]			

SUPPLEMENTAL REPORT FOR GASTROINTESTINAL ADVERSE EXPERIENCE

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

Was one of the tests positive?

☐ No

☐ Yes → *If 'Yes', and the patient has been randomized, please refer the patient to a gastroenterologist for a complete colonoscopy and answer the following questions.*

Has the patient had a nosebleed or bleeding gums in the 2 days prior to or during the fecal sample collection period?

☐ No

☐ Yes

If female, were the fecal samples collected during or within 3 days after a menstrual period?

☐ No

☐ Yes

☐ Not applicable

Does the patient have hemorrhoids?

☐ No

☐ Yes → If 'Yes', were the hemorrhoids bleeding when the fecal samples were collected?

☐ No

☐ Yes

Did the patient have blood in the urine when the fecal samples were collected?

☐ No

☐ Yes

Has the patient taken aspirin or other non-steroidal anti-inflammatory drugs within the 7 days prior to or during the sample collection?

☐ No

☐ Yes

Has the patient taken Vitamin C in excess of 250 mg from all sources, or eaten red meat including processed meats and liver, or eaten raw fruits and vegetables within the 72 hours prior to or during the sample collection period?

☐ No

☐ Yes

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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
☐ Colonoscopy
☐ Rectal/pelvic examination
☐ Stool for ova and parasites
☐ Ultrasound of the abdomen
☐ Other, specify: _____

(Note: Complete colonoscopy must be performed for all randomized patients with a GIAE of concern and melena or a positive fecal occult blood test.)

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 fax results as soon as available and record tests in the Medical Procedures page of the CRF.

Investigator's Remarks: _____

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Supplemental Report
207499/156		[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

_ _ _ _

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Investigator
207499/156		[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

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

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

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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) which cause concern or interfere with usual activity (including eating and sleeping) at any time during the study.

Report this gastrointestinal symptom(s) to the SB Medical Monitor by telephone within 24 hours of the first assessment and fax the completed Supplemental Gastrointestinal Adverse Experience Report within 24 hours of the first assessment.

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.

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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 on page 3) specify: _____

☐ Back

☐ Groin

☐ Shoulder tip

☐ Other, specify: _____ _____

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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 and questions. If the patient has been randomized, the patient must be referred to a gastroenterologist for a complete colonoscopy.*

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

If female, is bloody stool possibly menstrual or uterine in origin? ☐ No ☐ Yes ☐ Not applicable

Does the patient presently have hemorrhoids? ☐ No ☐ Yes

Is the patient taking NSAIDS/ASA? ☐ No ☐ Yes

PHYSICAL EXAMINATION

	Present	Absent
Abdominal tenderness	☐	☐
Abdominal masses	☐	☐
Peritoneal signs	☐	☐

Other clinically significant GI physical examination findings, please specify: _____

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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.*

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[redacted]			

SUPPLEMENTAL REPORT FOR GASTROINTESTINAL ADVERSE EXPERIENCE

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

Was one of the tests positive?

☐ No

☐ Yes → *If 'Yes', and the patient has been randomized, please refer the patient to a gastroenterologist for a complete colonoscopy and answer the following questions.*

Has the patient had a nosebleed or bleeding gums in the 2 days prior to or during the fecal sample collection period?

☐ No

☐ Yes

If female, were the fecal samples collected during or within 3 days after a menstrual period?

☐ No

☐ Yes

☐ Not applicable

Does the patient have hemorrhoids?

☐ No

☐ Yes → If 'Yes', were the hemorrhoids bleeding when the fecal samples were collected?

☐ No

☐ Yes

Did the patient have blood in the urine when the fecal samples were collected?

☐ No

☐ Yes

Has the patient taken aspirin or other non-steroidal anti-inflammatory drugs within the 7 days prior to or during the sample collection?

☐ No

☐ Yes

Has the patient taken Vitamin C in excess of 250 mg from all sources, or eaten red meat including processed meats and liver, or eaten raw fruits and vegetables within the 72 hours prior to or during the sample collection period?

☐ No

☐ Yes

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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
☐ Colonoscopy
☐ Rectal/pelvic examination
☐ Stool for ova and parasites
☐ Ultrasound of the abdomen
☐ Other, specify: _____

(Note: Complete colonoscopy must be performed for all randomized patients with a GIAE of concern and melena or a positive fecal occult blood test.)

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 fax results as soon as available and record tests in the Medical Procedures page of the CRF.

Investigator's Remarks: _____

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials	Supplemental Report
207499/156	[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

_ _ _ _

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Investigator
207499/156		[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

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

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

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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) which cause concern or interfere with usual activity (including eating and sleeping) at any time during the study.

Report this gastrointestinal symptom(s) to the SB Medical Monitor by telephone within 24 hours of the first assessment and fax the completed Supplemental Gastrointestinal Adverse Experience Report within 24 hours of the first assessment.

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.

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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 on page 3) specify: _____

☐ Back

☐ Groin

☐ Shoulder tip

☐ Other, specify: _____ _____

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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 and questions. If the patient has been randomized, the patient must be referred to a gastroenterologist for a complete colonoscopy.*

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

If female, is bloody stool possibly menstrual or uterine in origin? ☐ No ☐ Yes ☐ Not applicable

Does the patient presently have hemorrhoids? ☐ No ☐ Yes

Is the patient taking NSAIDS/ASA? ☐ No ☐ Yes

PHYSICAL EXAMINATION

	Present	Absent
Abdominal tenderness	☐	☐
Abdominal masses	☐	☐
Peritoneal signs	☐	☐

Other clinically significant GI physical examination findings, please specify: _ _ _ _ _ _ _ _ _ _ _ _ _ _ _

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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.*

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[redacted]			

SUPPLEMENTAL REPORT FOR GASTROINTESTINAL ADVERSE EXPERIENCE

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

Was one of the tests positive?

☐ No

☐ Yes → *If 'Yes', and the patient has been randomized, please refer the patient to a gastroenterologist for a complete colonoscopy and answer the following questions.*

Has the patient had a nosebleed or bleeding gums in the 2 days prior to or during the fecal sample collection period?

☐ No

☐ Yes

If female, were the fecal samples collected during or within 3 days after a menstrual period?

☐ No

☐ Yes

☐ Not applicable

Does the patient have hemorrhoids?

☐ No

☐ Yes → If 'Yes', were the hemorrhoids bleeding when the fecal samples were collected?

☐ No

☐ Yes

Did the patient have blood in the urine when the fecal samples were collected?

☐ No

☐ Yes

Has the patient taken aspirin or other non-steroidal anti-inflammatory drugs within the 7 days prior to or during the sample collection?

☐ No

☐ Yes

Has the patient taken Vitamin C in excess of 250 mg from all sources, or eaten red meat including processed meats and liver, or eaten raw fruits and vegetables within the 72 hours prior to or during the sample collection period?

☐ No

☐ Yes

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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
☐ Colonoscopy
☐ Rectal/pelvic examination
☐ Stool for ova and parasites
☐ Ultrasound of the abdomen
☐ Other, specify: _____

(Note: Complete colonoscopy must be performed for all randomized patients with a GIAE of concern and melena or a positive fecal occult blood test.)

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 fax results as soon as available and record tests in the Medical Procedures page of the CRF.

Investigator's Remarks: _____

_____

_____

_____

_____

_____

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Supplemental Report
207499/156		[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

_ _ _ _

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Investigator
207499/156		[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

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

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

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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) which cause concern or interfere with usual activity (including eating and sleeping) at any time during the study.

Report this gastrointestinal symptom(s) to the SB Medical Monitor by telephone within 24 hours of the first assessment and fax the completed Supplemental Gastrointestinal Adverse Experience Report within 24 hours of the first assessment.

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.

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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 on page 3) specify: _____

☐ Back

☐ Groin

☐ Shoulder tip

☐ Other, specify: _____ _____

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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 and questions. If the patient has been randomized, the patient must be referred to a gastroenterologist for a complete colonoscopy.*

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

If female, is bloody stool possibly menstrual or uterine in origin? ☐ No ☐ Yes ☐ Not applicable

Does the patient presently have hemorrhoids? ☐ No ☐ Yes

Is the patient taking NSAIDS/ASA? ☐ No ☐ Yes

PHYSICAL EXAMINATION

	Present	Absent
Abdominal tenderness	☐	☐
Abdominal masses	☐	☐
Peritoneal signs	☐	☐

Other clinically significant GI physical examination findings, please specify: _ _ _ _ _ _ _ _ _ _ _ _ _ _

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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.*

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[redacted]			

SUPPLEMENTAL REPORT FOR GASTROINTESTINAL ADVERSE EXPERIENCE

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

Was one of the tests positive?

☐ No

☐ Yes → *If 'Yes', and the patient has been randomized, please refer the patient to a gastroenterologist for a complete colonoscopy and answer the following questions.*

Has the patient had a nosebleed or bleeding gums in the 2 days prior to or during the fecal sample collection period?

☐ No

☐ Yes

If female, were the fecal samples collected during or within 3 days after a menstrual period?

☐ No

☐ Yes

☐ Not applicable

Does the patient have hemorrhoids?

☐ No

☐ Yes → If 'Yes', were the hemorrhoids bleeding when the fecal samples were collected?

☐ No

☐ Yes

Did the patient have blood in the urine when the fecal samples were collected?

☐ No

☐ Yes

Has the patient taken aspirin or other non-steroidal anti-inflammatory drugs within the 7 days prior to or during the sample collection?

☐ No

☐ Yes

Has the patient taken Vitamin C in excess of 250 mg from all sources, or eaten red meat including processed meats and liver, or eaten raw fruits and vegetables within the 72 hours prior to or during the sample collection period?

☐ No

☐ Yes

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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
☐ Colonoscopy
☐ Rectal/pelvic examination
☐ Stool for ova and parasites
☐ Ultrasound of the abdomen
☐ Other, specify: _____

(Note: Complete colonoscopy must be performed for all randomized patients with a GIAE of concern and melena or a positive fecal occult blood test.)

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 fax results as soon as available and record tests in the Medical Procedures page of the CRF.

Investigator's Remarks: _____

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Supplemental Report
207499/156		[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

_ _ _ _

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Investigator
207499/156		[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)

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_____

Site Monitor's Signature _____ Date Submitted ☐☐ Day ☐☐ Month ☐☐ Yr

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

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

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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) which cause concern or interfere with usual activity (including eating and sleeping) at any time during the study.

Report this gastrointestinal symptom(s) to the SB Medical Monitor by telephone within 24 hours of the first assessment and fax the completed Supplemental Gastrointestinal Adverse Experience Report within 24 hours of the first assessment.

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.

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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 on page 3) specify: _____

☐ Back

☐ Groin

☐ Shoulder tip

☐ Other, specify: _____

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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 and questions. If the patient has been randomized, the patient must be referred to a gastroenterologist for a complete colonoscopy.*

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

If female, is bloody stool possibly menstrual or uterine in origin? ☐ No ☐ Yes ☐ Not applicable

Does the patient presently have hemorrhoids? ☐ No ☐ Yes

Is the patient taking NSAIDS/ASA? ☐ No ☐ Yes

PHYSICAL EXAMINATION

	Present	Absent
Abdominal tenderness	☐	☐
Abdominal masses	☐	☐
Peritoneal signs	☐	☐

Other clinically significant GI physical examination findings, please specify: _____

SmithKline Beecham Pharmaceuticals

Page	G4

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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.*

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[redacted]			

SUPPLEMENTAL REPORT FOR GASTROINTESTINAL ADVERSE EXPERIENCE

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

Was one of the tests positive?

☐ No

☐ Yes → *If 'Yes', and the patient has been randomized, please refer the patient to a gastroenterologist for a complete colonoscopy and answer the following questions.*

Has the patient had a nosebleed or bleeding gums in the 2 days prior to or during the fecal sample collection period?

☐ No

☐ Yes

If female, were the fecal samples collected during or within 3 days after a menstrual period?

☐ No

☐ Yes

☐ Not applicable

Does the patient have hemorrhoids?

☐ No

☐ Yes → If 'Yes', were the hemorrhoids bleeding when the fecal samples were collected?

☐ No

☐ Yes

Did the patient have blood in the urine when the fecal samples were collected?

☐ No

☐ Yes

Has the patient taken aspirin or other non-steroidal anti-inflammatory drugs within the 7 days prior to or during the sample collection?

☐ No

☐ Yes

Has the patient taken Vitamin C in excess of 250 mg from all sources, or eaten red meat including processed meats and liver, or eaten raw fruits and vegetables within the 72 hours prior to or during the sample collection period?

☐ No

☐ Yes

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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
☐ Colonoscopy
☐ Rectal/pelvic examination
☐ Stool for ova and parasites
☐ Ultrasound of the abdomen
☐ Other, specify: _____

(Note: Complete colonoscopy must be performed for all randomized patients with a GIAE of concern and melena or a positive fecal occult blood test.)

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 fax results as soon as available and record tests in the Medical Procedures page of the CRF.

Investigator's Remarks: _____

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Supplemental Report
207499/156		[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

_ _ _ _

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Investigator
207499/156		[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

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

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

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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) which cause concern or interfere with usual activity (including eating and sleeping) at any time during the study.

Report this gastrointestinal symptom(s) to the SB Medical Monitor by telephone within 24 hours of the first assessment and fax the completed Supplemental Gastrointestinal Adverse Experience Report within 24 hours of the first assessment.

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.

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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 on page 3) specify: _____

☐ Back

☐ Groin

☐ Shoulder tip

☐ Other, specify: _____

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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 and questions. If the patient has been randomized, the patient must be referred to a gastroenterologist for a complete colonoscopy.*

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

If female, is bloody stool possibly menstrual or uterine in origin? ☐ No ☐ Yes ☐ Not applicable

Does the patient presently have hemorrhoids? ☐ No ☐ Yes

Is the patient taking NSAIDS/ASA? ☐ No ☐ Yes

PHYSICAL EXAMINATION

	Present	Absent
Abdominal tenderness	☐	☐
Abdominal masses	☐	☐
Peritoneal signs	☐	☐

Other clinically significant GI physical examination findings, please specify: _ _ _ _ _ _ _ _ _ _ _ _ _ _

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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.*

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[redacted]			

SUPPLEMENTAL REPORT FOR GASTROINTESTINAL ADVERSE EXPERIENCE

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

Was one of the tests positive?

☐ No

☐ Yes → *If 'Yes', and the patient has been randomized, please refer the patient to a gastroenterologist for a complete colonoscopy and answer the following questions.*

Has the patient had a nosebleed or bleeding gums in the 2 days prior to or during the fecal sample collection period?

☐ No

☐ Yes

If female, were the fecal samples collected during or within 3 days after a menstrual period?

☐ No

☐ Yes

☐ Not applicable

Does the patient have hemorrhoids?

☐ No

☐ Yes → If 'Yes', were the hemorrhoids bleeding when the fecal samples were collected?

☐ No

☐ Yes

Did the patient have blood in the urine when the fecal samples were collected?

☐ No

☐ Yes

Has the patient taken aspirin or other non-steroidal anti-inflammatory drugs within the 7 days prior to or during the sample collection?

☐ No

☐ Yes

Has the patient taken Vitamin C in excess of 250 mg from all sources, or eaten red meat including processed meats and liver, or eaten raw fruits and vegetables within the 72 hours prior to or during the sample collection period?

☐ No

☐ Yes

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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
☐ Colonoscopy
☐ Rectal/pelvic examination
☐ Stool for ova and parasites
☐ Ultrasound of the abdomen
☐ Other, specify: _____

(Note: Complete colonoscopy must be performed for all randomized patients with a GIAE of concern and melena or a positive fecal occult blood test.)

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 fax results as soon as available and record tests in the Medical Procedures page of the CRF.

Investigator's Remarks: _____

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Supplemental Report
207499/156		[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

_ _ _ _

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Investigator
207499/156		[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

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

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

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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) which cause concern or interfere with usual activity (including eating and sleeping) at any time during the study.

Report this gastrointestinal symptom(s) to the SB Medical Monitor by telephone within 24 hours of the first assessment and fax the completed Supplemental Gastrointestinal Adverse Experience Report within 24 hours of the first assessment.

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.

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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 on page 3) specify: _____

☐ Back

☐ Groin

☐ Shoulder tip

☐ Other, specify: _____ _____

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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 and questions. If the patient has been randomized, the patient must be referred to a gastroenterologist for a complete colonoscopy.*

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

If female, is bloody stool possibly menstrual or uterine in origin? ☐ No ☐ Yes ☐ Not applicable

Does the patient presently have hemorrhoids? ☐ No ☐ Yes

Is the patient taking NSAIDS/ASA? ☐ No ☐ Yes

PHYSICAL EXAMINATION

	Present	Absent
Abdominal tenderness	☐	☐
Abdominal masses	☐	☐
Peritoneal signs	☐	☐

Other clinically significant GI physical examination findings, please specify: _ _ _ _ _ _ _ _ _ _ _ _ _ _

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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.*

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[redacted]			

SUPPLEMENTAL REPORT FOR GASTROINTESTINAL ADVERSE EXPERIENCE

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

Was one of the tests positive?

☐ No

☐ Yes → *If 'Yes', and the patient has been randomized, please refer the patient to a gastroenterologist for a complete colonoscopy and answer the following questions.*

Has the patient had a nosebleed or bleeding gums in the 2 days prior to or during the fecal sample collection period?

☐ No

☐ Yes

If female, were the fecal samples collected during or within 3 days after a menstrual period?

☐ No

☐ Yes

☐ Not applicable

Does the patient have hemorrhoids?

☐ No

☐ Yes → If 'Yes', were the hemorrhoids bleeding when the fecal samples were collected?

☐ No

☐ Yes

Did the patient have blood in the urine when the fecal samples were collected?

☐ No

☐ Yes

Has the patient taken aspirin or other non-steroidal anti-inflammatory drugs within the 7 days prior to or during the sample collection?

☐ No

☐ Yes

Has the patient taken Vitamin C in excess of 250 mg from all sources, or eaten red meat including processed meats and liver, or eaten raw fruits and vegetables within the 72 hours prior to or during the sample collection period?

☐ No

☐ Yes

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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
☐ Colonoscopy
☐ Rectal/pelvic examination
☐ Stool for ova and parasites
☐ Ultrasound of the abdomen
☐ Other, specify: _____

(Note: Complete colonoscopy must be performed for all randomized patients with a GIAE of concern and melena or a positive fecal occult blood test.)

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 fax results as soon as available and record tests in the Medical Procedures page of the CRF.

Investigator's Remarks: _____

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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

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Pharmaceuticals

Protocol		Patient Number	Patient Initials		Supplemental Report
207499/156		[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

_ _ _ _

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Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Investigator
207499/156		[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

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

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

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Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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) which cause concern or interfere with usual activity (including eating and sleeping) at any time during the study.

Report this gastrointestinal symptom(s) to the SB Medical Monitor by telephone within 24 hours of the first assessment and fax the completed Supplemental Gastrointestinal Adverse Experience Report within 24 hours of the first assessment.

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.

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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 on page 3) specify: _____

☐ Back

☐ Groin

☐ Shoulder tip

☐ Other, specify: _____ _____

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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 and questions. If the patient has been randomized, the patient must be referred to a gastroenterologist for a complete colonoscopy.*

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

If female, is bloody stool possibly menstrual or uterine in origin? ☐ No ☐ Yes ☐ Not applicable

Does the patient presently have hemorrhoids? ☐ No ☐ Yes

Is the patient taking NSAIDS/ASA? ☐ No ☐ Yes

PHYSICAL EXAMINATION

	Present	Absent
Abdominal tenderness	☐	☐
Abdominal masses	☐	☐
Peritoneal signs	☐	☐

Other clinically significant GI physical examination findings, please specify: _ _ _ _ _ _ _ _ _ _ _ _ _ _

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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.*

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[redacted]			

SUPPLEMENTAL REPORT FOR GASTROINTESTINAL ADVERSE EXPERIENCE

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

Was one of the tests positive?

☐ No

☐ Yes → *If 'Yes', and the patient has been randomized, please refer the patient to a gastroenterologist for a complete colonoscopy and answer the following questions.*

Has the patient had a nosebleed or bleeding gums in the 2 days prior to or during the fecal sample collection period?

☐ No

☐ Yes

If female, were the fecal samples collected during or within 3 days after a menstrual period?

☐ No

☐ Yes

☐ Not applicable

Does the patient have hemorrhoids?

☐ No

☐ Yes → If 'Yes', were the hemorrhoids bleeding when the fecal samples were collected?

☐ No

☐ Yes

Did the patient have blood in the urine when the fecal samples were collected?

☐ No

☐ Yes

Has the patient taken aspirin or other non-steroidal anti-inflammatory drugs within the 7 days prior to or during the sample collection?

☐ No

☐ Yes

Has the patient taken Vitamin C in excess of 250 mg from all sources, or eaten red meat including processed meats and liver, or eaten raw fruits and vegetables within the 72 hours prior to or during the sample collection period?

☐ No

☐ Yes

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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
☐ Colonoscopy
☐ Rectal/pelvic examination
☐ Stool for ova and parasites
☐ Ultrasound of the abdomen
☐ Other, specify: _____

(Note: Complete colonoscopy must be performed for all randomized patients with a GIAE of concern and melena or a positive fecal occult blood test.)

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 fax results as soon as available and record tests in the Medical Procedures page of the CRF.

Investigator's Remarks: _____

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Supplemental Report
207499/156		[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

_ _ _ _

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Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Investigator
207499/156		[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

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

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

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Pharmaceuticals

Page	G1

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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) which cause concern or interfere with usual activity (including eating and sleeping) at any time during the study.

Report this gastrointestinal symptom(s) to the SB Medical Monitor by telephone within 24 hours of the first assessment and fax the completed Supplemental Gastrointestinal Adverse Experience Report within 24 hours of the first assessment.

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.

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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 on page 3) specify: _____

☐ Back

☐ Groin

☐ Shoulder tip

☐ Other, specify: _____

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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 and questions. If the patient has been randomized, the patient must be referred to a gastroenterologist for a complete colonoscopy.*

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

If female, is bloody stool possibly menstrual or uterine in origin? ☐ No ☐ Yes ☐ Not applicable

Does the patient presently have hemorrhoids? ☐ No ☐ Yes

Is the patient taking NSAIDS/ASA? ☐ No ☐ Yes

PHYSICAL EXAMINATION

	Present	Absent
Abdominal tenderness	☐	☐
Abdominal masses	☐	☐
Peritoneal signs	☐	☐

Other clinically significant GI physical examination findings, please specify: _____

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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.*

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[redacted]			

SUPPLEMENTAL REPORT FOR GASTROINTESTINAL ADVERSE EXPERIENCE

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

Was one of the tests positive?

☐ No

☐ Yes → *If 'Yes', and the patient has been randomized, please refer the patient to a gastroenterologist for a complete colonoscopy and answer the following questions.*

Has the patient had a nosebleed or bleeding gums in the 2 days prior to or during the fecal sample collection period?

☐ No

☐ Yes

If female, were the fecal samples collected during or within 3 days after a menstrual period?

☐ No

☐ Yes

☐ Not applicable

Does the patient have hemorrhoids?

☐ No

☐ Yes → If 'Yes', were the hemorrhoids bleeding when the fecal samples were collected?

☐ No

☐ Yes

Did the patient have blood in the urine when the fecal samples were collected?

☐ No

☐ Yes

Has the patient taken aspirin or other non-steroidal anti-inflammatory drugs within the 7 days prior to or during the sample collection?

☐ No

☐ Yes

Has the patient taken Vitamin C in excess of 250 mg from all sources, or eaten red meat including processed meats and liver, or eaten raw fruits and vegetables within the 72 hours prior to or during the sample collection period?

☐ No

☐ Yes

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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
☐ Colonoscopy
☐ Rectal/pelvic examination
☐ Stool for ova and parasites
☐ Ultrasound of the abdomen
☐ Other, specify: _____

(Note: Complete colonoscopy must be performed for all randomized patients with a GIAE of concern and melena or a positive fecal occult blood test.)

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 fax results as soon as available and record tests in the Medical Procedures page of the CRF.

Investigator's Remarks: _____

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Supplemental Report
207499/156		[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

_ _ _ _

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Investigator
207499/156		[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)

_____

_____

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Site Monitor's Signature _____ Date Submitted ☐☐ Day ☐☐ Month ☐☐ Yr

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

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

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Page	GF1

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[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:				
	☐	☐	☐	☐
	☐	☐	☐	☐
	☐	☐	☐	☐

SmithKline Beecham
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Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[redacted]			

SUPPLEMENTAL REPORT FOR GASTROINTESTINAL ADVERSE EXPERIENCE - FOLLOW UP

PHYSICAL EXAMINATION (*continued*)

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.*

SmithKline Beecham
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Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[redacted]			

SUPPLEMENTAL REPORT FOR GASTROINTESTINAL ADVERSE EXPERIENCE - FOLLOW UP

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

Was one of the tests positive?

☐ No

☐ Yes → *If 'Yes', and the patient has been randomized, please refer the patient to a gastroenterologist for a complete colonoscopy and answer the following questions.*

Has the patient had a nosebleed or bleeding gums in the 2 days prior to or during the fecal sample collection period?

☐ No

☐ Yes

If female, were the fecal samples collected during or within 3 days after a menstrual period?

☐ No

☐ Yes

☐ Not applicable

Does the patient have hemorrhoids?

☐ No

☐ Yes → If 'Yes', were the hemorrhoids bleeding when the fecal samples were collected?

☐ No

☐ Yes

Did the patient have blood in the urine when the fecal samples were collected?

☐ No

☐ Yes

Has the patient taken aspirin or other non-steroidal anti-inflammatory drugs within the 7 days prior to or during the sample collection?

☐ No

☐ Yes

Has the patient taken Vitamin C in excess of 250 mg from all sources, or eaten red meat including processed meats and liver, or eaten raw fruits and vegetables within the 72 hours prior to or during the sample collection period?

☐ No

☐ Yes

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[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
☐ Colonoscopy
☐ Rectal/pelvic examination
☐ Stool for ova and parasites
☐ Ultrasound of the abdomen
☐ Other, specify: _____

(Note: Complete colonoscopy must be performed for all randomized patients with a GIAE of concern and melena or a positive fecal occult blood test.)

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 fax results as soon as available and record tests in the Medical Procedures page of the CRF.

Investigator's Remarks: _____

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[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.

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Investigator
207499/156		[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*
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- *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)

_____

_____

_____

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_____

_____

Site Monitor's Signature _____ Date Submitted ☐☐ Day ☐☐ Month ☐☐ Yr

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

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

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[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:				
	☐	☐	☐	☐
	☐	☐	☐	☐
	☐	☐	☐	☐

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[redacted]			

SUPPLEMENTAL REPORT FOR GASTROINTESTINAL ADVERSE EXPERIENCE - FOLLOW UP

PHYSICAL EXAMINATION (*continued*)

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.*

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[redacted]			

SUPPLEMENTAL REPORT FOR GASTROINTESTINAL ADVERSE EXPERIENCE - FOLLOW UP

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

Was one of the tests positive?

☐ No

☐ Yes → *If 'Yes', and the patient has been randomized, please refer the patient to a gastroenterologist for a complete colonoscopy and answer the following questions.*

Has the patient had a nosebleed or bleeding gums in the 2 days prior to or during the fecal sample collection period?

☐ No

☐ Yes

If female, were the fecal samples collected during or within 3 days after a menstrual period?

☐ No

☐ Yes

☐ Not applicable

Does the patient have hemorrhoids?

☐ No

☐ Yes → If 'Yes', were the hemorrhoids bleeding when the fecal samples were collected?

☐ No

☐ Yes

Did the patient have blood in the urine when the fecal samples were collected?

☐ No

☐ Yes

Has the patient taken aspirin or other non-steroidal anti-inflammatory drugs within the 7 days prior to or during the sample collection?

☐ No

☐ Yes

Has the patient taken Vitamin C in excess of 250 mg from all sources, or eaten red meat including processed meats and liver, or eaten raw fruits and vegetables within the 72 hours prior to or during the sample collection period?

☐ No

☐ Yes

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[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
☐ Colonoscopy
☐ Rectal/pelvic examination
☐ Stool for ova and parasites
☐ Ultrasound of the abdomen
☐ Other, specify: _____

(Note: Complete colonoscopy must be performed for all randomized patients with a GIAE of concern and melena or a positive fecal occult blood test.)

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 fax results as soon as available and record tests in the Medical Procedures page of the CRF.

Investigator's Remarks: _____

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[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.

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Investigator
207499/156		[redacted]		

CRF TRACKING/REVIEW FORM

Please submit COMPLETE modules only. Do not submit whole blank modules.

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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	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

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

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[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:				
	☐	☐	☐	☐
	☐	☐	☐	☐
	☐	☐	☐	☐

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[redacted]			

SUPPLEMENTAL REPORT FOR GASTROINTESTINAL ADVERSE EXPERIENCE - FOLLOW UP

PHYSICAL EXAMINATION (*continued*)

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.*

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[redacted]			

SUPPLEMENTAL REPORT FOR GASTROINTESTINAL ADVERSE EXPERIENCE - FOLLOW UP

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

Was one of the tests positive?

☐ No

☐ Yes → *If 'Yes', and the patient has been randomized, please refer the patient to a gastroenterologist for a complete colonoscopy and answer the following questions.*

Has the patient had a nosebleed or bleeding gums in the 2 days prior to or during the fecal sample collection period?

☐ No

☐ Yes

If female, were the fecal samples collected during or within 3 days after a menstrual period?

☐ No

☐ Yes

☐ Not applicable

Does the patient have hemorrhoids?

☐ No

☐ Yes → If 'Yes', were the hemorrhoids bleeding when the fecal samples were collected?

☐ No

☐ Yes

Did the patient have blood in the urine when the fecal samples were collected?

☐ No

☐ Yes

Has the patient taken aspirin or other non-steroidal anti-inflammatory drugs within the 7 days prior to or during the sample collection?

☐ No

☐ Yes

Has the patient taken Vitamin C in excess of 250 mg from all sources, or eaten red meat including processed meats and liver, or eaten raw fruits and vegetables within the 72 hours prior to or during the sample collection period?

☐ No

☐ Yes

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[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
☐ Colonoscopy
☐ Rectal/pelvic examination
☐ Stool for ova and parasites
☐ Ultrasound of the abdomen
☐ Other, specify: _____

(Note: Complete colonoscopy must be performed for all randomized patients with a GIAE of concern and melena or a positive fecal occult blood test.)

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 fax results as soon as available and record tests in the Medical Procedures page of the CRF.

Investigator's Remarks: _____

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[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.

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Investigator
207499/156	[ ][ ][ ]	[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)

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_____

_____

Site Monitor's Signature _____ Date Submitted [ ][ ] [ ][ ] [ ][ ]
Day Month Yr

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

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

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Page	GF1

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[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:				
	☐	☐	☐	☐
	☐	☐	☐	☐
	☐	☐	☐	☐

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[redacted]			

SUPPLEMENTAL REPORT FOR GASTROINTESTINAL ADVERSE EXPERIENCE - FOLLOW UP

PHYSICAL EXAMINATION (*continued*)

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.*

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[redacted]			

SUPPLEMENTAL REPORT FOR GASTROINTESTINAL ADVERSE EXPERIENCE - FOLLOW UP

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

Was one of the tests positive?

☐ No

☐ Yes → *If 'Yes', and the patient has been randomized, please refer the patient to a gastroenterologist for a complete colonoscopy and answer the following questions.*

Has the patient had a nosebleed or bleeding gums in the 2 days prior to or during the fecal sample collection period?

☐ No

☐ Yes

If female, were the fecal samples collected during or within 3 days after a menstrual period?

☐ No

☐ Yes

☐ Not applicable

Does the patient have hemorrhoids?

☐ No

☐ Yes → If 'Yes', were the hemorrhoids bleeding when the fecal samples were collected?

☐ No

☐ Yes

Did the patient have blood in the urine when the fecal samples were collected?

☐ No

☐ Yes

Has the patient taken aspirin or other non-steroidal anti-inflammatory drugs within the 7 days prior to or during the sample collection?

☐ No

☐ Yes

Has the patient taken Vitamin C in excess of 250 mg from all sources, or eaten red meat including processed meats and liver, or eaten raw fruits and vegetables within the 72 hours prior to or during the sample collection period?

☐ No

☐ Yes

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[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
- ☐ Colonoscopy
- ☐ Rectal/pelvic examination
- ☐ Stool for ova and parasites
- ☐ Ultrasound of the abdomen
- ☐ Other, specify: _____

(Note: Complete colonoscopy must be performed for all randomized patients with a GIAE of concern and melena or a positive fecal occult blood test.)

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 fax results as soon as available and record tests in the Medical Procedures page of the CRF.

Investigator's Remarks: _____

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[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.

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Investigator
207499/156		[redacted]		_____

CRF TRACKING/REVIEW FORM

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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)

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Site Monitor's Signature _____ Date Submitted ☐☐ Day ☐☐ Month ☐☐ Yr

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

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

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[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:				
	☐	☐	☐	☐
	☐	☐	☐	☐
	☐	☐	☐	☐

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[redacted]			

SUPPLEMENTAL REPORT FOR GASTROINTESTINAL ADVERSE EXPERIENCE - FOLLOW UP

PHYSICAL EXAMINATION (*continued*)

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.*

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[redacted]			

SUPPLEMENTAL REPORT FOR GASTROINTESTINAL ADVERSE EXPERIENCE - FOLLOW UP

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

Was one of the tests positive?

☐ No

☐ Yes → *If 'Yes', and the patient has been randomized, please refer the patient to a gastroenterologist for a complete colonoscopy and answer the following questions.*

Has the patient had a nosebleed or bleeding gums in the 2 days prior to or during the fecal sample collection period?

☐ No

☐ Yes

If female, were the fecal samples collected during or within 3 days after a menstrual period?

☐ No

☐ Yes

☐ Not applicable

Does the patient have hemorrhoids?

☐ No

☐ Yes → If 'Yes', were the hemorrhoids bleeding when the fecal samples were collected?

☐ No

☐ Yes

Did the patient have blood in the urine when the fecal samples were collected?

☐ No

☐ Yes

Has the patient taken aspirin or other non-steroidal anti-inflammatory drugs within the 7 days prior to or during the sample collection?

☐ No

☐ Yes

Has the patient taken Vitamin C in excess of 250 mg from all sources, or eaten red meat including processed meats and liver, or eaten raw fruits and vegetables within the 72 hours prior to or during the sample collection period?

☐ No

☐ Yes

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[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
☐ Rectal/pelvic examination
☐ Ultrasound of the abdomen
☐ CT of abdomen
☐ Stool for ova and parasites
☐ Other, specify: _____
☐ Colonoscopy

(Note: Complete colonoscopy must be performed for all randomized patients with a GIAE of concern and melena or a positive fecal occult blood test.)

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 fax results as soon as available and record tests in the Medical Procedures page of the CRF.

Investigator's Remarks: _____

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[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.

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Investigator
207499/156		[redacted]		

CRF TRACKING/REVIEW FORM

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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)

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Site Monitor's Signature _____ Date Submitted ☐☐ Day ☐☐ Month ☐☐ Yr

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

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

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[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:				
	☐	☐	☐	☐
	☐	☐	☐	☐
	☐	☐	☐	☐

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[redacted]			

SUPPLEMENTAL REPORT FOR GASTROINTESTINAL ADVERSE EXPERIENCE - FOLLOW UP

PHYSICAL EXAMINATION (*continued*)

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.*

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[redacted]			

SUPPLEMENTAL REPORT FOR GASTROINTESTINAL ADVERSE EXPERIENCE - FOLLOW UP

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

Was one of the tests positive?

☐ No

☐ Yes → *If 'Yes', and the patient has been randomized, please refer the patient to a gastroenterologist for a complete colonoscopy and answer the following questions.*

Has the patient had a nosebleed or bleeding gums in the 2 days prior to or during the fecal sample collection period?

☐ No

☐ Yes

If female, were the fecal samples collected during or within 3 days after a menstrual period?

☐ No

☐ Yes

☐ Not applicable

Does the patient have hemorrhoids?

☐ No

☐ Yes → If 'Yes', were the hemorrhoids bleeding when the fecal samples were collected?

☐ No

☐ Yes

Did the patient have blood in the urine when the fecal samples were collected?

☐ No

☐ Yes

Has the patient taken aspirin or other non-steroidal anti-inflammatory drugs within the 7 days prior to or during the sample collection?

☐ No

☐ Yes

Has the patient taken Vitamin C in excess of 250 mg from all sources, or eaten red meat including processed meats and liver, or eaten raw fruits and vegetables within the 72 hours prior to or during the sample collection period?

☐ No

☐ Yes

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[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
☐ Colonoscopy
☐ Rectal/pelvic examination
☐ Stool for ova and parasites
☐ Ultrasound of the abdomen
☐ Other, specify: _____

(Note: Complete colonoscopy must be performed for all randomized patients with a GIAE of concern and melena or a positive fecal occult blood test.)

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 fax results as soon as available and record tests in the Medical Procedures page of the CRF.

Investigator's Remarks: _____

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[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.

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Investigator
207499/156		[redacted]		

CRF TRACKING/REVIEW FORM

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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)

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Site Monitor's Signature _____ Date Submitted ☐☐ Day ☐☐ Month ☐☐ Yr

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

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

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[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:				
	☐	☐	☐	☐
	☐	☐	☐	☐
	☐	☐	☐	☐

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[redacted]			

SUPPLEMENTAL REPORT FOR GASTROINTESTINAL ADVERSE EXPERIENCE - FOLLOW UP

PHYSICAL EXAMINATION (*continued*)

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.*

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[redacted]			

SUPPLEMENTAL REPORT FOR GASTROINTESTINAL ADVERSE EXPERIENCE - FOLLOW UP

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

Was one of the tests positive?

☐ No

☐ Yes → *If 'Yes', and the patient has been randomized, please refer the patient to a gastroenterologist for a complete colonoscopy and answer the following questions.*

Has the patient had a nosebleed or bleeding gums in the 2 days prior to or during the fecal sample collection period?

☐ No

☐ Yes

If female, were the fecal samples collected during or within 3 days after a menstrual period?

☐ No

☐ Yes

☐ Not applicable

Does the patient have hemorrhoids?

☐ No

☐ Yes → If 'Yes', were the hemorrhoids bleeding when the fecal samples were collected?

☐ No

☐ Yes

Did the patient have blood in the urine when the fecal samples were collected?

☐ No

☐ Yes

Has the patient taken aspirin or other non-steroidal anti-inflammatory drugs within the 7 days prior to or during the sample collection?

☐ No

☐ Yes

Has the patient taken Vitamin C in excess of 250 mg from all sources, or eaten red meat including processed meats and liver, or eaten raw fruits and vegetables within the 72 hours prior to or during the sample collection period?

☐ No

☐ Yes

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[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
☐ Rectal/pelvic examination
☐ Ultrasound of the abdomen
☐ CT of abdomen
☐ Stool for ova and parasites
☐ Other, specify: _____
☐ Colonoscopy

(Note: Complete colonoscopy must be performed for all randomized patients with a GIAE of concern and melena or a positive fecal occult blood test.)

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 fax results as soon as available and record tests in the Medical Procedures page of the CRF.

Investigator's Remarks: _____

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[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.

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Investigator
207499/156		[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)

_____

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Site Monitor's Signature _____ Date Submitted ☐☐ Day ☐☐ Month ☐☐ Yr

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

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

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[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:				
	☐	☐	☐	☐
	☐	☐	☐	☐
	☐	☐	☐	☐

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[redacted]			

SUPPLEMENTAL REPORT FOR GASTROINTESTINAL ADVERSE EXPERIENCE - FOLLOW UP

PHYSICAL EXAMINATION (*continued*)

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.*

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[redacted]			

SUPPLEMENTAL REPORT FOR GASTROINTESTINAL ADVERSE EXPERIENCE - FOLLOW UP

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

Was one of the tests positive?

☐ No

☐ Yes → *If 'Yes', and the patient has been randomized, please refer the patient to a gastroenterologist for a complete colonoscopy and answer the following questions.*

Has the patient had a nosebleed or bleeding gums in the 2 days prior to or during the fecal sample collection period?

☐ No

☐ Yes

If female, were the fecal samples collected during or within 3 days after a menstrual period?

☐ No

☐ Yes

☐ Not applicable

Does the patient have hemorrhoids?

☐ No

☐ Yes → If 'Yes', were the hemorrhoids bleeding when the fecal samples were collected?

☐ No

☐ Yes

Did the patient have blood in the urine when the fecal samples were collected?

☐ No

☐ Yes

Has the patient taken aspirin or other non-steroidal anti-inflammatory drugs within the 7 days prior to or during the sample collection?

☐ No

☐ Yes

Has the patient taken Vitamin C in excess of 250 mg from all sources, or eaten red meat including processed meats and liver, or eaten raw fruits and vegetables within the 72 hours prior to or during the sample collection period?

☐ No

☐ Yes

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[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
- ☐ Colonoscopy
- ☐ Rectal/pelvic examination
- ☐ Stool for ova and parasites
- ☐ Ultrasound of the abdomen
- ☐ Other, specify: _____

(Note: Complete colonoscopy must be performed for all randomized patients with a GIAE of concern and melena or a positive fecal occult blood test.)

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 fax results as soon as available and record tests in the Medical Procedures page of the CRF.

Investigator's Remarks: _____

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[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.

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Investigator
207499/156		[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*
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- *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	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

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

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[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:				
	☐	☐	☐	☐
	☐	☐	☐	☐
	☐	☐	☐	☐

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[redacted]			

SUPPLEMENTAL REPORT FOR GASTROINTESTINAL ADVERSE EXPERIENCE - FOLLOW UP

PHYSICAL EXAMINATION (*continued*)

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.*

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[redacted]			

SUPPLEMENTAL REPORT FOR GASTROINTESTINAL ADVERSE EXPERIENCE - FOLLOW UP

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

Was one of the tests positive?

☐ No

☐ Yes → *If 'Yes', and the patient has been randomized, please refer the patient to a gastroenterologist for a complete colonoscopy and answer the following questions.*

Has the patient had a nosebleed or bleeding gums in the 2 days prior to or during the fecal sample collection period?

☐ No

☐ Yes

If female, were the fecal samples collected during or within 3 days after a menstrual period?

☐ No

☐ Yes

☐ Not applicable

Does the patient have hemorrhoids?

☐ No

☐ Yes → If 'Yes', were the hemorrhoids bleeding when the fecal samples were collected?

☐ No

☐ Yes

Did the patient have blood in the urine when the fecal samples were collected?

☐ No

☐ Yes

Has the patient taken aspirin or other non-steroidal anti-inflammatory drugs within the 7 days prior to or during the sample collection?

☐ No

☐ Yes

Has the patient taken Vitamin C in excess of 250 mg from all sources, or eaten red meat including processed meats and liver, or eaten raw fruits and vegetables within the 72 hours prior to or during the sample collection period?

☐ No

☐ Yes

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[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
☐ Colonoscopy
☐ Rectal/pelvic examination
☐ Stool for ova and parasites
☐ Ultrasound of the abdomen
☐ Other, specify: _____

(Note: Complete colonoscopy must be performed for all randomized patients with a GIAE of concern and melena or a positive fecal occult blood test.)

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 fax results as soon as available and record tests in the Medical Procedures page of the CRF.

Investigator's Remarks: _____

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[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.

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Investigator
207499/156	[ ][ ][ ]	[redacted]	[ ][ ][ ][ ]	_____

CRF TRACKING/REVIEW FORM

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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)

_____

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_____

_____

Site Monitor's Signature _____ Date Submitted [ ][ ][ ] Day Month Yr

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

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

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[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:				
	☐	☐	☐	☐
	☐	☐	☐	☐
	☐	☐	☐	☐

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[redacted]			

SUPPLEMENTAL REPORT FOR GASTROINTESTINAL ADVERSE EXPERIENCE - FOLLOW UP

PHYSICAL EXAMINATION (*continued*)

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.*

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[redacted]			

SUPPLEMENTAL REPORT FOR GASTROINTESTINAL ADVERSE EXPERIENCE - FOLLOW UP

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

Was one of the tests positive?

☐ No

☐ Yes → *If 'Yes', and the patient has been randomized, please refer the patient to a gastroenterologist for a complete colonoscopy and answer the following questions.*

Has the patient had a nosebleed or bleeding gums in the 2 days prior to or during the fecal sample collection period?

☐ No

☐ Yes

If female, were the fecal samples collected during or within 3 days after a menstrual period?

☐ No

☐ Yes

☐ Not applicable

Does the patient have hemorrhoids?

☐ No

☐ Yes → If 'Yes', were the hemorrhoids bleeding when the fecal samples were collected?

☐ No

☐ Yes

Did the patient have blood in the urine when the fecal samples were collected?

☐ No

☐ Yes

Has the patient taken aspirin or other non-steroidal anti-inflammatory drugs within the 7 days prior to or during the sample collection?

☐ No

☐ Yes

Has the patient taken Vitamin C in excess of 250 mg from all sources, or eaten red meat including processed meats and liver, or eaten raw fruits and vegetables within the 72 hours prior to or during the sample collection period?

☐ No

☐ Yes

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[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
☐ Colonoscopy
☐ Rectal/pelvic examination
☐ Stool for ova and parasites
☐ Ultrasound of the abdomen
☐ Other, specify: _____

(Note: Complete colonoscopy must be performed for all randomized patients with a GIAE of concern and melena or a positive fecal occult blood test.)

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 fax results as soon as available and record tests in the Medical Procedures page of the CRF.

Investigator's Remarks: _____

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[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.

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Investigator
207499/156		[redacted]		

CRF TRACKING/REVIEW FORM

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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)

_____

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_____

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Site Monitor's Signature _____ Date Submitted ☐☐ Day ☐☐ Month ☐☐ Yr

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

CONFIDENTIAL

SmithKline Beecham
Pharmaceuticals

PROTOCOL 207499/156

BOOK 1 : SCREENING TO RANDOMIZATION

A RANDOMIZED, 24-WEEK, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY, SAFETY AND TOLERABILITY OF ARIFLO™ (15 MG BID) IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

GENERAL INSTRUCTIONS

- *Write clearly in capital letters using a ball point pen.*
- *Do not write in shaded areas*
- *Answer ALL questions on every page*
- *Enter "N/A" if information requested is not available*
- *Initial and date all changes, additions or deletions. Use a single pen stroke to remove an incorrect entry*
- *Enter the patient initials on all pages on which information has been entered and the patient number and center number where required*

DATE

Please use the following three-letter abbreviations for the months

January	JAN
February	FEB
March	MAR
April	APR
May	MAY
June	JUN
July	JUL
August	AUG
September	SEP
October	OCT
November	NOV
December	DEC

e.g. | 0 1 | J A N | 0 0 | = *1st January 2000*

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

PATIENT INITIALS

Please use the following format:

e.g. [redacted]

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*

STUDY PROCEDURES CHART 207499/156

Visit	1	2	3	3a	4	5	6	7	8	9	10		
Time relative to baseline (weeks)	Screen -4	-2	Baseline 0	+1	+2	+4	+8	+12	+16	+20	End Double-blind +24	Early Withdrawal[1]	Final Safety Follow-up +25
Signed written informed consent	x												
Medical & surgical history	x												
Physical examination[2]	x		x								x	x	x[3]
Pulmonary history & symptoms	x												
Postero-anterior chest radiograph[4]	x												
Exacerbation assessment/resource use	x	x	x	x	x	x	x	x	x	x	x	x	x
Medication history	x												
Overall breathlessness (modified Borg)	x	x	x		x	x	x	x	x	x	x		
Resting 12-lead ECG	x		x	x	x	x	x	x	x	x	x	x	x[3]
Vital signs (BP, HR)	x[5]	x	x[5]	x	x	x	x	x	x	x	x[5]	x[5]	x
Exercise Tolerance (6-Minute walk)	x	x	x			x	x	x	x	x	x	x	
Post-exercise SaO2 & breathlessness	x	x	x			x	x	x	x	x	x	x	
CO Diffusing Capacity (DLCO)[6]	x												
Albuterol reversibility[7]	x												
Laboratory tests	x		x[8]	x	x	x	x	x	x[9]	x[9]	x[8]	x[8]	x[3,9]
Dispense single-blind medication	x	x											
Albuterol Use		x	x	x	x	x	x	x	x	x	x		
Concomitant medication/medical procedures		x	x	x	x	x	x	x	x	x	x	x	x
PFTs (in absence of albuterol)[10]		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	
Baseline signs and symptoms/AEs[11]		x	x	x	x	x	x	x	x	x	x	x	x
Health status assessment: SGRQ			x					x			x	x	
Quality of life assessment: SF-36			x								x	x	
Cough and sputum assessments			x					x			x	x	
Pharmacokinetic evaluations[12]			x			x		x			x		
Arterial blood gas/SaO2[13]			x								x		
Hourly PFTs for 4 hrs post first/last dose [14]			x								x		
Dispense double-blind medication			x	x	x	x	x	x	x	x			
Investigator/Patient global assessment											x	x	
Study conclusion record												x	x

1 Patients who stop taking study medication between clinic visits will attend the clinic within 24 hours for an early withdrawal visit.

2 To include a respiratory examination.

3 If abnormalities at previous visit for patients who complete Visit 10 or withdraw from the study.

4 Postero-anterior chest X-ray must be performed at Visit 1 unless the film from a chest X-ray within the 12 weeks prior to Visit 1 is available to the Investigator.

5 Including Orthostatic vital signs.

6 DLCO should be done between Visit 1 and Visit 3 if not performed during the previous 24 weeks or if the results are unavailable.

7 Before and 15 to 30 (± 5) minutes after administration of 180 mcg albuterol via a MDI with a spacer to determine % predicted FEV_1, FVC, FEF_{25-75}, PEFR, and FEV_1: FVC.

8 In addition to usual laboratory tests, three fecal occult blood tests will be performed between Visits 1 and 3, between Visits 9 and 10, and at early withdrawal; amylase will be measured at Visit 3.

9 Urinary beta-HCG tests will be performed in females of childbearing potential. No other laboratory samples will be collected at Visits 8 and 9.

10 Includes FEV_1, FVC, FEF_{25-75}, PEFR, and FEV_1:FVC measured by centralized spirometry by the same person at each visit.

11 A diary will be used to record if patients feel different since starting study medication.

12 Visit 3: 3 hours post-dose. Visit 5: trough and 0.5-3 hours post-dose. Visit 7: trough and 3-10 hours post-dose. Visit 10: trough only.

13 In patients with <40% of predicted FEV_1 at Visit 1 and resting SaO_2 <88% or if the patient lives at a high altitude.

14 Pulmonary function tests 30 (± 5) minutes after albuterol followed by 4-hour post-double-blind drug assessments at Visits 3 and 10.

VISIT 1 - SCREENING

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Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

MOD1

Please do not split modules

Module 1 : Visit 1 Screening

CRF Pages 1 - 18

Unprocessed Forms : Within this module the following occur which will generate attachments that need to be brought in-house.

None

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Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	
207499/156		[redacted]			Visit 1 Screening

PRESENTATION TO CLINIC

Record time of presentation to clinic ☐☐ (24hr:min)

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?

☐ NA → Patient is not using beta$_2$ agonist.

☐ 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?

☐ NA → Patient is not using anticholinergic.

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: ☐☐☐ (Day Month Yr) ☐☐ (24hr:min)

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.

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:* ☐☐

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes

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Protocol		Patient Number	Patient Initials		Visit 1 Screening
207499/156		[redacted]			

CONSENT

Date of signed informed consent to participate in this study ☐☐ ☐☐☐ ☐☐ Day Month Yr

DEMOGRAPHY

Date of Birth ☐☐ ☐☐☐ ☐☐☐☐ Day Month Year

Gender
[M] ☐ Male
[F] ☐ Female

Race
[1] ☐ White
[2] ☐ Black
[3] ☐ Oriental
[4] ☐ Other → *specify:* _ _ _ _ _ _ _ _ _

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Protocol		Patient Number	Patient Initials		Visit 1 Screening
207499/156		[redacted]			

SIGNIFICANT MEDICAL/SURGICAL HISTORY AND PHYSICAL EXAMINATION
(INCLUDING RESPIRATORY EXAMINATION)

Is the patient suffering from or has he/she ever suffered from any **significant** medical or surgical condition, including any significant medical conditions detected during the physical examination?

☐ No

☑ Yes → *If 'Yes' please list below one diagnosis per line.*

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	[1] Past	[2] Ongoing
CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)			
For SB	☐☐☐☐	☐	☑
For SB	☐☐☐☐	☐	☐
For SB	☐☐☐☐	☐	☐
For SB	☐☐☐☐	☐	☐
For SB	☐☐☐☐	☐	☐
For SB	☐☐☐☐	☐	☐
For SB	☐☐☐☐	☐	☐
For SB	☐☐☐☐	☐	☐
For SB	☐☐☐☐	☐	☐

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Protocol		Patient Number	Patient Initials		Visit 1 Screening
207499/156		[redacted]			

SIGNIFICANT MEDICAL/SURGICAL HISTORY AND PHYSICAL EXAMINATION (cont)

Diagnosis	Year of first diagnosis	[1] Past	[2] Ongoing
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			
For SB			

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®
Selected short-acting inhaled $beta_2$-agonists	All **except** Ventolin®
Long-acting inhaled $beta_2$-agonists	Serevent®
Oral $beta_2$-agonists	Proventil®, Ventolin®, Volmax®, Brethine®
Nebulized $beta_2$-agonists	albuterol, metaproterenol, Alupent®, Isuprel®, Proventil®, Tornalate®, Ventolin®
Nebulized anticholinergics	Atrovent®
Inhaled cromolyn sodium	Intal®
Inhaled nedocromil	Tilade®
Oral xanthines	Slo-Bid®, Theo-Dur®
Leukotriene modifiers	Accolate®, Zyflo®, Singulair®
Mucolytics*	Mucomyst®, Mucosal®
Long-term oxygen therapy (LTOT)**	N/A

* Mucolytic administration should not be started during the study. Stable doses taken prior to study start may continue.

** 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. bid, prn)	**Route***	**Medical Illness/ Diagnosis** (or symptom in absence of a diagnosis)	**Start Date** (be as precise as possible) Day Mth Yr	**End Date** (or if Continuing mark box) Day Mth Yr	
TRADE NAME HERE	***200mcg***	***bid***	***IH***	***COPD***	15 JUN 00		✓
For SB							
							☐
For SB							

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Protocol		Patient Number	Patient Initials		Visit 1 Screening
207499/156		[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.*

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. 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.*

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Protocol		Patient Number	Patient Initials		Visit 1 Screening
207499/156		[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. 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 SB							

** For Route, see general instructions for acceptable abbreviations.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 1 Screening
207499/156		[redacted]			

AVERAGE ALCOHOL INTAKE

Number of units per week ☐☐

Note : A unit of alcohol is defined as 8 oz. (250 mL, half a pint) of beer, 4 oz. (125 mL, a medium-sized glass) of wine or 1 oz. (24mL, a measure) of spirits.

CHEST X-RAY

Perform a postero-anterior (PA) chest X-ray (unless one has been performed in the previous 12 weeks 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.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 1 Screening
207499/156		[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 or antibiotics, that required treatment to be prescribed by a physician, or for which the patient was hospitalized?

   ☐ 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	Patient Initials		Visit 1 Screening
207499/156		[redacted]			

HEALTHCARE RESOURCE UTILIZATION

1. COPD-related emergency department visits

   How many times did the patient go to the emergency room / Urgent Care Center for COPD treatment during the past year?

   [0] ☐ 0
   [1] ☐ 1
   [2] ☐ 2
   [3] ☐ 3 - 4
   [4] ☐ 5 or more

2. COPD-related hospitalization

   How many times was the patient admitted to the hospital for COPD treatment during the past year?

   [0] ☐ 0
   [1] ☐ 1
   [2] ☐ 2
   [3] ☐ 3 - 4
   [4] ☐ 5 or more

INDIRECT COST

Does the patient perform work for which they are paid?

☐ No

☐ Yes → *If 'Yes', on average, how many hours per **week** does the patient work?*

☐☐.☐ Hours

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Protocol		Patient Number	Patient Initials		Visit 1 Screening
207499/156		[redacted]			

OVERALL BREATHLESSNESS ASSESSMENT

Give the patient a copy of the following scale when assessing breathlessness.

Please ask the patient the following question and record the answer below.

"Generally speaking, how has your breathlessness been during the previous week when you carried out tasks that usually cause you to be short of breath (e.g. walking, carrying shopping, climbing stairs, etc)?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Overall breathlessness score ☐☐.☐

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 1 Screening
207499/156		[redacted]			

INVESTIGATOR INSTRUCTIONS

The following procedures (Vital Signs, ECG, and Exercise Tolerance Test) must be performed greater than 4 hours after the patient's last albuterol administration.

VITAL SIGNS

Height	Weight (light clothes, no shoes)	After Sitting for 5 Minutes	
		Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
☐ cm ☐ in	☐ kg ☐ lb	☐☐☐/☐☐☐	☐☐☐

Were any clinically significant abnormalities noted?

☐ No

☐ Yes → *Record on the Significant Medical/Surgical History and Physical Examination page*

VITAL SIGNS - ORTHOSTATIC CHANGE

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)
☐☐☐/☐☐☐	☐☐☐	☐☐☐/☐☐☐	☐☐☐

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 ≥10 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'.*

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Protocol		Patient Number	Patient Initials		Visit 1 Screening
207499/156		[redacted]			

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant abnormalities noted at this examination?

☐ No

☐ Yes → *If 'Yes', enter details on the Significant Medical/Surgical History and Physical Examination page.*

EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted? The distance walked should be entered even if the patient did not walk for 6 minutes.

☐ No

☐ Yes → *If 'Yes', Distance walked* ☐☐☐ [M] Meters ☐

[YD] Yards ☐

Record any adverse experiences which occur during the exercise tolerance test in the Baseline Signs and Symptoms section.

SmithKline Beecham Pharmaceuticals

Protocol	Patient Number	Patient Initials	Visit
207499/156	[redacted]		Visit 1 Screening

POST-EXERCISE ASSESSMENTS *(Immediately after the patient completes the exercise tolerance)*

Heart Rate ☐☐☐ beats/min

SaO_2 ☐☐☐ %

Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

"How short of breath do you feel right now?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Post-exercise breathlessness score ☐☐.☐

INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise test (rest for at least 10 minutes) before performing the pulmonary function tests.

CARBON MONOXIDE DIFFUSING CAPACITY (DLCO)

A carbon monoxide diffusing capacity test (DLCO) should be done if one has not been performed within the previous 24 weeks or the results are not available. DLCO assessments may be scheduled between Visits 1 and 3.

Date of DLCO test ☐☐ ☐☐ ☐☐ (Day Month Yr)

Mean DLCO ☐☐.☐☐

Units *(Mark appropriate)* ☐ $mL.min^{-1}.mmHg^{-1}$ ☐ $mmol.min^{-1}.kPa^{-1}$

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 1 Screening
207499/156		[redacted]			

PRE-ALBUTEROL 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 confirm that the pulmonary function tests were performed

[1] ☐ Not performed

[2] ☐ Performed

Is the patient's pre-albuterol 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-albuterol Pulmonary Function Tests.*

POST-ALBUTEROL PULMONARY FUNCTION TESTS

Provide the patient with an albuterol MDI and spacer. Administer 180 mcg (2 puffs) of albuterol via MDI with a spacer. Remind the patient to use this inhaler (with or without the spacer), rather than any albuterol inhaler they may have at home, for "as required" rescue-medication use during the study. ***Record the start date for this prn albuterol use in the Prior and Concomitant medication section.***

Record the time of albuterol inhalation ☐☐ 24hr:min

Wait 15 - 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 confirm that the pulmonary function tests were performed

[1] ☐ Not performed

[2] ☐ Performed

Does the patient have a ≤ 15% and/or ≤ 200 ml increase in FEV_1 after administration of albuterol?

☐ 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-albuterol 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

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Protocol		Patient Number	Patient Initials		Visit 1 Screening
207499/156		[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)*

SmithKline Beecham
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Protocol	Patient Number	Patient Initials	Visit 1 Screening
207499/156	[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. Patients with a clinical diagnosis of COPD, as defined by American Thoracic Society Guidelines (see Appendix G of the protocol).	☐	☐
3. Patients with a cigarette smoking history of ≥10 pack years (1 pack year = 20 cigarettes smoked per day for 1 year or the equivalent). Both current smokers and ex-smokers are eligible.	☐	☐
4. Patients with a pre-albuterol FEV_1 to FVC ratio (FEV_1:FVC) ≤ 0.7 at Visit 1 (Screening).	☐	☐
5. Patients with fixed airway obstruction, defined by ≤ 15% **or** ≤ 200 ml (or both) increase in FEV_1 after the administration of albuterol 180 mcg via MDI with a spacer at Visit 1 (Screening).	☐	☐
6. Patients with a post-albuterol FEV_1 between ≥30% and ≤ 70% of predicted normal for height, age and gender at Visit 1. Patients will be assessed 15 to 30 (± 5) minutes after receiving albuterol 180 mcg via MDI with a spacer.	☐	☐
7. Patients who give their signed written informed consent to participate.	☐	☐

Do not admit the patient to this study if any "NO" box has been marked.

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Protocol		Patient Number	Patient Initials		Visit 1 Screening
207499/156		[redacted]			

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. Patients with poorly controlled COPD, defined as the occurrence of any of the following in the 2 weeks prior to Visit 1: acute worsening of COPD that is managed by the patient at home by self-treatment with corticosteroids or antibiotics, that requires treatment prescribed by a physician, or for which the patient is hospitalized.	☐	☐
4. Patients with active tuberculosis, lung cancer, or clinically overt bronchiectasis.	☐	☐
5. Patients with clinically significant cardiovascular, neurological, renal, endocrine, or hematological abnormalities that are uncontrolled on permitted therapy.	☐	☐
6. Patients with clinically significant gastrointestinal or hepatic abnormalities.	☐	☐
7. Patients with clinically significant orthostatic changes in blood pressure or heart rate at Visit 1 (Protocol Section 5.4.2).	☐	☐
8. Patients with a history of hypersensitivity to PDE4 inhibitors.	☐	☐
9. Patients with a history (or suspected history) of alcohol misuse or any other recreational substance abuse.	☐	☐
10. Patients who require treatment with inhaled cromolyn sodium or nedocromil, inhaled long-acting $beta_2$-agonists, oral $beta_2$-agonists, nebulized $beta_2$-agonists, nebulized anticholinergics, xanthines, leukotriene modifiers or oral/inhaled corticosteroids beyond Visit 1. All COPD medications except anticholinergic medication or albuterol via MDI should be withdrawn prior to or at Visit 1 (Screening).	☐	☐
11. Patients receiving treatment with long term oxygen therapy (LTOT), patients who require supplemental oxygen more often than on an occasional (prn) basis, or patients who require nocturnal positive pressure for sleep apnea.	☐	☐
12. Patients who have participated in a Pulmonary Rehabilitation Program within 4 weeks prior to Visit 1 (Screening) or who will enter a Pulmonary Rehabilitation Program during the study.	☐	☐
13. Patients 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).	☐	☐
14. Patients who have previously participated in an Ariflo (SB 207499) study and who received randomized study medication.	☐	☐
15. Patients unable to comply with study procedures (including completion of the health status questionnaires).	☐	☐

Do not admit the patient to this study if any "YES" box has been marked.
Additional Exclusion Criteria will be evaluated at Visit 3.

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 1

- *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 a diary card and remind the patient to use the card to record if they feel differently since starting the study.*

    - *Issue the patient the fecal occult blood test kit. Instruct the patient to follow the Patient Instructions provided with the kit. 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 10am + / - 2 hours.*

    - ***Remind the patient:***

        i *__not__ to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit (eg if study medication is taken at 08:00, the visit must be 16:00 or later).*

        ii *to refrain from using albuterol or anticholinergic agents during the **4 hours** immediately preceding the 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 albuterol inhaler and spacer, and the diary card.*

        v *to continue to take the anticholinergic medication, if prescribed, at a constant dose.*

        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, diarrhea, 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	Patient Initials		Visit 1 Screening
207499/156		[redacted]			

STUDY MEDICATION LABEL

Register the patient with SB's Registration and Medication Ordering System (RAMOS) by calling 1-866-726-6760. Issue the patient 20 days supply of **single-blind study medication** (2 bottles). The first 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.

Attach the tear-off labels from the study medication bottles 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	Attach label here

Date and time visit dose was taken ____ ____ ____ (Day Month Yr) ____ ____ (24hr:min)

PATIENT ACTIVITY POSTCARD

Please complete the patient activity postcard for ***Visit 1 Screening*** located in the postcard section of this CRF. Detach the postcard and mail promptly. Postage has been prepaid.

VISIT 2, WEEK -2
SINGLE-BLIND RUN-IN

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

MOD2

Please do not split modules

Module 2 : Visit 2, Visit 3 (Pre-Randomization), Baseline Signs and Symptoms, Concomitant Medications, Medical Procedures, COPD Exacerbations, Resource Utilization

CRF Pages 19 - 63

Unprocessed Forms : Within this module the following occur which will generate attachments that need to be brought in-house.

None

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Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	Visit 2 Single-blind Run-in Week -2
207499/156		[redacted]			

PRESENTATION TO CLINIC

Record time of presentation to clinic ☐☐ 24hr:min

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?

☐ NA → Patient is not using beta$_2$ agonist.

☐ 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?

☐ NA → Patient is not using anticholinergic.

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: ☐☐☐ 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 : ☐☐

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 2 Single-blind Run-in Week -2
207499/156		[redacted]			

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes ⟶ If 'Yes' please record details below.

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

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

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

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of excerbation (maximum level)	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1
	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2
	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3

If a patient experienced a COPD exacerbation that was treated with corticosteroids or antibiotics, 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.

RESOURCE UTILIZATION

If the patient has received any COPD exacerbation-related medical care since the last visit, record details in the Resource Utilization section at the back of this module.

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 2 Single-blind Run-in Week -2
207499/156		[redacted]			

INDIRECT COST

Does the patient work?

☐ No

☐ Yes → *If 'Yes'*, has the patient missed work due to COPD-related symptoms, excluding scheduled protocol visits, since the last visit?

☐ No

☐ Yes → *If 'Yes', please record lost work days below:*

Start Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence

How many days since your last visit have you been restricted in performing your leisure activities, due to your COPD-related symptoms? *(please enter number of days below, if not restricted, enter 0)*

☐☐ Days

Since your last visit, how many hours per week did you require paid or unpaid assistance by a relative, friend or professional with your daily activities such as dressing, bathing, cooking, etc., due to your COPD-related symptoms? *(please enter number of hours below, if no paid or unpaid assistance, enter 0 in each instance)*

☐☐☐ Hours per week of **paid** assistance

☐☐☐ Hours per week of **unpaid** assistance

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 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.

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 2 Single-blind Run-in Week -2
207499/156		[redacted]			

"AS NEEDED" ALBUTEROL USE

Record the patient's evaluation of their 'as needed' albuterol use since the last visit.

[1] ☐ Much less than usual
[2] ☐ Less than usual
[3] ☐ About the same as usual
[4] ☐ More than usual
[5] ☐ Much more than usual

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.

FECAL OCCULT BLOOD TEST

The fecal 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.

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

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'.

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Protocol		Patient Number	Patient Initials		Visit 2 Single-blind Run-in Week -2
207499/156		[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. bid)

Date and time of last dose of study medication prior to the study visit ☐☐ ☐☐☐ ☐☐ Day Month Yr ☐☐ 24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
40	☐☐	☐☐	☐☐	☐☐	☐☐☐

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance ≥ 80% and ≤120%?

☐ No → *If 'No' please remind the patient of the importance of taking the medication according to the protocol.*

☐ Yes

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Protocol	Patient Number	Patient Initials	Visit 2 Single-blind Run-in Week -2
207499/156	[redacted]		

OVERALL BREATHLESSNESS ASSESSMENT

Give the patient a copy of the following scale when assessing breathlessness.

Please ask the patient the following question and record the answer below.

"Generally speaking, how has your breathlessness been during the previous week when you carried out tasks that usually cause you to be short of breath (e.g. walking, carrying shopping, climbing stairs, etc)?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Overall breathlessness score ☐☐.☐

PULMONARY REHABILITATION PROGRAM

Has the patient entered a Pulmonary Rehabilitation Program since the last visit?

☐ No

☐ Yes

INVESTIGATOR INSTRUCTIONS

The following procedures (Vital Signs and Exercise Tolerance Test) must be performed more than 4 hours after the patient's last albuterol administration.

SmithKline Beecham Pharmaceuticals

Protocol	Patient Number	Patient Initials	Visit 2 Single-blind Run-in Week -2
207499/156	[redacted]		

VITAL SIGNS

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 module.*

EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted? The distance walked should be entered even if the patient did not walk for 6 minutes.

☐ No

☐ Yes → *If 'Yes', Distance walked* ☐☐☐ Meters ☐

Yards ☐

Record any adverse experiences which occur during the exercise tolerance test in the Baseline Signs and Symptoms section.

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Protocol		Patient Number	Patient Initials		Visit 2 Single-blind Run-in Week -2
207499/156		[redacted]			

POST-EXERCISE ASSESSMENTS *(Immediately after the patient completes the exercise tolerance)*

Heart Rate ☐☐☐ beats/min

SaO_2 ☐☐☐ %

Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

"How short of breath do you feel right now?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Post-exercise breathlessness score ☐☐.☐

INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise tolerance test (rest for at least 10 minutes) before performing the pulmonary function tests.

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Protocol		Patient Number	Patient Initials		Visit 2 Single-blind Run-in Week -2
207499/156		[redacted]			

PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed at least 4 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 confirm that the pulmonary function tests were performed

[1] ☐ Not performed

[2] ☐ Performed

Has the patient's absolute value of FEV$_1$ increased or decreased by > 20% between Visits 1 and 2?

☐ No

☐ Yes ⟶ *If 'Yes please withdraw the patient and complete the Study Continuation/Withdrawal page at the back of this book.*

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 2

- *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 a new diary card and remind the patient to use the card to record if they feel differently since starting the study.*

    - *Ask the patient to return for the next visit in 14 +/- 3 days at 10:00 +/- 2 hours.*

    - ***Remind the patient:***

        i *__not__ to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).*

        ii *to refrain from using albuterol or anticholinergic agents during the **4 hours** immediately preceding the 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 albuterol inhaler and spacer, and the diary card.*

        v *to continue to take the anticholinergic medication, if prescribed, at a constant dose.*

        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, diarrhea, 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 fecal occult blood test(s) by the next visit if not already done.*

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Protocol		Patient Number	Patient Initials		Visit 2 Single-blind Run-in Week -2
207499/156		[redacted]			

STUDY MEDICATION LABEL

Issue the patient 20 days supply of **single-blind study medication** (2 bottles) and an albuterol MDI and spacer for 'as required' use if applicable (remind the patient to use this inhaler rather than any albuterol inhaler they may have at home). The first 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.

Attach the tear-off labels from the study medication bottles 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

Attach label here

Date and time visit dose was taken ☐☐☐☐☐☐ ☐☐
Day Month Yr 24hr:min

PATIENT ACTIVITY POSTCARD

Please complete the patient activity postcard for ***Visit 2 Single Blind Run-In*** located in the postcard section of this CRF. Detach the postcard and mail promptly. Postage has been prepaid.

VISIT 3, DAY 1
BASELINE
(PRE-RANDOMIZATION)

(PRE-RANDOMIZATION)

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	Visit 3 Baseline Pre-randomization Day1
207499/156		[redacted]			

PRESENTATION TO CLINIC

Record time of presentation to clinic ☐☐ 24hr:min

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?

☐ NA → Patient is not using beta$_2$ agonist.

☐ 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?

☐ NA → Patient is not using anticholinergic.

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: ☐☐☐ 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 : ☐☐

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes

ST. GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

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

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Protocol		Patient Number	Patient Initials		Visit 3
207499/156		[redacted]			

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. US version adapted and modified with permission by Judith Barr, Sc.D., Northeastern Univ., Boston, MA.

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Protocol		Patient Number	Patient Initials		Visit 3
207499/156		[redacted]			

SF - 36 (HEALTH STATUS QUESTIONNAIRE) (Page 1 of 5)

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Protocol		Patient Number	Patient Initials		Visit 3 Baseline Pre-randomization Day1
207499/156		[redacted]			

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes → *If 'Yes' please record details below.*

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

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

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

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of excerbation (maximum level)	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1
	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2
	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3

If a patient experienced a COPD exacerbation that was treated with corticosteroids or antibiotics, 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.

RESOURCE UTILIZATION

Please complete the COPD Resource Utilization section at the back of this module.

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 3 Baseline Pre-randomization Day1
207499/156		[redacted]			

INDIRECT COST

Does the patient work?

☐ No

☐ Yes → *If 'Yes'*, has the patient missed work due to COPD-related symptoms, excluding scheduled protocol visits, since the last visit?

☐ No

☐ Yes → *If 'Yes', please record lost work days below:*

Start Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence

How many days since your last visit have you been restricted in performing your leisure activities, due to your COPD-related symptoms? *(please enter number of days below, if not restricted, enter 0)*

☐☐ Days

Since your last visit, how many hours per week did you require paid or unpaid assistance by a relative, friend or professional with your daily activities such as dressing, bathing, cooking, etc., due to your COPD-related symptoms? *(please enter number of hours below, if no paid or unpaid assistance, enter 0 in each instance)*

☐☐☐ Hours per week of **paid** assistance

☐☐☐ Hours per week of **unpaid** assistance

BASELINE SIGNS AND SYMPTOMS

Please complete the Baseline Signs and Symptoms 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 Baseline Signs and Symptoms section at the back of this module. The patient should refer to the notes in their diary when answering this question.

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 3 Baseline Pre-randomization Day1
207499/156		[redacted]			

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.

"AS NEEDED" ALBUTEROL USE

Record the patient's evaluation of their 'as needed' albuterol use since the last visit.

[1] ☐ Much less than usual
[2] ☐ Less than usual
[3] ☐ About the same as usual
[4] ☐ More than usual
[5] ☐ Much more than usual

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.

FECAL OCCULT BLOOD TEST

If not completed previously, record results from the test(s) in the Fecal Occult Blood Test section in Visit 2.

Has the patient had a positive fecal 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 module.*

SmithKline Beecham
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Protocol		Patient Number	Patient Initials		Visit 3 Baseline Pre-randomization Day1
207499/156		[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. bid)

Date and time of last dose of study medication prior to the study visit ☐☐☐☐☐☐ Day Month Yr ☐☐☐☐ 24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
40	☐☐	☐☐	☐☐	☐☐	☐☐☐

Note: If this is a morning visit, patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance ≥ 80% and ≤120%?

☐ No → *If 'No' please withdraw the patient and complete the Study Continuation/Withdrawal page at the back of this book.*

☐ Yes

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Protocol		Patient Number	Patient Initials		Visit 3 Baseline Pre-randomization Day1
207499/156		[redacted]			

OVERALL BREATHLESSNESS ASSESSMENT

Give the patient a copy of the following scale when assessing breathlessness.

Please ask the patient the following question and record the answer below.

"Generally speaking, how short of breath have you been during the previous week when you carried out tasks that usually cause you to be short of breath (e.g. walking, carrying shopping, climbing stairs, etc)?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Overall breathlessness score ☐☐.☐

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 3 Baseline Pre-randomization Day1
207499/156		[redacted]			

COUGH AND SPUTUM PRODUCTION ASSESSMENTS

*Please ask the patient the following questions and record the answers below (Mark **one** box per section only.)*

COUGH

How troubled have you been by cough today?

[0] ☐ No symptoms at all

[1] ☐ Some symptoms, but hardly noticeable

[2] ☐ Symptoms noticeable and a little uncomfortable

[3] ☐ Symptoms definitely noticeable and uncomfortable

[4] ☐ Symptoms very bad and extremely uncomfortable

SPUTUM PRODUCTION

How much sputum have you produced today?

[0] ☐ No sputum at all

[1] ☐ Some sputum, but not as much as usual

[2] ☐ As much as usual

[3] ☐ More than usual

[4] ☐ A lot more than usual

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 Exercise Tolerance Test) must be performed greater than 4 hours after the patient's last albuterol administration.

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Protocol		Patient Number	Patient Initials		Visit 3 Baseline Pre-randomization Day1
207499/156		[redacted]			

VITAL SIGNS

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 module.*

VITAL SIGNS - ORTHOSTATIC CHANGE

1st Measurement: After 5 Minutes Supine

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
☐☐☐/☐☐☐	☐☐☐

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
☐☐☐/☐☐☐	☐☐☐

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 ≥ 10 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	Patient Initials		Visit 3 Baseline Pre-randomization Day1
207499/156		[redacted]			

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant changes noted at this examination compared to Screening?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Baseline Signs and Symptoms section at the back of this module.*

RESTING SaO_2

Measure Resting SaO_2 by pulse oximetry for all patients with an FEV_1 < 40% of predicted for age, height and gender at Visit 1.

[1] ☐ Measurement not required (patient's FEV_1 at Visit 1 ≥ 40% of predicted)

[2] ☐ Measurement required but not performed

[3] ☐ Measurement taken, *please record value below:*

Resting SaO_2 ☐☐☐ %

EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted? The distance walked should be entered even if the patient did not walk for 6 minutes.

☐ No

☐ Yes → *If 'Yes', Distance walked* ☐☐☐ Meters [M] ☐

Yards [YD] ☐

Record any adverse experiences which occur during the exercise tolerance test in the Baseline Signs and Symptoms section at the back of this module.

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 3 Baseline Pre-randomization Day1
207499/156		[redacted]			

POST-EXERCISE ASSESSMENTS *(Immediately after the patient completes the exercise tolerance test)*

Heart Rate ☐☐☐ beats/min

SaO_2 ☐☐☐ %

Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

"How short of breath do you feel right now?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Post-exercise breathlessness score ☐☐.☐

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 3 Baseline Pre-randomization Day1
207499/156		[redacted]			

INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise tolerance test (rest for at least 10 minutes) before performing the pulmonary function tests.

PULMONARY FUNCTION TESTS - PRE-ALBUTEROL

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 randomized, additional pulmonary function tests will be performed after a dose of study albuterol is given in the clinic (Book 2) AND prior to the first dose of randomized 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 confirm that the pulmonary function tests were performed

[1] ☐ Not performed

[2] ☐ Performed

RANDOMIZATION CRITERION

Has the patient's absolute value of FEV$_1$ increased or decreased by > 20% between Visits 1 and 3?

☐ Yes → *If 'Yes' please withdraw the patient and complete the Study Continuation/Withdrawal page at the back of this book.*

☐ No

ADDITIONAL EXCLUSION CRITERIA

Complete the following exclusion criteria.	Yes	No
1. The patient has had a positive fecal occult blood test result between Visit 1 and 3.	☐	☐
2. The patient has a clinically significant orthostatic change in blood pressure or heart rate at Visit 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.

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 is 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 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 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

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156					

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)

If no baseline events prior to randomization into study please mark this box ☐

Baseline Event *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***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 randomization	[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 Concomitant Medication and/or Medical Procedures section if appropriate*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific event?	☐ Yes ☐ No	☐ Yes ☐ No

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		
207499/156		[redacted]			

BASELINE SIGNS AND SYMPTOMS (or events, or diagnoses) - Continued

*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)

If no baseline events prior to randomization into study please mark this box ☐

Baseline Event *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***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 randomization	[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 Concomitant Medication and/or Medical Procedures section if appropriate*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific event?	☐ Yes ☐ No	☐ Yes ☐ No

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		
207499/156		[redacted]			

BASELINE SIGNS AND SYMPTOMS (or events, or diagnoses) - Continued

*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)

If no baseline events prior to randomization into study please mark this box ☐

Baseline Event *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***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 randomization	[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 Concomitant Medication and/or Medical Procedures section if appropriate*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific event?	☐ Yes ☐ No	☐ Yes ☐ No

CONCOMITANT MEDICATION
excluding treatment for COPD Exacerbations
(These are recorded in the COPD Exacerbations section)

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[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 (albuterol) 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 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 Route, see General Instructions for acceptable abbreviations.*

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[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 (albuterol) 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 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 Route, see General Instructions for acceptable abbreviations.*

MEDICAL PROCEDURES
excluding treatment for COPD Exacerbations
(These are recorded in the COPD Exacerbations section)

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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			

COPD EXACERBATION SECTION

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[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***

If no COPD Exacerbations prior to randomization please mark this box. ☐

Baseline Event	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***If patient died, STOP: go to SAE COPD Exacerbation pages.***	[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) *See definitions page for Baseline Signs & Symptoms form.*	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Relationship to study procedures performed prior to randomization	[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 on the COPD Medications or Procedures page*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific event prior to randomization?	☐ Yes ☐ No	☐ Yes ☐ No

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

DETAILS OF COPD EXACERBATIONS - CONTINUED

*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***

If no COPD Exacerbations prior to randomization please mark this box. ☐

Baseline Event	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***If patient died, STOP: go to SAE COPD Exacerbation pages.***	[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) *See definitions page for Baseline Signs & Symptoms form.*	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Relationship to study procedures performed prior to randomization	[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 on the COPD Medications or Procedures page*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific event prior to randomization?	☐ Yes ☐ No	☐ Yes ☐ No

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 minimize 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	Center Number	Patient Number	Patient Initials
207499/156		[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

Specify reason(s) for considering this a serious AE. Mark all that apply.

- [1] ☐ fatal
- [2] ☐ life threatening
- [3] ☐ disabling/incapacitating
- [4] ☐ results in hospitalization (excluding elective surgery or routine clinical procedures)
- [5] ☐ hospitalization 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 COPD Concomitant Medication section* — ☐ Yes ☐ No

Was patient withdrawn due to this specific SAE ? — ☐ Yes ☐ No

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 randomization code broken at investigational site? ☐ No ☐ Yes

Randomization 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 _____

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible) Day Mth Yr	End Date (or if Continuing mark box) Day Mth Yr	
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							

* For Route, see General Instructions for acceptable abbreviations.

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			

RESOURCE UTILIZATION

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

RESOURCE UTILIZATION

Has the patient utilized any COPD Exacerbation-related medical care between Visits 1 and 3?

☐ No

☐ Yes → *If 'Yes', please record details below*

Has the patient had any **Physician Visits** (COPD care excluding scheduled protocol visits) between Visits 1 and 3?

☐ No

☐ Yes → *If 'Yes', please record details below*

Date of Visit Day Mth Yr	Reason for Visit

Has the patient had any **Emergency Room (ER)/Urgent Care Visits/Procedures (i.e., lung surgery)** between Visits 1 and 3?

☐ No

☐ Yes → *If 'Yes', please record details below*

Date of Visit Day Mth Yr	Reason for Visit	Patient Admitted from ER? Yes	No
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

RESOURCE UTILIZATION - (cont)

Has the patient had any **Hospitalizations** between Visits 1 and 3?

☐ No

☐ Yes → *If 'Yes', please record details below* ***(also record details of any hospitalization in the Serious Adverse Experience - COPD Exacerbation section)***

Name of Hospital & City	Date of Admission Day Mth Yr	Date of Discharge Day Mth Yr	Reason for Admission

Has the patient had any **Intensive Care Unit (ICU) stays** ***(did the patient stay in the ICU during any of the above hospitalizations?)*** between Visits 1 and 3?

☐ 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

STUDY CONTINUATION / WITHDRAWAL

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

CONC1

Please do not split modules

Module: Study Continuation / Withdrawal

CRF Pages: 64

Unprocessed Forms: Within this module, the following occur which will generate attachments that need to be brought in-house.

None

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156			

STUDY CONTINUATION/WITHDRAWAL

Is the patient continuing into the double-blind treatment phase of the study?

☐ Yes → *If 'Yes' please sign in the appropriate space below and continue immediately to Book 2.*

☐ No → *If 'No' please mark the **PRIMARY** cause of withdrawal and sign the box below.*

[1] ☐ Baseline sign/symptom (complete BS&S form)

[10] ☐ Does not meet inclusion/exclusion criteria

[3] ☐ Protocol deviation (including non-compliance)

[4] ☐ Lost to follow-up

[5] ☐ Other - specify: _____

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

PATIENT ACTIVITY POSTCARD

Please complete the patient activity postcard for ***Visit 3 Pre-randomization***, located in the postcard section of this CRF. Detach the postcard and mail promptly. Postage has been prepaid.

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	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

SAE1

Please do not split modules

Module: Serious Adverse Experiences

CRF Pages: 65 - 66

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	SB Receipt Date Day Month Year
207499/156		[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 hospitalization (excluding elective surgery or routine clinical procedures)
[5] ☐ hospitalization 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 section
☐ Yes ☐ No

Was patient withdrawn due to this specific SAE ?
☐ Yes ☐ No

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 randomization code broken at investigational site? ☐ No ☐ Yes

Randomization 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 _____

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

FORMD1

Please do not split modules

Module: Form D

CRF Pages: 67

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

FORM D

Certified Cause of Death _____

Date of Death Day Month Yr → *Please complete Serious Adverse Experience section.*

Was a post-mortem examination carried out?

☐ No

☐ Yes → *If 'Yes' please summarize findings (include diagnosis):*

_____

_____

_____

_____

Reporting Physician's Signature _____ Date Day Month Yr

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		OPTIONAL Repeat Lab
207499/156		[redacted]			

RPLAB1

Please do not split modules

Module: Repeat Lab

CRF Pages: 68

Unprocessed Forms: Within this module, the following tests / procedures occur which may generate attachments.

None

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		OPTIONAL Repeat Lab
207499/156		[redacted]			

REPEAT 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.*

REPEAT 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	Center Number	Patient Number	Patient Initials	Investigator
207499/156		[redacted]		

CRF TRACKING/REVIEW FORM

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 - 18	☐	☐	
MOD2	V2, V3, BSS, CM, MP, COPD, RU	19 - 63	☐	☐	
CONC1	Continuation/Withdrawal	64	☐	☐	
SAE1	Serious Adverse Experiences	65 - 66	☐	☐	
FORMD1	Form D	67	☐	☐	
RPLAB1	Repeat Labs	68	☐	☐	

If multiple modules are submitted together, please ensure they are sorted according to the order above

Site Monitor's Comments (e.g. protocol violations or deviations)

Site Monitor's Signature _____ Date Submitted ☐☐ Day ☐☐ Month ☐☐ Yr

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

CONFIDENTIAL

SmithKline Beecham
Pharmaceuticals

PROTOCOL 207499/156

BOOK 2 : RANDOMIZATION TO VISIT 7

A RANDOMIZED, 24-WEEK, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY, SAFETY AND TOLERABILITY OF ARIFLO™ (15 MG BID) IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

Attach pharmacokinetic sampling group identification label here

GENERAL INSTRUCTIONS

- *Write clearly in capital letters using a black ball point pen and press firmly so that all copies are legible*
- *Do not write in shaded areas*
- *Answer ALL questions on every page*
- *Enter "N/A" if information requested is not available*
- *Initial and date all changes, additions or deletions. Use a single pen stroke to remove an incorrect entry*
- *Enter the patient initials on all pages on which information has been entered and the patient number and center number where required*

Do not enter additional data/information after the set of CRF pages has been split/separated

The cover flap or plastic writing board should be used to divide each set of pages before writing on them with a ball point pen

DATE

Please use the following three-letter abbreviations for the months

January	JAN
February	FEB
March	MAR
April	APR
May	MAY
June	JUN
July	JUL
August	AUG
September	SEP
October	OCT
November	NOV
December	DEC

e.g. | 0 | 1 | J | A | N | 0 | 0 | = *1st January 2000*

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

PATIENT INITIALS

Please use the following format:

e.g. [redacted]

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*

STUDY PROCEDURES CHART 207499/156

Visit	1	2	3	3a	4	5	6	7	8	9	10		
	Screen		Baseline								End Double-blind	Early Withdrawal[1]	Final Safety Follow-up
Time relative to baseline (weeks)	-4	-2	0	+1	+2	+4	+8	+12	+16	+20	+24		+25
Signed written informed consent	x												
Medical & surgical history	x												
Physical examination[2]	x		x								x	x	x[3]
Pulmonary history & symptoms	x												
Postero-anterior chest radiograph[4]	x												
Exacerbation assessment/resource use	x	x	x	x	x	x	x	x	x	x	x	x	x
Medication history	x												
Overall breathlessness (modified Borg)	x	x	x		x	x	x	x	x	x	x		
Resting 12-lead ECG	x		x	x	x	x	x	x	x	x	x	x	x[3]
Vital signs (BP, HR)	x[5]	x	x[5]	x	x	x	x	x	x	x	x[5]	x[5]	x
Exercise Tolerance (6-Minute walk)	x	x	x			x	x	x	x	x	x	x	
Post-exercise SaO2 & breathlessness	x	x	x			x	x	x	x	x	x	x	
CO Diffusing Capacity (DLCO)[6]	x												
Albuterol reversibility[7]	x												
Laboratory tests	x		x[8]	x	x	x	x	x	x[9]	x[9]	x[8]	x[8]	x[3,9]
Dispense single-blind medication	x	x											
Albuterol Use		x	x	x	x	x	x	x	x	x	x		
Concomitant medication/medical procedures		x	x	x	x	x	x	x	x	x	x	x	x
PFTs (in absence of albuterol)[10]		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	
Baseline signs and symptoms/AEs[11]		x	x	x	x	x	x	x	x	x	x	x	x
Health status assessment: SGRQ			x					x			x	x	
Quality of life assessment: SF-36			x								x	x	
Cough and sputum assessments			x					x			x	x	
Pharmacokinetic evaluations[12]			x			x		x			x		
Arterial blood gas/SaO2[13]			x								x		
Hourly PFTs for 4 hrs post first/last dose [14]			x								x		
Dispense double-blind medication			x	x	x	x	x	x	x	x			
Investigator/Patient global assessment											x	x	
Study conclusion record												x	x

1 Patients who stop taking study medication between clinic visits will attend the clinic within 24 hours for an early withdrawal visit.

2 To include a respiratory examination.

3 If abnormalities at previous visit for patients who complete Visit 10 or withdraw from the study.

4 Postero-anterior chest X-ray must be performed at Visit 1 unless the film from a chest X-ray within the 12 weeks prior to Visit 1 is available to the Investigator.

5 Including Orthostatic vital signs.

6 DLCO should be done between Visit 1 and Visit 3 if not performed during the previous 24 weeks or if the results are unavailable.

7 Before and 15 to 30 (± 5) minutes after administration of 180 mcg albuterol via a MDI with a spacer to determine % predicted FEV_1, FVC, FEF_{25-75}, PEFR, and FEV_1: FVC.

8 In addition to usual laboratory tests, three fecal occult blood tests will be performed between Visits 1 and 3, between Visits 9 and 10, and at early withdrawal; amylase will be measured at Visit 3.

9 Urinary beta-HCG tests will be performed in females of childbearing potential. No other laboratory samples will be collected at Visits 8 and 9.

10 Includes FEV_1, FVC, FEF_{25-75}, PEFR, and FEV_1:FVC measured by centralized spirometry by the same person at each visit.

11 A diary will be used to record if patients feel different since starting study medication.

12 Visit 3: 3 hours post-dose. Visit 5: trough and 0.5-3 hours post-dose. Visit 7: trough and 3-10 hours post-dose. Visit 10: trough only.

13 In patients with <40% of predicted FEV_1 at Visit 1 and resting SaO_2 <88% or if the patient lives at a high altitude.

14 Pulmonary function tests 30 (± 5) minutes after albuterol followed by 4-hour post-double-blind drug assessments at Visits 3 and 10.

VISIT 3, DAY 1
POST-RANDOMIZATION

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

MOD3

Please do not split modules

Module 3 : Visit 3 (Post-Randomization), Visit 3A, Visit 4, Visit 5, Adverse Experiences, Concomitant Medication, Medical Procedures, COPD Exacerbations, Resource Utilization

CRF Pages 69 - 126

Unprocessed Forms : Within this module the following occur which will generate attachments that need to be brought in-house.

None

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	Visit 3 Post-randomization Day 1
207499/156		[redacted]			

LABORATORY TESTS

Please take blood samples for hematology, 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. If the pregnancy test is positive, please withdraw the patient from the study, complete the Serious Adverse Experiences form and forward it to SB within 24 hours. Complete the Visit for Early Withdrawal between Scheduled Visits and the Study Continuation/ Withdrawal section at the back of this book.

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 (If a re-test is necessary, please use the Repeat Lab page at the end of this book)*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 3 Post-randomization Day 1
207499/156		[redacted]			

ARTERIAL BLOOD GASES

If a resting SaO2 test was required at this visit AND the patient's resting SaO2 < 88% OR the patient lives at a high altitude, please take an arterial blood gas sample for analysis if feasible. The patient should be rested (5 to 10 minute rest) after pulmonary function tests.

☐ Not required

☐ Sample required but not taken

PO_2 (mmHg)	PCO_2 (mmHg)	HCO_3- (mEq/L)	pH	SaO_2 %
			.	

POST-ALBUTEROL PULMONARY FUNCTION TESTS

Issue the patient an albuterol inhaler for 'as-required' use and retrieve their old inhaler.
Administer 180mcg (2 puffs) of albuterol via MDI with a spacer.

Record the time of albuterol inhalation ☐☐:☐☐ 24hr:min

Wait 30 minutes *(+/-5 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 manuals)****. For each set of three FEV_1 measurements, one FEV_1 must be within 10% of the highest.*

Please confirm that the pulmonary function tests were performed

[1] ☐ Not Performed

[2] ☐ Performed

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 3 Post-randomization Day 1
207499/156		[redacted]			

PATIENT RANDOMIZATION

Following completion of all preceding assessments contact RAMOS (1-866-726-6760) to obtain the container and randomization numbers assigned to the patient.

Please enter the 5-digit Randomization 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

Enter 6-digit Code as it appears on the study medication label ☐☐☐☐☐☐

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)

The patient should remain in the clinic for the next 4 hours, during which time the patient will be observed and will undergo hourly pulmonary function testing (to be recorded on the following pages).

PHARMACOKINETIC EVALUATION

Assign the patient to the 'Early' or 'Late' group for pharmacokinetic sampling.

[1] ☐ Early

[2] ☐ Late

Select the appropriate label ('early' or 'late') from those supplied and affix it to the cover of this book.

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 3 Post-randomization Day 1
207499/156		[redacted]			

POST-DOSE PULMONARY FUNCTION TESTS

Pulmonary function tests will be completed every hour in the 4-hour period following administration of the first dose of study medication.

Ask the patient to avoid using additional albuterol or anticholinergic medication and to refrain from smoking if at all possible.

If the patient uses their albuterol or anticholinergic medication during this period, the tests should be abandoned.

Time post-dose	Completed?	
	Yes	No
1 Hour	☐	☐
2 Hours	☐	☐
Perform ECG and Pharmacokinetic Evaluation		
3 Hours	☐	☐
4 Hours	☐	☐

ADVERSE EXPERIENCES

Record any adverse experiences which occur during the pulmonary function tests in the Adverse Experience section at the back of this module.

12 LEAD ELECTROCARDIOGRAM - 3 HOURS POST DOSE

The ECG should be performed before the 3-hour post-dose pulmonary function test and after the patient has been semi-supine for 5 minutes.

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant changes noted at this examination compared to Baseline?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of this module.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 3 Post-randomization Day 1
207499/156		[redacted]			

PHARMACOKINETIC EVALUATIONS - 3 HOURS POST DOSE

Collect a blood sample (5mL) 3 hours post dose (after the ECG and before the 3-hour post-dose pulmonary function test) for pharmacokinetic evaluation.

Was a pharmacokinetic sample taken?

☐ No

☐ Yes → *If 'Yes'*, 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)

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 3

- *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 a diary card and remind the patient to use the card to record if they feel differently since starting the study.*

    - *Ask the patient to return for Visit 3A in 7 +/- 2 days and for Visit 4 in 14 +/- 3 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. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).*

        iii *to refrain from using albuterol or anticholinergic agents during the **4 hours** immediately preceding the 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 albuterol inhaler and spacer, and the diary card.*

        vi *to continue to take the anticholinergic medication, if prescribed, at a constant dose.*

        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, diarrhea, 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.*

VISIT 3A, WEEK 1

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	
207499/156		[redacted]			Visit 3A Week 1

PRESENTATION TO CLINIC

Record time of presentation to clinic ☐☐ 24hr:min

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?

☐ NA → Patient is not using beta$_2$ agonist.

☐ 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?

☐ NA → Patient is not using anticholinergic.

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: ☐☐☐ 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 : ☐☐

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes

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Protocol		Patient Number	Patient Initials		Visit 3A Week 1
207499/156		[redacted]			

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes → *If 'Yes' please record details below. If the patient has had more than three Level 2 or 3 exacerbations since the start of double-blind medication, patient may be withdrawn after consultation with the Medical Monitor. If withdrawing, complete the assessments scheduled at this visit and the Assessments for Patients Withdrawing at Visit 3A. The SGRQ and SF-36 should be completed before any additional assessments.*

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

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

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

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of excerbation (maximum level)	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1
	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2
	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations, including an increase in usual COPD medications, must be recorded in the COPD Medications or Procedures pages.

RESOURCE UTILIZATION

If the patient has received any COPD exacerbation-related medical care since the last visit, record details in the Resource Utilization section at the back of this module.

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 3A Week 1
207499/156		[redacted]			

INDIRECT COST

Does the patient work?

☐ No

☐ Yes → *If 'Yes'*, has the patient missed work due to COPD-related symptoms, excluding scheduled protocol visits, since the last visit?

☐ No

☐ Yes → *If 'Yes', please record lost work days below:*

Start Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence

How many days since your last visit have you been restricted in performing your leisure activities, due to your COPD-related symptoms? *(please enter number of days below, if not restricted, enter 0)*

☐☐ Days

Since your last visit, how many hours per week did you require paid or unpaid assistance by a relative, friend or professional with your daily activities such as dressing, bathing, cooking, etc., due to your COPD-related symptoms? *(please enter number of hours below, if no paid or unpaid assistance, enter 0 in each instance)*

☐☐☐ Hours per week of **paid** assistance

☐☐☐ Hours per week of **unpaid** assistance

ADVERSE EXPERIENCES

If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

CONCOMITANT MEDICATION

If there has been any change in the patient's concomitant medication excluding treatment for COPD exacerbations (this is recorded in the COPD Exacerbations section) since the last visit, please record details in the Concomitant Medication section at the back of this module:

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Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 3A Week 1
207499/156		[redacted]			

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.

"AS NEEDED" ALBUTEROL USE

Record the patient's evaluation of their 'as needed' albuterol use since the last visit.

[1] ☐ Much less than usual
[2] ☐ Less than usual
[3] ☐ About the same as usual
[4] ☐ More than usual
[5] ☐ Much more than usual

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 3A Week 1
207499/156		[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. bid)

Date and time of last dose of study medication prior to the study visit ☐☐☐☐☐☐ Day Month Yr ☐☐☐☐ 24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
20	☐☐	☐☐	☐☐	☐☐	☐☐☐

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance ≥ 80% and ≤120%?

☐ No → *If 'No' please remind the patient of the importance of taking the medication according to the protocol.*

☐ Yes

PULMONARY REHABILITATION PROGRAM

Has the patient entered a Pulmonary Rehabilitation Program since the last visit?

☐ No

☐ Yes

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Protocol		Patient Number	Patient Initials		Visit 3A Week 1
207499/156		[redacted]			

INVESTIGATOR INSTRUCTIONS

The following procedures (Vital Signs and ECG) must be performed greater than 4 hours after the patient's last albuterol administration.

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
☐☐☐/☐☐☐	☐☐☐

Are there any **clinically significant worsenings** since Baseline?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes.

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant changes noted at this examination compared to Baseline?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of this module.*

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 3A Week 1
207499/156		[redacted]			

LABORATORY TESTS

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 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.

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes', please record the findings and/or diagnosis in the Adverse Experiences section (If a re-test is necessary, please use the Repeat Lab page at the end of this book)*

STUDY MEDICATION LABEL

Issue the patient a 10 day supply of study medication (20 tablets).

Attach the tear-off label from the study medication bottle dispensed at this visit in the space below. Record the start date in the Study Medication Record section in the next visit.

Attach label here

Enter 6-digit Code as it appears on the study medication label ☐☐☐☐☐☐

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

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 3A

- *If the patient **is not continuing** in the study, please complete the assessments for Visit 3A and Assessments for Patients Withdrawing at Visit 3A.*
- *If the patient **is continuing** in the study, please:*
  - *Issue the patient a diary card and remind the patient to use the card to record if they feel differently since starting the study.*
  - *Ask the patient to return to the clinic for Visit 4 as previously scheduled.*
  - ***Remind the patient:***

    i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after breakfast.*

    ii ***not** to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).*

    iii *to refrain from using albuterol or anticholinergic agents during the **4 hours** immediately preceding the 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 albuterol inhaler and spacer, and the diary card.*

    vi *to continue to take the anticholinergic medication, if prescribed, at a constant dose.*

    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, diarrhea, 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.*

PATIENT ACTIVITY POSTCARD

Please complete the patient activity postcard for ***Visit 3A*** located in the postcard section of this CRF. Detach the postcard and mail promptly. Postage has been prepaid.

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Withdrawal at Visit 3A Week 1
207499/156		[redacted]			

ASSESSMENTS FOR PATIENTS WITHDRAWING AT VISIT 3A

Complete the assessments below only for patients who are withdrawing from the study.

ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

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

COUGH AND SPUTUM PRODUCTION ASSESSMENTS

*Please ask the patient the following questions and record the answers below (Mark **one** box per section only.)*

COUGH

How troubled have you been by cough today?

[0] ☐ No symptoms at all

[1] ☐ Some symptoms, but hardly noticeable

[2] ☐ Symptoms noticeable and a little uncomfortable

[3] ☐ Symptoms definitely noticeable and uncomfortable

[4] ☐ Symptoms very bad and extremely uncomfortable

SPUTUM PRODUCTION

How much sputum have you produced today?

[0] ☐ No sputum at all

[1] ☐ Some sputum, but not as much as usual

[2] ☐ As much as usual

[3] ☐ More than usual

[4] ☐ A lot more than usual

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Protocol		Patient Number	Patient Initials		Withdrawal at Visit 3A Week 1
207499/156		[redacted]			

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a **clinically significant worsening** in the patient's physical condition since the previous examination?

☐ No

☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of this module.*

EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted? The distance walked should be entered even if the patient did not walk for 6 minutes.

☐ No

☐ Yes → *If 'Yes', Distance walked* ☐☐☐ Meters ☐

Yards ☐

Record any adverse experiences which occur during the exercise tolerance test in the Adverse Experience section at the back of this module.

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Protocol		Patient Number	Patient Initials		Withdrawal at Visit 3A Week 1
207499/156		[redacted]			

POST-EXERCISE ASSESSMENTS *(Immediately after the patient completes the exercise tolerance)*

Heart Rate ☐☐☐ beats/min

SaO_2 ☐☐☐ %

Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

"How short of breath do you feel right now?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Post-exercise breathlessness score ☐☐.☐

INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise test (rest for at least 10 minutes) before performing the pulmonary function tests.

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Protocol		Patient Number	Patient Initials		Withdrawal at Visit 3A Week 1
207499/156		[redacted]			

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 confirm that the pulmonary function tests were performed

[1] ☐ Not performed

[2] ☐ Performed

FECAL OCCULT BLOOD TEST

Issue the patient the fecal occult blood test kit. Instruct the patient to follow the Patient Instructions provided with the kit. Samples should be collected as specified on three consecutive bowel movements or three bowel movements closely spaced in time and returned to the clinic as soon as possible.

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

Are these findings clinically significant?

☐ No

☐ Yes → *If 'Yes' please record the details in the Adverse Experience section at the back of this module.*

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Protocol		Patient Number	Patient Initials		Withdrawal at Visit 3A Week 1
207499/156		[redacted]			

VITAL SIGNS - ORTHOSTATIC CHANGE

1st Measurement: After 5 Minutes Supine

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
___ / ___	___

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
___ / ___	___

Are there any **clincially significant worsenings** since Baseline?

☐ No

☐ Yes → *If 'Yes' please record details in the Adverse Experience section at the back of this module.*

INVESTIGATOR GLOBAL ASSESSMENT

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

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Protocol		Patient Number	Patient Initials		Withdrawal at Visit 3A Week 1
207499/156		[redacted]			

PATIENT GLOBAL ASSESSMENT

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

INVESTIGATOR INSTRUCTIONS

Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return for the Safety Follow-Up Visit in 7 +/- 3 days.

VISIT 4, WEEK 2

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Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	
207499/156		[redacted]			Visit 4 Week 2

PRESENTATION TO CLINIC

Record time of presentation to clinic ☐☐ 24hr:min

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?

☐ NA → Patient is not using beta$_2$ agonist.

☐ 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?

☐ NA → Patient is not using anticholinergic.

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: ☐☐☐ 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 : ☐☐

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes

SmithKline Beecham Pharmaceuticals

Protocol	Patient Number	Patient Initials	Visit 4 Week 2
207499/156	[redacted]		

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes → *If 'Yes' please record details below. If the patient has had more than three Level 2 or 3 exacerbations since the start of double-blind medication, patient may be withdrawn after consultation with the Medical Monitor. If withdrawing, complete the assessments scheduled at this visit and the Assessments for Patients Withdrawing at Visit 4. The SGRQ and SF-36 should be completed before any additional assessments.*

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

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

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

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of excerbation (maximum level)	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1
	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2
	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations, including an increase in usual COPD medications, must be recorded in the COPD Medications or Procedures pages.

RESOURCE UTILIZATION

If the patient has received any COPD exacerbation-related medical care since the last visit, record details in the Resource Utilization section at the back of this module.

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 4 Week 2
207499/156		[redacted]			

INDIRECT COST

Does the patient work?

☐ No

☐ Yes → *If 'Yes', has the patient missed work due to COPD-related symptoms, excluding scheduled protocol visits, since the last visit?*

☐ No

☐ Yes → *If 'Yes', please record lost work days below:*

Start Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence

How many days since your last visit have you been restricted in performing your leisure activities, due to your COPD-related symptoms? *(please enter number of days below, if not restricted, enter 0)*

☐☐ Days

Since your last visit, how many hours per week did you require paid or unpaid assistance by a relative, friend or professional with your daily activities such as dressing, bathing, cooking, etc., due to your COPD-related symptoms? *(please enter number of hours below, if no paid or unpaid assistance, enter 0 in each instance)*

☐☐☐ Hours per week of **paid** assistance

☐☐☐ Hours per week of **unpaid** assistance

ADVERSE EXPERIENCES

If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

CONCOMITANT MEDICATION

If there has been any change in the patient's concomitant medication excluding treatment for COPD exacerbations (this is recorded in the COPD Exacerbations section) since the last visit, please record details in the Concomitant Medication section at the back of this module.

SmithKline Beecham
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Protocol		Patient Number	Patient Initials		Visit 4 Week 2
207499/156		[redacted]			

"AS NEEDED" ALBUTEROL USE

Record the patient's evaluation of their 'as needed' albuterol use since the last visit.

[1] ☐ Much less than usual
[2] ☐ Less than usual
[3] ☐ About the same as usual
[4] ☐ More than usual
[5] ☐ Much more than usual

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
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Protocol		Patient Number	Patient Initials		Visit 4 Week 2
207499/156		[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. bid)

Date and time of last dose of study medication prior to the study visit ____ Day Month Yr ____ 24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
20					

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance < 80% or >120%?

☐ No

☐ Yes → *If 'Yes' please check the percent compliance at the previous visit. If compliance was <80% or >120% at the last visit, please contact the Medical Monitor to discuss patient withdrawal. If the patient is to be withdrawn from the study, complete the assessments scheduled at this visit and the Assessments for Patients Withdrawing at Visit 4. The SGRQ and SF-36 should be completed before any additional assessments.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 4 Week 2
207499/156		[redacted]			

OVERALL BREATHLESSNESS ASSESSMENT

Give the patient a copy of the following scale when assessing breathlessness.

Please ask the patient the following question and record the answer below.

"Generally speaking, how has your breathlessness been during the previous week when you carried out tasks that usually cause you to be short of breath (e.g. walking, carrying shopping, climbing stairs, etc)?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Overall breathlessness score ☐☐.☐

PULMONARY REHABILITATION PROGRAM

Has the patient entered a Pulmonary Rehabilitation Program since the last visit?

☐ No

☐ Yes

INVESTIGATOR INSTRUCTIONS

The following procedures (Vital Signs and ECG) must be performed greater than 4 hours after the patient's last albuterol administration.

SmithKline Beecham Pharmaceuticals

Protocol	Patient Number	Patient Initials	Visit 4 Week 2
207499/156	[redacted]		

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
☐☐☐/☐☐☐	☐☐☐

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes.

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant changes noted at this examination compared to the last visit?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of this module.*

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 confirm that the pulmonary function tests were performed

[1] ☐ Not Performed

[2] ☐ Performed

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials	Visit 4 Week 2
207499/156	[redacted]		

LABORATORY TESTS

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 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.

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes', please record the findings and/or diagnosis in the Adverse Experiences section (If a re-test is necessary, please use the Repeat Lab page at the end of this book)*

STUDY MEDICATION LABEL

Issue the patient a 20 day supply of study medication (2 bottles, 20 tablets per bottle). Attach the tear-off label from each of the study medication bottles 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

Attach study medication label here

Enter 6-digit Code as it appears on the study medication label ☐☐☐☐☐☐

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

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 4

- *If the patient **is not continuing** in the study, please complete the assessments for Visit 4 and the Assessments for Patients Withdrawing at Visit 4.*
- *If the patient **is continuing** in the study, please:*
    - *Issue the patient a diary card and and remind the patient to use the card to record if they feel differently since starting the study.*
    - *Ask the patient to return for the next visit in 14 +/- 3 days at 10:00 (+/-2 hours). Visit 5 must be performed in the morning.*
    - ***Remind the patient:***
        - i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after breakfast.*
        - ii ***not** to take the morning dose of study medication at home on the day of the next clinic visit.*
        - iii *to refrain from using albuterol or anticholinergic agents during the **4 hours** immediately preceding the 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 albuterol inhaler and spacer, and the diary card.*
        - vi *to continue to take the anticholinergic medication, if prescribed, at a constant dose.*
        - 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, diarrhea, 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.*

PHARMACOKINETIC EVALUATION REMINDER

Check the label on the front cover of this book to find out which sampling group (Early or Late) the patient was assigned to at Randomization (switching between groups is not permitted). Remind the patient that they will be having 2 blood samples drawn at the following visit and that the samples will be taken up to 2 hours post-dose for those in the Early group and up to 3 hours post-dose for those in the Late group.

PATIENT ACTIVITY POSTCARD

Please complete the patient activity postcard for ***Visit 4*** located in the postcard section of this CRF. Detach the postcard and mail promptly. Postage has been prepaid.

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Withdrawal at Visit 4 Week 2
207499/156		[redacted]			

ASSESSMENTS FOR PATIENTS WITHDRAWING AT VISIT 4

Complete the assessments below only for patients who are withdrawing from the study.

ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

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

INVESTIGATOR GLOBAL ASSESSMENT

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

PATIENT GLOBAL ASSESSMENT

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SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Withdrawal at Visit 4 Week 2
207499/156		[redacted]			

COUGH AND SPUTUM PRODUCTION ASSESSMENTS

*Please ask the patient the following questions and record the answers below (Mark **one** box per section only.)*

COUGH

How troubled have you been by cough today?

[0] ☐ No symptoms at all

[1] ☐ Some symptoms, but hardly noticeable

[2] ☐ Symptoms noticeable and a little uncomfortable

[3] ☐ Symptoms definitely noticeable and uncomfortable

[4] ☐ Symptoms very bad and extremely uncomfortable

SPUTUM PRODUCTION

How much sputum have you produced today?

[0] ☐ No sputum at all

[1] ☐ Some sputum, but not as much as usual

[2] ☐ As much as usual

[3] ☐ More than usual

[4] ☐ A lot more than usual

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a **clinically significant worsening** in the patient's physical condition since the previous examination?

☐ No

☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of this module.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Withdrawal at Visit 4 Week 2
207499/156		[redacted]			

FECAL OCCULT BLOOD TEST

Issue the patient the fecal occult blood test kit. Instruct the patient to follow the Patient Instructions provided with the kit. Samples should be collected as specified on three consecutive bowel movements or three bowel movements closely spaced in time and returned to the clinic as soon as possible.

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

Are these findings clinically significant?

☐ No

☐ Yes → *If 'Yes' please record the details in the Adverse Experience section at the back of this module.*

VITAL SIGNS - ORTHOSTATIC CHANGE

1st Measurement: After 5 Minutes Supine

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
☐☐☐ / ☐☐☐	☐☐☐

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
☐☐☐ / ☐☐☐	☐☐☐

Are there any **clincially significant worsenings** since Baseline?

☐ No

☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of this module.*

INVESTIGATOR INSTRUCTIONS

Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return for the Safety Follow-Up Visit in 7 +/- 3 days.

VISIT 5, WEEK 4

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	
207499/156		[redacted]			Visit 5 Week 4

PRESENTATION TO CLINIC

Record time of presentation to clinic ☐☐ 24hr:min

Visit 5 must be performed in the morning at 10:00 (± 2 hours).

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?

☐ NA → Patient is not using beta$_2$ agonist.

☐ 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?

☐ NA → Patient is not using anticholinergic.

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: ☐☐☐ 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 : ☐☐

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes

SmithKline Beecham Pharmaceuticals

Protocol	Patient Number	Patient Initials	Visit 5 Week 4
207499/156	[redacted]		

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes → *If 'Yes' please record details below. If the patient has had more than three Level 2 or 3 exacerbations since the start of double-blind medication, patient maybe withdrawn after consultation with the Medical Monitor. If withdrawing, complete the assessments scheduled at this visit (except for the post-dose pharmacokinetic blood sample) and the Assessments for Patients Withdrawing at Visit 5. The SGRQ and SF-36 should be completed before any additional assessments.*

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

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

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

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of excerbation (maximum level)	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1
	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2
	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations, including an increase in usual COPD medications, must be recorded in the COPD Medications or Procedures pages.

RESOURCE UTILIZATION

Please complete the Resource Utilization section at the back of this module. If the patient has received any COPD exacerbation-related medical care since the last visit, record details in the Resource Utilization section at the back of this module.

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Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 5 Week 4
207499/156		[redacted]			

INDIRECT COST

Does the patient work?

☐ No

☐ Yes → *If 'Yes'*, has the patient missed work due to COPD-related symptoms, excluding scheduled protocol visits, since the last visit?

☐ No

☐ Yes → *If 'Yes', please record lost work days below:*

Start Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence

How many days since your last visit have you been restricted in performing your leisure activities, due to your COPD-related symptoms? *(please enter number of days below, if not restricted, enter 0)*

☐☐ Days

Since your last visit, how many hours per week did you require paid or unpaid assistance by a relative, friend or professional with your daily activities such as dressing, bathing, cooking, etc., due to your COPD-related symptoms? *(please enter number of hours below, if no paid or unpaid assistance, enter 0 in each instance)*

☐☐☐ Hours per week of **paid** assistance

☐☐☐ Hours per week of **unpaid** assistance

ADVERSE EXPERIENCES

Please complete the Adverse Experience section at the back of this module. If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

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Pharmaceuticals

Protocol		Patient Number	Patient Initials		
207499/156		[redacted]			Visit 5 Week 4

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.

"AS NEEDED" ALBUTEROL USE

Record the patient's evaluation of their 'as needed' albuterol use since the last visit.

[1] ☐ Much less than usual
[2] ☐ Less than usual
[3] ☐ About the same as usual
[4] ☐ More than usual
[5] ☐ Much more than usual

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	Patient Initials	Visit 5 Week 4
207499/156	[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. bid)

Date and time of last dose of study medication prior to the study visit ☐☐☐☐☐☐ Day Month Yr ☐☐☐☐ 24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
40	☐☐	☐☐	☐☐	☐☐	☐☐☐

Note: Patients should not have taken the morning dose of study medication prior to this visit.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance < 80% or > 120%?

☐ No

☐ Yes → *If 'Yes' please check the percent compliance at the previous visit. If compliance was <80% or >120% at the last visit, please contact the Medical Monitor to discuss patient withdrawal. If the patient is to be withdrawn, complete the assessments scheduled at this visit (except for the post-dose pharmacokinetics blood sample) and the Assessments for Patients Withdrawing at Visit 5. The SGRQ and SF-36 should be completed before any additional assessments.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 5 Week 4
207499/156		[redacted]			

OVERALL BREATHLESSNESS ASSESSMENT

Give the patient a copy of the following scale when assessing breathlessness.

Please ask the patient the following question and record the answer below.

"Generally speaking, how has your breathlessness been during the previous week when you carried out tasks that usually cause you to be short of breath (e.g. walking, carrying shopping, climbing stairs, etc)?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Overall breathlessness score ☐☐.☐

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 Exercise Tolerance Test) must be performed greater than 4 hours after the patient's last albuterol administration.

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 5 Week 4
207499/156		[redacted]			

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
☐☐☐/☐☐☐	☐☐☐

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes.

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant changes noted at this examination compared to the last visit?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of this module.*

EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted? The distance walked should be entered even if the patient did not walk for 6 minutes.

☐ No

☐ Yes → *If 'Yes', Distance walked* ☐☐☐ [M] Meters ☐

[YD] Yards ☐

Record any adverse experiences which occur during the exercise tolerance test in the Adverse Experience section at the back of this module.

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 5 Week 4
207499/156		[redacted]			

POST-EXERCISE ASSESSMENTS *(Immediately after the patient completes the exercise tolerance)*

Heart Rate ☐☐☐ beats/min

SaO_2 ☐☐☐ %

Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

"How short of breath do you feel right now?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Post-exercise breathlessness score ☐☐.☐

INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise test (rest for at least 10 minutes) before performing the pulmonary function tests.

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 5 Week 4
207499/156		[redacted]			

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 confirm that the pulmonary function tests were performed

[1] ☐ Not Performed

[2] ☐ Performed

LABORATORY TESTS

Please take blood samples for hematology, 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. If the pregnancy test is positive, please withdraw the patient from the study, complete the Serious Adverse Experiences form and forward it to SB within 24 hours. Complete the Visit for Early Withdrawal Between Scheduled Visits and the Study Continuation/ Withdrawal section at the back of this book.

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes', please record the findings and/or diagnosis in the Adverse Experiences section (If a re-test is necessary, please use the Repeat Lab page at the end of this book)*

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 5 Week 4
207499/156		[redacted]			

PHARMACOKINETIC EVALUATIONS - PRE-DOSE BLOOD SAMPLE

Record the date and time of the previous two doses of study medication.

Study Medication Taken	Date Day Mth Yr	Time 24hr:min	Did the patient take this dose with food ?	
Yesterday's Morning Dose			☐ Yes	☐ No
Yesterday's Evening Dose			☐ Yes	☐ No

Collect a pre-dose blood sample (5mL) for pharmacokinetic evaluation.

Was a pharmacokinetic sample taken?

☐ No

☐ Yes → *If 'Yes'*, 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)

Did the patient accidentally take this morning's dose prior to attending the clinic?

☐ No

☐ Yes → *If 'Yes', check that the Study Medication Record for this visit is recorded correctly.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 5 Week 4
207499/156		[redacted]			

STUDY MEDICATION LABEL

Issue the patient a 35 day supply of study medication (1 bottle, 70 tablets). Attach the tear-off label from the study medication bottle dispensed at this visit in the space below. Record the start date in the Study Medication Record section in the next visit section. Issue the patient an albuterol inhaler and retrieve their old inhaler for 'as-required' use.

Attach study medication label here

Enter 6-digit Code as it appears on the study medication label ☐☐☐☐☐☐

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

Reminder: The patient's evening dose of study medication must not be taken until the post-dose pharmacokinetic sample has been taken.

PHARMACOKINETIC EVALUATIONS - POST-DOSE BLOOD SAMPLE

A blood sample is to be collected for pharmacokinetic evaluation, but not immediately. Please read the instructions below carefully before proceeding and refer to the label on the front cover of this book for which group (Early or Late) the patient was assigned to. 'Early' sample is to be collected between 0.5 and 2 hours post dose at this visit. 'Late' sample is to be collected between 1.5 and 3 hours post dose at this visit. ***Note: it is very important that samples from different patients are obtained over a broad range of times within each of these pre-defined sampling "windows" to prevent data-bunching at the extremes of each window (e.g. do not routinely collect samples at 0.5 hours in every "Early" group patient, instead collect samples at random times between 0.5 and 2 hours in different patients in this group. The same applies for the other sampling window).***

Collect a blood sample (5mL) for pharmacokinetic evaluation.

Was a pharmacokinetic sample taken?

☐ No

☐ Yes → *If 'Yes'*, 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)

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 5

- *If the patient **is not continuing** in the study, please complete the assessments for Visit 5 (except the post-dose pharmacokinetics blood sample) and the Assessments for Patients Withdrawing at Visit 5.*
- *If the patient **is continuing** in the study, please:*
  - *Issue the patient a diary card and and remind the patient to use the card to record if they feel differently since starting the study.*
  - *Ask the patient to return for the next visit in 28 +/- 6 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 breakfast.*

    ii ***not** to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).*

    iii *to refrain from using albuterol or anticholinergic agents during the **4 hours** immediately preceding the 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 albuterol inhaler and spacer, and the diary card.*

    vi *to continue to take the anticholinergic medication, if prescribed, at a constant dose.*

    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, diarrhea, 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.*

PATIENT ACTIVITY POSTCARD

Please complete the patient activity postcard for ***Visit 5*** located in the postcard section of this CRF. Detach the postcard and mail promptly. Postage has been prepaid.

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Withdrawal at Visit 5 Week 4
207499/156		[redacted]			

ASSESSMENTS FOR PATIENTS WITHDRAWING AT VISIT 5

Complete the assessments below only for patients who are withdrawing from the study.

ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

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INVESTIGATOR GLOBAL ASSESSMENT

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PATIENT GLOBAL ASSESSMENT

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SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Withdrawal at Visit 5 Week 4
207499/156		[redacted]			

COUGH AND SPUTUM PRODUCTION ASSESSMENTS

*Please ask the patient the following questions and record the answers below (Mark **one** box per section only.)*

COUGH

How troubled have you been by cough today?

[0] ☐ No symptoms at all

[1] ☐ Some symptoms, but hardly noticeable

[2] ☐ Symptoms noticeable and a little uncomfortable

[3] ☐ Symptoms definitely noticeable and uncomfortable

[4] ☐ Symptoms very bad and extremely uncomfortable

SPUTUM PRODUCTION

How much sputum have you produced today?

[0] ☐ No sputum at all

[1] ☐ Some sputum, but not as much as usual

[2] ☐ As much as usual

[3] ☐ More than usual

[4] ☐ A lot more than usual

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a **clinically significant worsening** in the patient's physical condition since the previous examination?

☐ No

☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of this module.*

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Withdrawal at Visit 5 Week 4
207499/156		[redacted]			

FECAL OCCULT BLOOD TEST

Issue the patient the fecal occult blood test kit. Instruct the patient to follow the Patient Instructions provided with the kit. Samples should be collected as specified on three consecutive bowel movements or three bowel movements closely spaced in time and returned to the clinic as soon as possible.

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

Are these findings clinically significant?

☐ No

☐ Yes → *If 'Yes' please record the details in the Adverse Experience section at the back of this module.*

VITAL SIGNS - ORTHOSTATIC CHANGE

1st Measurement: After 5 Minutes Supine

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
☐☐☐/☐☐☐	☐☐☐

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
☐☐☐/☐☐☐	☐☐☐

Are there any **clincially significant worsenings** since Baseline?

☐ No

☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of this module.*

INVESTIGATOR INSTRUCTIONS

Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return for the Safety Follow-Up Visit in 7 +/- 3 days.

ADVERSE EXPERIENCES (Non-serious)

DEFINITIONS

INTENSITY (Maximum)

MILD	*Adverse experience which is easily tolerated*
MODERATE	*Adverse experience sufficiently discomforting to interfere with daily activities*
SEVERE	*Adverse experience which prevents normal everyday activities*

RELATIONSHIP TO INVESTIGATIONAL DRUG

NOT RELATED	*The adverse experience is definitely not related to the test drug*
UNLIKELY	*There are other more likely causes and the drug is not suspected as a cause*
SUSPECTED (REASONABLE POSSIBILITY)	*A direct cause and effect relationship between the drug and the adverse experience has not been demonstrated but there is a reasonable possibility that the experience was caused by the drug*
PROBABLE	*There probably is a direct cause and effect relationship between the adverse experience and the study drug*

SERIOUS ADVERSE EXPERIENCE (SAE)

An SAE is any 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	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

ADVERSE EXPERIENCES (Non-serious)

*Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Have you felt different in any way since starting the treatment or since the 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).

If no adverse experiences occured since Randomization, please mark this box. ☐

Adverse Experience *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***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) *See definitions page for Adverse Experience*	[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 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	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

ADVERSE EXPERIENCES (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

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the Serious Adverse Experience (SAE) section (See opposite for definitions of an SAE).

If no adverse experiences occured since Randomization, please mark this box. ☐

Adverse Experience *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***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) *See definitions page for Adverse Experience*	[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 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	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

ADVERSE EXPERIENCES (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

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the Serious Adverse Experience (SAE) section (See opposite for definitions of an SAE).

If no adverse experiences occured since Randomization, please mark this box. ☐

Adverse Experience *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***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) *See definitions page for Adverse Experience*	[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 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)

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

CONCOMITANT MEDICATION

Record any changes in concomitant medication taken since Randomization. (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 (albuterol) use, using the date the study inhaler was returned.

☐ No concomitant medication changes since Randomization

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 Route, see General Instructions for acceptable abbreviations.*

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 (albuterol) 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 Route, see General Instructions for acceptable abbreviations.*

MEDICAL PROCEDURES
excluding treatment for COPD Exacerbations
(These are recorded in the COPD Exacerbations section)

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 Randomization?

☐ 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			

COPD EXACERBATION SECTION

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[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 Randomization should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages***

If no COPD Exacerbations since randomization, please mark this box. ☐

Adverse Experience	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***If patient died, STOP: go to SAE COPD Exacerbation pages.***	[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) *See definitions page for Adverse Experience*	[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 COPD Medication and/or Medical Procedures section*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156					

DETAILS OF COPD EXACERBATIONS - CONTINUED

*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 Randomization should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages***

If no COPD Exacerbations since randomization, please mark this box. ☐

Adverse Experience	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***If patient died, STOP: go to SAE COPD Exacerbation pages.***	[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) *See definitions page for Adverse Experience*	[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 COPD Medication and/or Medical Procedures section*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No

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	Center Number	Patient Number	Patient Initials	SB Receipt Date (Day Month Year)
207499/156		[redacted]		

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation

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

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 Medication and Medical Procedures 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 hospitalization (excluding elective surgery or routine clinical procedures)
[5] ☐ hospitalization 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 _____

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation (cont)

Relevant Laboratory Data
Please provide relevant abnormal laboratory data below

Test	Date	Value	Units	Normal Range
	Day Month Yr			
	Day Month Yr			
	Day Month Yr			
	Day Month Yr			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomization code broken at investigational site? ☐ No ☐ Yes

Randomization 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 _____

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

SERIOUS ADVERSE EXPERIENCE - COPD EXACERBATION (Cont.) PHARMACOKINETIC EVALUATION

If the patient presents to the clinic within 24 hours of the onset of a serious adverse experience (SAE) COPD Exacerbation or with an ongoing SAE COPD Exacerbation, please collect a blood sample (5mL) for pharmacokinetic evaluation.

Was a pharmacokinetic sample taken?

☐ No

☐ Yes → *If 'Yes'*, 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 taken prior to the onset of the serious adverse experience - COPD exacerbation

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 serious adverse experience - COPD exacerbation?

☐ No

☐ Yes → *If 'Yes'*, record date and time of last dose of study medication taken prior to collection of the pharmacokinetic sample.

Day Month Yr 24hr:min

Was this dose taken with food?

☐ No

☐ Yes

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

MEDICATION FOR COPD EXACERBATIONS

Has the patient taken any medication for COPD exacerbations since Randomization?

☐ No

☐ Yes → *If 'Yes', please record details below*

Drug Name (Trade Name Preferred)	Unit Dose (eg 500mg)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible) Day Mth Yr	End Date (or if Continuing mark box) Day Mth Yr	
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							

** For Route, see General Instructions for acceptable abbreviations.*

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

MEDICAL PROCEDURES FOR COPD EXACERBATIONS

Have any non-medication, therapeutic, diagnostic or surgical procedures been performed for COPD exacerbations since Randomization?

☐ 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		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			

RESOURCE UTILIZATION

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

RESOURCE UTILIZATION

Has the patient utilized any COPD Exacerbation-related medical care since Randomization?

☐ No

☐ Yes → *If 'Yes', please record details below*

Has the patient had any **Physician Visits** (COPD care excluding scheduled protocol visits) since Randomization?

☐ No

☐ Yes → *If 'Yes', please record details below*

Date of Visit Day Mth Yr	Reason for Visit

Has the patient had any **Emergency Room (ER)/Urgent Care Visits/Procedures (i.e., lung surgery)** since Randomization?

☐ No

☐ Yes → *If 'Yes', please record details below*

Date of Visit Day Mth Yr	Reason for Visit	Patient Admitted from ER? Yes	No
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

RESOURCE UTILIZATION - (cont)

Has the patient had any **Hospitalizations** since Randomization?

☐ No

☐ Yes → *If 'Yes', please record details below* ***(also record details of any hospitalization in the Serious Adverse Experience - COPD Exacerbation section)***

Name of Hospital & City	Date of Admission Day Mth Yr	Date of Discharge Day Mth Yr	Reason for Admission

Has the patient had any **Intensive Care Unit (ICU) stays** ***(did the patient stay in the ICU during any of the above hospitalizations?)*** since Randomization?

☐ 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

VISIT 6, WEEK 8

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

MOD4

Please do not split modules

Module 4 :	**Visit 6, Visit 7, Adverse Experiences, Concomitant Medication, Medical Procedures, COPD Exacerbations, Resource Utilization**
CRF Pages	**127 - 173**
Unprocessed Forms :	**Within this module the following occur which will generate attachments that need to be brought in-house.**
	None

SmithKline Beecham
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Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	
207499/156		[redacted]			Visit 6 Week 8

PRESENTATION TO CLINIC

Record time of presentation to clinic ☐☐ 24hr:min

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?

☐ NA → Patient is not using beta$_2$ agonist.

☐ 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?

☐ NA → Patient is not using anticholinergic.

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: ☐☐☐ 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 : ☐☐

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		
207499/156		[redacted]			Visit 6 Week 8

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes → *If 'Yes' please record details below. If the patient has had more than three Level 2 or 3 exacerbations since the start of double-blind medication, patient may be withdrawn after consultation with the Medical Monitor. If withdrawing, complete the assessments scheduled at this visit and the Assessments for Patients Withdrawing at Visit 6. The SGRQ and SF-36 should be completed before any additional assessments.*

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

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

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

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of excerbation (maximum level)	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1
	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2
	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations, including an increase in usual COPD medications, must be recorded in the COPD Medications or Procedures pages.

RESOURCE UTILIZATION

If the patient has received any COPD exacerbation-related medical care since the last visit, record details in the Resource Utilization section at the back of this module.

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 6 Week 8
207499/156		[redacted]			

INDIRECT COST

Does the patient work?

☐ No

☐ Yes → *If 'Yes', has the patient missed work due to COPD-related symptoms, excluding scheduled protocol visits, since the last visit?*

☐ No

☐ Yes → *If 'Yes', please record lost work days below:*

Start Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence

How many days since your last visit have you been restricted in performing your leisure activities, due to your COPD-related symptoms? *(please enter number of days below, if not restricted, enter 0)*

☐☐ Days

Since your last visit, how many hours per week did you require paid or unpaid assistance by a relative, friend or professional with your daily activities such as dressing, bathing, cooking, etc., due to your COPD-related symptoms? *(please enter number of hours below, if no paid or unpaid assistance, enter 0 in each instance)*

☐☐☐ Hours per week of **paid** assistance

☐☐☐ Hours per week of **unpaid** assistance

ADVERSE EXPERIENCES

If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

CONCOMITANT MEDICATION

If there has been any change in the patient's concomitant medication excluding treatment for COPD exacerbations (this is recorded in the COPD Exacerbations section) since the last visit, please record details in the Concomitant Medication section at the back of this module.

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 6 Week 8
207499/156		[redacted]			

"AS NEEDED" ALBUTEROL USE

Record the patient's evaluation of their 'as needed' albuterol use since the last visit.

[1] ☐ Much less than usual
[2] ☐ Less than usual
[3] ☐ About the same as usual
[4] ☐ More than usual
[5] ☐ Much more than usual

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	Patient Initials		Visit 6 Week 8
207499/156		[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. bid)

Date and time of last dose of study medication prior to the study visit ____ Day Month Yr ____ 24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
70					

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance < 80% or >120%?

☐ No

☐ Yes → *If 'Yes' please check the percent compliance at the previous visit. If compliance was <80% or >120% at the last visit, please contact the Medical Monitor to discuss patient withdrawal. If the patient is to be withdrawn, complete the assessments scheduled at this visit and the Assessments for Patients Withdrawing at Visit 6. The SGRQ and SF-36 should be completed before any additional assessments.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 6 Week 8
207499/156		[redacted]			

OVERALL BREATHLESSNESS ASSESSMENT

Give the patient a copy of the following scale when assessing breathlessness.

Please ask the patient the following question and record the answer below.

"Generally speaking, how has your breathlessness been during the previous week when you carried out tasks that usually cause you to be short of breath (e.g. walking, carrying shopping, climbing stairs, etc)?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Overall breathlessness score ☐☐.☐

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 Exercise Tolerance Test) must be performed greater than 4 hours after the patient's last albuterol administration.

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials	Visit 6 Week 8
207499/156	[redacted]		

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
___ / ___	___

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes.

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant changes noted at this examination compared to the last visit?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of this module.*

EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted? The distance walked should be entered even if the patient did not walk for 6 minutes.

☐ No

☐ Yes → *If 'Yes', Distance walked* ___ [M] Meters ☐

[YD] Yards ☐

Record any adverse experiences which occur during the exercise tolerance test in the Adverse Experience section at the back of this module.

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 6 Week 8
207499/156		[redacted]			

POST-EXERCISE ASSESSMENTS *(Immediately after the patient completes the exercise tolerance)*

Heart Rate ☐☐☐ beats/min

SaO_2 ☐☐☐ %

Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

"How short of breath do you feel right now?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Post-exercise breathlessness score ☐☐.☐

INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise test (rest for at least 10 minutes) before performing the pulmonary function tests.

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 6 Week 8
207499/156		[redacted]			

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 confirm that the pulmonary function tests were performed

[1] ☐ Not Performed

[2] ☐ Performed

LABORATORY TESTS

Please take blood samples for hematology, 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. If the pregnancy test is positive, please withdraw the patient from the study, complete the Serious Adverse Experiences form and forward it to SB within 24 hours. Complete the Visit for Early Withdrawal between Scheduled Visits and the Study Continuation/ Withdrawal section at the back of this book.

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes', please record the findings and/or diagnosis in the Adverse Experiences section (If a re-test is necessary, please use the Repeat Lab page at the end of this book)*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 6 Week 8
207499/156		[redacted]			

STUDY MEDICATION LABEL

Issue the patient a 35 day supply of study medication (1 bottle, 70 tablets). Attach the tear-off label from the study medication bottle dispensed at this visit in the space below. Record the start date in the Study Medication Record section in the next visit section. Issue the patient an albuterol inhaler and retrieve their old inhaler for 'as-required' use.

Attach study medication label here

Enter 6-digit Code as it appears on the study medication label ☐☐☐☐☐☐

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

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 6

- *If the patient **is not continuing** in the study, please complete the assessments for Visit 6 and the Assessments for Patients Withdrawing at Visit 6.*
- *If the patient **is continuing** in the study, please:*
  - *Issue the patient a diary card and and remind the patient to use the card to record if they feel differently since starting the study.*
  - *Ask the patient to return for the next visit in 28 +/- 6 days at 10:00 (+/- 2 hours). Visit 7 must be performed in the morning.*
  - ***Remind the patient:***
    - i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after breakfast.*
    - ii ***not** to take the morning dose of study medication at home on the day of the next clinic visit.*
    - iii *to refrain from using albuterol or anticholinergic agents during the **4 hours** immediately preceding the 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 albuterol inhaler and spacer, and the diary card.*
    - vi *to continue to take the anticholinergic medication, if prescribed, at a constant dose.*
    - 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, diarrhea, 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.*

PHARMACOKINETIC EVALUATION REMINDER

Check the label on the front cover of this book to find out which sampling group (Early or Late) the patient was assigned to at Randomization (switching between groups is not permitted). Remind the patient that they will be having 2 blood samples drawn at the following visit and that the samples will be taken up to 6 hours post-dose for those in the Early group and up to 10 hours post-dose for those in the Late group. If the patient expresses unwillingness to stay in the clinic for so long at Visit 7, then the patient has the option of going home and coming back the same day.

PATIENT ACTIVITY POSTCARD

Please complete the patient activity postcard for ***Visit 6*** located in the postcard section of this CRF. Detach the postcard and mail promptly. Postage has been prepaid.

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Withdrawal at Visit 6 Week 8
207499/156		[redacted]			

ASSESSMENTS FOR PATIENTS WITHDRAWING AT VISIT 6

Complete the assessments below only for patients who are withdrawing from the study.

ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

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

INVESTIGATOR GLOBAL ASSESSMENT

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

PATIENT GLOBAL ASSESSMENT

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	Patient Initials		Withdrawal at Visit 6 Week 8
207499/156		[redacted]			

COUGH AND SPUTUM PRODUCTION ASSESSMENTS

*Please ask the patient the following questions and record the answers below (Mark **one** box per section only.)*

COUGH

How troubled have you been by cough today?

[0] ☐ No symptoms at all

[1] ☐ Some symptoms, but hardly noticeable

[2] ☐ Symptoms noticeable and a little uncomfortable

[3] ☐ Symptoms definitely noticeable and uncomfortable

[4] ☐ Symptoms very bad and extremely uncomfortable

SPUTUM PRODUCTION

How much sputum have you produced today?

[0] ☐ No sputum at all

[1] ☐ Some sputum, but not as much as usual

[2] ☐ As much as usual

[3] ☐ More than usual

[4] ☐ A lot more than usual

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a **clinically significant worsening** in the patient's physical condition since the previous examination?

☐ No

☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of this module.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Withdrawal at Visit 6 Week 8
207499/156		[redacted]			

FECAL OCCULT BLOOD TEST

Issue the patient the fecal occult blood test kit. Instruct the patient to follow the Patient Instructions provided with the kit. Samples should be collected as specified on three consecutive bowel movements or three bowel movements closely spaced in time and returned to the clinic as soon as possible.

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

Are these findings clinically significant?

☐ No

☐ Yes → *If 'Yes' please record the details in the Adverse Experience section at the back of this module.*

VITAL SIGNS - ORTHOSTATIC CHANGE

1st Measurement: After 5 Minutes Supine

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
☐☐☐/☐☐☐	☐☐☐

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
☐☐☐/☐☐☐	☐☐☐

Are there any **clincially significant worsenings** since Baseline?

☐ No

☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of this module.*

INVESTIGATOR INSTRUCTIONS

Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return for the Safety Follow-Up Visit in 7 +/- 3 days.

VISIT 7, WEEK 12

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	Visit 7 Week 12
207499/156		[redacted]			

PRESENTATION TO CLINIC

Record time of presentation to clinic ☐☐ 24hr:min

Visit 7 must be performed in the morning at 10:00 (± 2 hours).

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?

☐ NA → Patient is not using beta$_2$ agonist.

☐ 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?

☐ NA → Patient is not using anticholinergic.

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: ☐☐☐ 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 : ☐☐

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes

ST. GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE

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

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 7 Week 12
207499/156		[redacted]			

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. US version adapted and modified with permission by Judith Barr, Sc.D., Northeastern Univ., Boston, MA.

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Protocol		Patient Number	Patient Initials		Visit 7 Week 12
207499/156		[redacted]			

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes → *If 'Yes' please record details below. If the patient has had more than three Level 2 or 3 exacerbations since the start of double-blind medication, patient may be withdrawn after consultation with the Medical Monitor. If withdrawing, complete the assessments scheduled at this visit (except for the post-dose pharmacokinetic blood sample) and the Assessments for Patients Withdrawing at Visit 7. The SGRQ and SF-36 should be completed before any additional assessments.*

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

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

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

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of excerbation (maximum level)	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1
	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2
	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations, including an increase in usual COPD medications, must be recorded in the COPD Medications or Procedures pages.

RESOURCE UTILIZATION

Please complete the Resource Utilization section at the back of this module. If the patient has received any COPD exacerbation related medical care since the previous visit, please complete the COPD Resource Utilization section at the back of this module.

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 7 Week 12
207499/156		[redacted]			

INDIRECT COST

Does the patient work?

☐ No

☐ Yes → *If 'Yes'*, has the patient missed work due to COPD-related symptoms, excluding scheduled protocol visits, since the last visit?

☐ No

☐ Yes → *If 'Yes', please record lost work days below:*

Start Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence

How many days since your last visit have you been restricted in performing your leisure activities, due to your COPD-related symptoms? *(please enter number of days below, if not restricted, enter 0)*

☐☐ Days

Since your last visit, how many hours per week did you require paid or unpaid assistance by a relative, friend or professional with your daily activities such as dressing, bathing, cooking, etc., due to your COPD-related symptoms? *(please enter number of hours below, if no paid or unpaid assistance, enter 0 in each instance)*

☐☐☐ Hours per week of **paid** assistance

☐☐☐ Hours per week of **unpaid** assistance

ADVERSE EXPERIENCES

Please complete the Adverse Experience section at the back of this module. If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 7 Week 12
207499/156		[redacted]			

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.

"AS NEEDED" ALBUTEROL USE

Record the patient's evaluation of their 'as needed' albuterol use since the last visit.

[1] ☐ Much less than usual
[2] ☐ Less than usual
[3] ☐ About the same as usual
[4] ☐ More than usual
[5] ☐ Much more than usual

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	Patient Initials		Visit 7 Week 12
207499/156		[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. bid)

Date and time of last dose of study medication prior to the study visit ____ ____ ____ (Day Month Yr) ____ ____ (24hr:min)

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
70					

Note: Patients should not have taken the morning dose of study medication prior to this visit.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance < 80% or >120%?

☐ No

☐ Yes → *If 'Yes' please check the percent compliance at the previous visit. If compliance was <80% or >120% at the last visit, please contact the Medical Monitor to discuss patient withdrawal. If the patient is to be withdrawn, complete the assessments scheduled at this visit (except for the post-dose pharmacokinetics blood sample) and the Assessments for Patients Withdrawing at Visit 7. The SF-36 should be completed before any additional assessments.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 7 Week 12
207499/156		[redacted]			

OVERALL BREATHLESSNESS ASSESSMENT

Give the patient a copy of the following scale when assessing breathlessness.

Please ask the patient the following question and record the answer below.

"Generally speaking, how has your breathlessness been during the previous week when you carried out tasks that usually cause you to be short of breath (e.g. walking, carrying shopping, climbing stairs, etc)?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Overall breathlessness score ☐☐.☐

PULMONARY REHABILITATION PROGRAM

Has the patient entered a Pulmonary Rehabilitation Program since the last visit?

☐ No

☐ Yes

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 7 Week 12
207499/156		[redacted]			

COUGH AND SPUTUM PRODUCTION ASSESSMENTS

*Please ask the patient the following questions and record the answers below (Mark **one** box per section only.)*

COUGH

How troubled have you been by cough today?

[0] ☐ No symptoms at all

[1] ☐ Some symptoms, but hardly noticeable

[2] ☐ Symptoms noticeable and a little uncomfortable

[3] ☐ Symptoms definitely noticeable and uncomfortable

[4] ☐ Symptoms very bad and extremely uncomfortable

SPUTUM PRODUCTION

How much sputum have you produced today?

[0] ☐ No sputum at all

[1] ☐ Some sputum, but not as much as usual

[2] ☐ As much as usual

[3] ☐ More than usual

[4] ☐ A lot more than usual

INVESTIGATOR INSTRUCTIONS

The following procedures (Vital Signs, ECG, and Exercise Tolerance Test) must be performed greater than 4 hours after the patient's last albuterol administration.

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
☐☐☐ / ☐☐☐	☐☐☐

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 7 Week 12
207499/156		[redacted]			

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes.

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant changes noted at this examination compared to the last visit?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of this module.*

EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted? The distance walked should be entered even if the patient did not walk for 6 minutes.

☐ No

☐ Yes → *If 'Yes', Distance walked* ☐☐☐ [M] Meters ☐

[YD] Yards ☐

Record any adverse experiences which occur during the exercise tolerance test in the Adverse Experience section at the back of this module.

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 7 Week 12
207499/156		[redacted]			

POST-EXERCISE ASSESSMENTS *(Immediately after the patient completes the exercise tolerance)*

Heart Rate ☐☐☐ beats/min

SaO_2 ☐☐☐ %

Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

"How short of breath do you feel right now?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Post-exercise breathlessness score ☐☐.☐

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials	Visit 7 Week 12
207499/156	[redacted]		

INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise tolerance test (rest for at least 10 minutes) before performing the pulmonary function tests.

PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed 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 confirm that the pulmonary function tests were performed

[1] ☐ Not Performed

[2] ☐ Performed

LABORATORY TESTS

Please take blood samples for hematology, 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. If the pregnancy test is positive, please withdraw the patient from the study, complete the Serious Adverse Experiences form and forward it to SB within 24 hours. Complete the Visit for Early Withdrawal Between Scheduled Visits and the Study Continuation/ Withdrawal section at the back of this book.

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes', please record the findings and/or diagnosis in the Adverse Experiences section (If a re-test is necessary, please use the Repeat Lab page at the end of this book)*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 7 Week 12
207499/156		[redacted]			

PHARMACOKINETIC EVALUATIONS - PRE-DOSE BLOOD SAMPLE

Record the date and time of the previous two doses of study medication.

Study Medication Taken	Date Day Mth Yr	Time 24hr:min	Did the patient take this dose with food ?	
Yesterday's Morning Dose			☐ Yes	☐ No
Yesterday's Evening Dose			☐ Yes	☐ No

Collect a pre-dose blood sample (5mL) for pharmacokinetic evaluation.

Was a pharmacokinetic sample taken?

☐ No

☐ Yes → *If 'Yes'*, 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)

Did the patient accidentally take this morning's dose prior to attending the clinic?

☐ No

☐ Yes → *If 'Yes', check that the Study Medication Record for this visit is recorded correctly.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 7 Week 12
207499/156		[redacted]			

STUDY MEDICATION LABEL

Issue the patient a 35 day supply of study medication (1 bottle, 70 tablets). Attach the tear-off label from the study medication bottle dispensed at this visit in the space below. Record the start date in the Study Medication Record section in the next visit section. Issue the patient an albuterol inhaler and retrieve their old inhaler for 'as-required' use.

Attach study medication label here

Enter 6-digit Code as it appears on the study medication label ☐☐☐☐☐☐

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

Reminder: The patient's evening dose of study medication must not be taken until the post-dose pharmacokinetic sample has been taken.

PHARMACOKINETIC EVALUATIONS - POST-DOSE BLOOD SAMPLE

A blood sample is to be collected for pharmacokinetic evaluation, but not immediately. Please read the instructions below carefully before proceeding and refer to the label on the front cover of this book for which group (Early or Late) the patient was assigned to. 'Early' sample is to be collected between 3 and 6 hours post dose at this visit. 'Late' sample is to be collected between 5 and 10 hours post dose at this visit. ***Note: it is very important that samples from different patients are obtained over a broad range of times within each of these pre-defined sampling "windows" to prevent data-bunching at the extremes of each window (e.g. do not routinely collect samples at 3 hours in every "Early" group patient, instead collect samples at random times between 3 and 6 hours in different patients in this group. The same applies for the other sampling window).***

Collect a blood sample (5mL) for pharmacokinetic evaluation.

Was a pharmacokinetic sample taken?

☐ No

☐ Yes → *If 'Yes'*, 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)

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 7

- *If the patient **is not continuing** in the study, please complete the assessments for Visit 7 (except the post-dose pharmacokinetics blood sample) and the Assessments for Patients Withdrawing at Visit 7.*
- *If the patient **is continuing** in the study, please:*
  - *Issue the patient a diary card and and remind the patient to use the card to record if they feel differently since starting the study.*
  - *Ask the patient to return for the next visit in 28 +/- 6 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. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).*
    - iii *to refrain from using albuterol or anticholinergic agents during the **4 hours** immediately preceding the 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 albuterol inhaler and spacer, and the diary card.*
    - vi *to continue to take the anticholinergic medication, if prescribed, at a constant dose.*
    - 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, diarrhea, 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.*

PATIENT ACTIVITY POSTCARD

Please complete the patient activity postcard for ***Visit 7*** located in the postcard section of this CRF. Detach the postcard and mail promptly. Postage has been prepaid.

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Withdrawal at Visit 7 Week 12
207499/156		[redacted]			

ASSESSMENTS FOR PATIENTS WITHDRAWING AT VISIT 7

Complete the assessments below only for patients who are withdrawing from the study.

SF-36 QUESTIONNAIRE

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

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a **clinically significant worsening** in the patient's physical condition since the previous examination?

☐ No

☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of this module.*

INVESTIGATOR GLOBAL ASSESSMENT

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

PATIENT GLOBAL ASSESSMENT

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	Patient Initials		Withdrawal at Visit 7 Week 12
207499/156		[redacted]			

FECAL OCCULT BLOOD TEST

Issue the patient the fecal occult blood test kit. Instruct the patient to follow the Patient Instructions provided with the kit. Samples should be collected as specified on three consecutive bowel movements or three bowel movements closely spaced in time and returned to the clinic as soon as possible.

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

Are these findings clinically significant?

☐ No

☐ Yes → *If 'Yes' please record the details in the Adverse Experience section at the back of this module.*

VITAL SIGNS - ORTHOSTATIC CHANGE

1st Measurement: After 5 Minutes Supine

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
☐☐☐ / ☐☐☐	☐☐☐

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
☐☐☐ / ☐☐☐	☐☐☐

Are there any **clincially significant worsenings** since Baseline?

☐ No

☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of this module.*

INVESTIGATOR INSTRUCTIONS

Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return for the Safety Follow-Up Visit in 7 +/- 3 days.

ADVERSE EXPERIENCES (Non-serious)

DEFINITIONS

INTENSITY (Maximum)

MILD	*Adverse experience which is easily tolerated*
MODERATE	*Adverse experience sufficiently discomforting to interfere with daily activities*
SEVERE	*Adverse experience which prevents normal everyday activities*

RELATIONSHIP TO INVESTIGATIONAL DRUG

NOT RELATED	*The adverse experience is definitely not related to the test drug*
UNLIKELY	*There are other more likely causes and the drug is not suspected as a cause*
SUSPECTED (REASONABLE POSSIBILITY)	*A direct cause and effect relationship between the drug and the adverse experience has not been demonstrated but there is a reasonable possibility that the experience was caused by the drug*
PROBABLE	*There probably is a direct cause and effect relationship between the adverse experience and the study drug*

SERIOUS ADVERSE EXPERIENCE (SAE)

An SAE is any 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	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

ADVERSE EXPERIENCES (Non-serious)

*Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Have you felt different in any way since starting the treatment or since the 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).

If no adverse experiences occured since the previous module (i.e., since Visit 5), please mark this box. ☐

Adverse Experience *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***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) *See definitions page for Adverse Experience*	[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 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	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

ADVERSE EXPERIENCES (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

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the Serious Adverse Experience (SAE) section (See opposite for definitions of an SAE).

If no adverse experiences occured since the previous module (i.e., since Visit 5), please mark this box. ☐

Adverse Experience *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***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) *See definitions page for Adverse Experience*	[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 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	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

ADVERSE EXPERIENCES (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

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the Serious Adverse Experience (SAE) section (See opposite for definitions of an SAE).

If no adverse experiences occured since the previous module (i.e., since Visit 5), please mark this box. ☐

Adverse Experience *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***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) *See definitions page for Adverse Experience*	[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 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)

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

CONCOMITANT MEDICATION

Record any changes in concomitant medication taken since the previous module (i.e., since Visit 5). (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 (albuterol) use, using the date the study inhaler was returned.

☐ No concomitant medication changes since the previous module (i.e., since Visit 5)

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 Route, see General Instructions for acceptable abbreviations.*

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 (albuterol) 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 Route, see General Instructions for acceptable abbreviations.

MEDICAL PROCEDURES
excluding treatment for COPD Exacerbations
(These are recorded in the COPD Exacerbations section)

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 (i.e., since Visit 5)?

☐ 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			

COPD EXACERBATION SECTION

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 Visit 5 should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages***

If no COPD Exacerbations since previous module (i.e., since Visit 5), please mark this box. ☐

Adverse Experience	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***If patient died, STOP: go to SAE COPD Exacerbation pages.***	[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) *See definitions page for Adverse Experience*	[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 COPD Medication 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	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

DETAILS OF COPD EXACERBATIONS - CONTINUED

*An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy.*
All exacerbations of COPD since the previous module (i.e., since Visit 5) should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). ***COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages***

If no COPD Exacerbations since previous module (i.e., since Visit 5), please mark this box. ☐

Adverse Experience	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***If patient died, STOP: go to SAE COPD Exacerbation pages.***	[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) *See definitions page for Adverse Experience*	[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 COPD Medication and/or Medical Procedures section if appropriate*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No

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	Center Number	Patient Number	Patient Initials	SB Receipt Date (Day Month Year)
207499/156		[redacted]		

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation

Person Reporting SAE _____ *(Please print clearly)*

AEGIS Number _____

Serious Adverse Experience *(Please print clearly)*	**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 Medication and/or Medical Procedures 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 hospitalization (excluding elective surgery or routine clinical procedures)
- [5] ☐ hospitalization 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 _____

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation (cont)

Relevant Laboratory Data
Please provide relevant abnormal laboratory data below

Test	Date	Value	Units	Normal Range
	Day Month Yr			
	Day Month Yr			
	Day Month Yr			
	Day Month Yr			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomization code broken at investigational site? ☐ No ☐ Yes

Randomization 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 _____

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Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

SERIOUS ADVERSE EXPERIENCE - COPD EXACERBATION (Cont.) PHARMACOKINETIC EVALUATION

If the patient presents to the clinic within 24 hours of the onset of a serious adverse experience (SAE) COPD Exacerbation or with an ongoing SAE COPD Exacerbation, please collect a blood sample (5mL) for pharmacokinetic evaluation.

Was a pharmacokinetic sample taken?

☐ No

☐ Yes → *If 'Yes',* 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 taken prior to the onset of the serious adverse experience - COPD exacerbation

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 serious adverse experience - COPD exacerbation?

☐ No

☐ Yes → *If 'Yes',* record date and time of last dose of study medication taken prior to collection of the pharmacokinetic sample.

Day Month Yr 24hr:min

Was this dose taken with food?

☐ No

☐ Yes

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Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

MEDICATION FOR COPD EXACERBATIONS

Has the patient taken any medication for COPD exacerbations since the previous module (i.e., since Visit 5)?

☐ No

☐ Yes → *If 'Yes', please record details below*

Drug Name (Trade Name Preferred)	Unit Dose (eg 500mg)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible) Day Mth Yr	End Date (or if Continuing mark box) Day Mth Yr	
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							
				COPD EXACERBATION			☐
For SB							

* *For Route, see General Instructions for acceptable abbreviations.*

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Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

MEDICAL PROCEDURES FOR COPD EXACERBATIONS

Have any non-medication, therapeutic, diagnostic or surgical procedures been performed for COPD exacerbations since the previous module (i.e., since Visit 5)?

☐ 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		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			

RESOURCE UTILIZATION

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Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

RESOURCE UTILIZATION

Has the patient utilized any COPD Exacerbation-related medical care since the previous module (i.e., since Visit 5)?

☐ No

☐ Yes → *If 'Yes', please record details below*

Has the patient had any **Physician Visits** (COPD care excluding scheduled protocol visits) since the previous module (i.e., since Visit 5)?

☐ No

☐ Yes → *If 'Yes', please record details below*

Date of Visit Day Mth Yr	Reason for Visit

Has the patient had any **Emergency Room (ER)/Urgent Care Visits/Procedures (i.e., lung surgery)** since the previous module (i.e., since Visit 5)?

☐ No

☐ Yes → *If 'Yes', please record details below*

Date of Visit Day Mth Yr	Reason for Visit	Patient Admitted from ER? Yes	No
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐

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Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

RESOURCE UTILIZATION - (cont)

Has the patient had any **Hospitalizations** since the previous module (i.e., since Visit 5)?

☐ No

☐ Yes → *If 'Yes', please record details below* ***(also record details of any hospitalization in the Serious Adverse Experience - COPD Exacerbation section)***

Name of Hospital & City	Date of Admission Day Mth Yr	Date of Discharge Day Mth Yr	Reason for Admission

Has the patient had any **Intensive Care Unit (ICU) stays** ***(did the patient stay in the ICU during any of the above hospitalizations?)*** since the previous module (i.e., since Visit 5)?

☐ 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

EARLY WITHDRAWAL BETWEEN SCHEDULED VISITS

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Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

EW1

Please do not split modules

Module: Early Withdrawal between scheduled visits

CRF Pages 174 - 184

Unprocessed Forms : Within this module the following occur which will generate attachments that need to be brought in-house.

SGRQ Quality of Life Assessment
SF-36

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Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

Complete these assessments ONLY for patients who withdraw from the study between scheduled clinic visits. These assessments should be completed within 24 hours of stopping study medication.

PRESENTATION TO CLINIC

Record time of presentation to clinic ☐☐ 24hr:min

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?

☐ NA → Patient is not using $beta_2$ agonist.

☐ 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?

☐ NA → Patient is not using anticholinergic.

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: ☐☐☐ 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 : ☐☐

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes

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Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

ST. GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

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

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes ⟶ *If 'Yes' please record details below.*

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

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

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

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of excerbation (maximum level)	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1
	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2
	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of the module that contains the visit (or visit interval) at which the patient withdrew, 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.

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Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

RESOURCE UTILIZATION

If the patient has received any COPD exacerbation related medical care since the previous visit, record details in the Resource Utilization section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.

INDIRECT COST

Does the patient work?

☐ No

☐ Yes → *If 'Yes'*, has the patient missed work due to COPD-related symptoms, excluding scheduled protocol visits, since the last visit?

☐ No

☐ Yes → *If 'Yes', please record lost work days below:*

Start Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence

How many days since your last visit have you been restricted in performing your leisure activities, due to your COPD-related symptoms? *(please enter number of days below, if not restricted, enter 0)*

☐☐ Days

Since your last visit, how many hours per week did you require paid or unpaid assistance by a relative, friend or professional with your daily activities such as dressing, bathing, cooking, etc., due to your COPD-related symptoms? *(please enter number of hours below, if no paid or unpaid assistance, enter 0 in each instance)*

☐☐☐ Hours per week of **paid** assistance

☐☐☐ Hours per week of **unpaid** assistance

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Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

ADVERSE EXPERIENCES

If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of the module which contains the visit (or visit interval) at which the patient withdrew. 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 the module which contains the visit (or visit interval) at which the patient withdrew.

"AS NEEDED" ALBUTEROL USE

Record the patient's evaluation of their 'as needed' albuterol use since the last visit.

[1] ☐ Much less than usual
[2] ☐ Less than usual
[3] ☐ About the same as usual
[4] ☐ More than usual
[5] ☐ Much more than usual

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 the module which contains the visit (or visit interval) at which the patient withdrew.

INVESTIGATOR GLOBAL ASSESSMENT

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

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Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

PATIENT GLOBAL ASSESSMENT

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

COUGH AND SPUTUM PRODUCTION ASSESSMENTS

*Please ask the patient the following questions and record the answers below (Mark **one** box per section only.)*

COUGH

How troubled have you been by cough today?

[0] ☐ No symptoms at all

[1] ☐ Some symptoms, but hardly noticeable

[2] ☐ Symptoms noticeable and a little uncomfortable

[3] ☐ Symptoms definitely noticeable and uncomfortable

[4] ☐ Symptoms very bad and extremely uncomfortable

SPUTUM PRODUCTION

How much sputum have you produced today?

[0] ☐ No sputum at all

[1] ☐ Some sputum, but not as much as usual

[2] ☐ As much as usual

[3] ☐ More than usual

[4] ☐ A lot more than usual

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a **clinically significant worsening** in the patient's physical condition since the previous examination?

☐ No

☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of this module.*

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Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

FECAL OCCULT BLOOD TEST

Issue the patient the fecal occult blood test kit. Instruct the patient to follow the Patient Instructions provided with the kit. Samples should be collected as specified on three consecutive bowel movements or three bowel movements closely spaced in time and returned to the clinic as soon as possible.

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

Are these findings clinically significant?

☐ No

☐ Yes → *If 'Yes' please record the details in the Adverse Experience section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.*

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Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[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. bid)

Date and time of last dose of study medication prior to the study visit ☐☐ ☐☐☐ ☐☐ Day Month Yr ☐☐:☐☐ 24hr:min

Did the patient take their last dose with food?

☐ No

☐ Yes

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
☐☐	☐☐	☐☐	☐☐	☐☐	☐☐☐

Note: If this is a morning visit, patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance ≥ 80% and ≤120%?

☐ No

☐ Yes

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Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[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 and ECG) must be performed greater than 4 hours after the patient's last albuterol administration.

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
☐☐☐/☐☐☐	☐☐☐

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.*

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Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

VITAL SIGNS - ORTHOSTATIC CHANGE

1st Measurement: After 5 Minutes Supine

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
___ / ___	___

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
___ / ___	___

Are there any clinically significant worsenings since Baseline?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes.

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant changes noted at this examination compared to the last visit?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.*

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Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted? The distance walked should be entered even if the patient did not walk for 6 minutes.

☐ No

☐ Yes → *If 'Yes', Distance walked* ☐☐☐ [M] Meters ☐

[YD] Yards ☐

Record any adverse experiences which occur during the exercise tolerance test in the Adverse Experience section at the back of the module which contains the visit (or visit interval) at which the patient withdrew).

POST-EXERCISE ASSESSMENTS *(Immediately after the patient completes the exercise tolerance)*

Heart Rate ☐☐☐ beats/min

SaO_2 ☐☐☐ %

Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

"How short of breath do you feel right now?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Post-exercise breathlessness score ☐☐.☐

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Protocol	Patient Number	Patient Initials	Early Withdrawal between Scheduled Visits
207499/156	[redacted]		

INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise test (rest for at least 10 minutes) before performing the pulmonary function tests.

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 confirm that the pulmonary function tests were performed

[1] ☐ Not performed

[2] ☐ Performed

LABORATORY TESTS

Please take blood samples for hematology, 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. If the pregnancy test is positive, please complete the Serious Adverse Experiences form and forward it to SB within 24 hours.

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes', please record the findings and/or diagnosis in the Adverse Experiences section (If a re-test is necessary, please use the Repeat Lab page at the end of this book)*

INSTRUCTION TO THE INVESTIGATOR

Please complete the Study Continuation / Withdrawal page at the end of Book 2.
Ask the patient to return for the Safety Follow-Up Visit in 7 +/- 3 days.

PATIENT ACTIVITY POSTCARD

Please complete the patient activity postcard for ***Early Withdrawal Between Scheduled Visits*** located in the postcard section of this CRF. Detach the postcard and mail promptly. Postage has been prepaid.

SAFETY FOLLOW-UP

SmithKline Beecham
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Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

SFU1

Please do not split modules

Module: Safety Follow-Up

CRF Pages 185 - 190

Unprocessed Forms : Within this module the following occur which will generate attachments that need to be brought in-house.

None

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Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	Safety Follow-Up
207499/156		[redacted]			

INVESTIGATOR INSTRUCTIONS

Complete these assessments only for those patients who have withdrawn from the study. These assessments should be completed within 7 +/- 3 days after discontinuation of study medication.

PRESENTATION TO CLINIC

Record time of presentation to clinic ☐☐ 24hr:min

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?

☐ NA → Patient is not using $beta_2$ agonist.

☐ 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?

☐ NA → Patient is not using anticholinergic.

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: ☐☐☐☐ 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 : ☐☐

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes

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Protocol		Patient Number	Patient Initials		Safety Follow-Up
207499/156		[redacted]			

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes → *If 'Yes' please record details below.*

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

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

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

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of excerbation (maximum level)	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1
	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2
	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of the module which contains the visit (or the visit interval) at which the patient withdrew, 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 UTILIZATION

If the patient has received any COPD exacerbation related medical care since the previous visit, record details in the Resource Utilization section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.

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Protocol		Patient Number	Patient Initials		Safety Follow-Up
207499/156		[redacted]			

INDIRECT COST

Does the patient work?

☐ No

☐ Yes → *If 'Yes'*, has the patient missed work due to COPD-related symptoms, excluding scheduled protocol visits, since the last visit?

☐ No

☐ Yes → *If 'Yes', please record lost work days below:*

Start Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence

How many days since your last visit have you been restricted in performing your leisure activities, due to your COPD-related symptoms? *(please enter number of days below, if not restricted, enter 0)*

☐☐ Days

Since your last visit, how many hours per week did you require paid or unpaid assistance by a relative, friend or professional with your daily activities such as dressing, bathing, cooking, etc., due to your COPD-related symptoms? *(please enter number of hours below, if no paid or unpaid assistance, enter 0 in each instance)*

☐☐☐ Hours per week of **paid** assistance

☐☐☐ Hours per week of **unpaid** assistance

ADVERSE EXPERIENCES

If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.

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Protocol		Patient Number	Patient Initials		Safety Follow-Up
207499/156		[redacted]			

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 the module which contains the visit (or visit interval) at which the patient withdrew. ***At the patient's final study visit, record the end date for prn study rescue medication (albuterol) use, using the date the study inhaler was returned.***

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 the module which contains the visit (or visit interval) at which the patient withdrew.

PULMONARY REHABILITATION PROGRAM

Has the patient entered a Pulmonary Rehabilitation Program since the last visit?

☐ No

☐ Yes

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
☐☐☐ / ☐☐☐	☐☐☐

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Safety Follow-Up
207499/156		[redacted]			

12 LEAD ELECTROCARDIOGRAM

If any abnormalities were observed at the last visit, please perform a 12-lead ECG. The ECG should be performed after the patient has been semi-supine for 5 minutes.

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant changes noted at this examination compared to the last visit?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.*

LABORATORY TESTS

If abnormal laboratory results were reported at the previous visit, 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 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.

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes', please record the findings and/or diagnosis in the Adverse Experiences section at the back of the module which contains the visit (or visit interval) at which the patient withdrew. (If a re-test is necessary, please use the Repeat Lab page at the end of this book)*

SmithKline Beecham
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Protocol		Patient Number	Patient Initials		Safety Follow-Up
207499/156		[redacted]			

PREGNANCY TEST

Is the patient a female of child-bearing potential?

☐ No

☐ Yes → *If 'Yes' please perform a urine pregnancy test locally.*

Urine Sample Date ☐☐ ☐☐ ☐☐
Day Month Yr

Is the patient pregnant?

☐ No

☐ Yes → *If the pregnancy test is positive, complete the Serious Adverse Experiences form and forward it to SB within 24 hours.*

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

If any abnormalities were noted at the last visit, please perform a physical examination (including respiratory examination).

Were any clinically significant changes noted at this examination compared to the last visit?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.*

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 confirm that the pulmonary function tests were performed

[1] ☐ Not performed

[2] ☐ Performed

PATIENT ACTIVITY POSTCARD

Please complete the patient activity postcard for ***Safety Follow-Up Visit*** located in the postcard section of this CRF. Detach the postcard and mail promptly. Postage has been prepaid.

STUDY CONTINUATION / WITHDRAWAL

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

CONC2

Please do not split modules

Module: Study Continuation / Withdrawal

CRF Pages 191

Unprocessed Forms : Within this module the following occur which will generate attachments that need to be brought in-house.

None

SmithKline Beecham
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Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

STUDY CONTINUATION/WITHDRAWAL

Is the patient continuing in the study?

☐ Yes → *If 'Yes' please continue in Book 3.*

☐ No → *If 'No' please mark the **PRIMARY** cause of withdrawal and record the date of final visit and date of final dose.*

[1] ☐ Adverse experience (complete AE form)

[2] ☐ Insufficient therapeutic effect

[3] ☐ Protocol deviation (including non-compliance)

[4] ☐ Lost to follow-up

[7] ☐ Other - specify: _____

Date of Final Visit ☐☐ ☐☐ ☐☐
Day Month Yr

Date of Final Dose ☐☐ ☐☐ ☐☐
Day Month Yr

INVESTIGATOR SIGNATURE

I certify that I have reviewed the data on this case report form, 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	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

SAE2

Please do not split modules

Module: Serious Adverse Experiences, Pharmacokinetic Evaluation for Serious Adverse Experiences

CRF Pages 192 - 194

Unprocessed Forms : Within this module the following occur which will generate attachments that need to be brought in-house.

None

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	SB Receipt Date (Day Month Year)
207499/156		[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

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 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 hospitalization (excluding elective surgery or routine clinical procedures)
[5] ☐ hospitalization 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 _____

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 randomization code broken at investigational site? ☐ No ☐ Yes

Randomization 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

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		
207499/156		[redacted]			

SERIOUS ADVERSE EXPERIENCE (Cont.) PHARMACOKINETIC EVALUATION

If the patient presents to the clinic within 24 hours of the onset of a serious adverse experience (SAE) or with an ongoing SAE, please collect a blood sample (5mL) for pharmacokinetic evaluation.

Was a pharmacokinetic sample taken?

☐ No

☐ Yes → *If 'Yes'*, 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 taken prior to the onset of the serious adverse experience

☐☐☐ ☐☐
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 serious adverse experience?

☐ No

☐ Yes → *If 'Yes'*, record date and time of last dose of study medication taken prior to collection of the pharmacokinetic sample.

☐☐☐ ☐☐
Day Month Yr 24hr:min

Was this dose taken with food?

☐ No

☐ Yes

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

FORMD2

Please do not split modules

Module: Form D

CRF Pages: 195

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

FORM D

Certified Cause of Death _____

Date of Death Day Month Yr → *Please complete Serious Adverse Experience section.*

Was a post-mortem examination carried out?

☐ No

☐ Yes → *If 'Yes' please summarize findings (include diagnosis):*

_____

_____

_____

_____

Reporting Physician's Signature _____ Date Day Month Yr

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		OPTIONAL Repeat Lab
207499/156		[redacted]			

RPLAB2

Please do not split modules

Module: Repeat Lab

CRF Pages: 196

Unprocessed Forms: Within this module, the following tests / procedures occur which may generate attachments.

None

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		OPTIONAL Repeat Lab
207499/156		[redacted]			

REPEAT 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, complete the Early Withdrawal between Scheduled Visits 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.*

REPEAT 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, complete the Early Withdrawal between Scheduled Visits 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	Center Number	Patient Number	Patient Initials	Investigator
207499/156		[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	
MOD3	Vst 3-5, AE, CM, MP, COPD, RU	69 - 126	☐	☐	
MOD4	V6, V7 , AE, CM, MP, COPD, RU	127 - 173	☐	☐	
EW1	Early Withdrawal	174 - 184	☐	☐	
SFU1	Safety Follow-Up	185 - 190	☐	☐	
CONC2	Continuation/Withdrawal	191	☐	☐	
SAE2	Serious Adverse Experiences	192 - 194	☐	☐	
FORMD2	Form D	195	☐	☐	
RPLAB2	Repeat Lab	196	☐	☐	

If multiple modules are submitted together, please ensure they are sorted according to the order above

Site Monitor's Comments (e.g. protocol violations or deviations)

Site Monitor's Signature _____ Date Submitted ☐☐ ☐☐ ☐☐
Day Month Yr

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

CONFIDENTIAL

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Pharmaceuticals

PROTOCOL 207499/156

BOOK 3 : VISIT 8 TO STUDY CONCLUSION

A RANDOMIZED, 24-WEEK, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY, SAFETY AND TOLERABILITY OF ARIFLO™ (15 MG BID) IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

GENERAL INSTRUCTIONS

- *Write clearly in capital letters using a black ball point pen and press firmly so that all copies are legible*
- *Do not write in shaded areas*
- *Answer ALL questions on every page*
- *Enter "N/A" if information requested is not available*
- *Initial and date all changes, additions or deletions. Use a single pen stroke to remove an incorrect entry*
- *Enter the patient initials on all pages on which information has been entered and the patient number and center number where required*

Do not enter additional data/information after the set of CRF pages has been split/separated

The cover flap or plastic writing board should be used to divide each set of pages before writing on them with a ball point pen

DATE

Please use the following three-letter abbreviations for the months

January	JAN
February	FEB
March	MAR
April	APR
May	MAY
June	JUN
July	JUL
August	AUG
September	SEP
October	OCT
November	NOV
December	DEC

e.g. | 0 1 | J A N | 0 0 | = *1st January 2000*

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

PATIENT INITIALS

Please use the following format:

e.g. [redacted]

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*

STUDY PROCEDURES CHART 207499/156

Visit	1	2	3	3a	4	5	6	7	8	9	10		
	Screen		Baseline								End Double-blind	Early Withdrawal[1]	Final Safety Follow-up
Time relative to baseline (weeks)	-4	-2	0	+1	+2	+4	+8	+12	+16	+20	+24		+25
Signed written informed consent	x												
Medical & surgical history	x												
Physical examination[2]	x		x								x	x	x[3]
Pulmonary history & symptoms	x												
Postero-anterior chest radiograph[4]	x												
Exacerbation assessment/resource use	x	x	x	x	x	x	x	x	x	x	x	x	x
Medication history	x												
Overall breathlessness (modified Borg)	x	x	x		x	x	x	x	x	x	x		
Resting 12-lead ECG	x		x	x	x	x	x	x	x	x	x	x	x[3]
Vital signs (BP, HR)	x[5]	x	x[5]	x	x	x	x	x	x	x	x[5]	x[5]	x
Exercise Tolerance (6-Minute walk)	x	x	x			x	x	x	x	x	x	x	
Post-exercise SaO2 & breathlessness	x	x	x			x	x	x	x	x	x	x	
CO Diffusing Capacity (DLCO)[6]	x												
Albuterol reversibility[7]	x												
Laboratory tests	x		x[8]	x	x	x	x	x	x[9]	x[9]	x[8]	x[8]	x[3,9]
Dispense single-blind medication	x	x											
Albuterol Use		x	x	x	x	x	x	x	x	x	x		
Concomitant medication/medical procedures		x	x	x	x	x	x	x	x	x	x	x	x
PFTs (in absence of albuterol)[10]		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	
Baseline signs and symptoms/AEs[11]		x	x	x	x	x	x	x	x	x	x	x	x
Health status assessment: SGRQ			x					x			x	x	
Quality of life assessment: SF-36			x								x	x	
Cough and sputum assessments			x					x			x	x	
Pharmacokinetic evaluations[12]			x			x		x			x		
Arterial blood gas/SaO2[13]			x								x		
Hourly PFTs for 4 hrs post first/last dose [14]			x								x		
Dispense double-blind medication			x	x	x	x	x	x	x	x			
Investigator/Patient global assessment											x	x	
Study conclusion record												x	x

1 Patients who stop taking study medication between clinic visits will attend the clinic within 24 hours for an early withdrawal visit.

2 To include a respiratory examination.

3 If abnormalities at previous visit for patients who complete Visit 10 or withdraw from the study.

4 Postero-anterior chest X-ray must be performed at Visit 1 unless the film from a chest X-ray within the 12 weeks prior to Visit 1 is available to the Investigator.

5 Including Orthostatic vital signs.

6 DLCO should be done between Visit 1 and Visit 3 if not performed during the previous 24 weeks or if the results are unavailable.

7 Before and 15 to 30 (± 5) minutes after administration of 180 mcg albuterol via a MDI with a spacer to determine % predicted FEV_1, FVC, FEF_{25-75}, PEFR, and FEV_1: FVC.

8 In addition to usual laboratory tests, three fecal occult blood tests will be performed between Visits 1 and 3, between Visits 9 and 10, and at early withdrawal; amylase will be measured at Visit 3.

9 Urinary beta-HCG tests will be performed in females of childbearing potential. No other laboratory samples will be collected at Visits 8 and 9.

10 Includes FEV_1, FVC, FEF_{25-75}, PEFR, and FEV_1:FVC measured by centralized spirometry by the same person at each visit.

11 A diary will be used to record if patients feel different since starting study medication.

12 Visit 3: 3 hours post-dose. Visit 5: trough and 0.5-3 hours post-dose. Visit 7: trough and 3-10 hours post-dose. Visit 10: trough only.

13 In patients with <40% of predicted FEV_1 at Visit 1 and resting SaO_2 <88% or if the patient lives at a high altitude.

14 Pulmonary function tests 30 (± 5) minutes after albuterol followed by 4-hour post-double-blind drug assessments at Visits 3 and 10.

VISIT 8, WEEK 16

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

MOD5

Please do not split modules

Module 5 :	**Visit 8, Visit 9, Adverse Experiences, Concomitant Medications, Medical Procedures, COPD Exacerbations, Resource Utilization**
CRF Pages	**197 - 240**
Unprocessed Forms :	**Within this module the following occur which will generate attachments that need to be brought in-house.**
	None

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	
207499/156		[redacted]			Visit 8 Week 16

PRESENTATION TO CLINIC

Record time of presentation to clinic ☐☐ 24hr:min

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?

☐ NA → Patient is not using beta$_2$ agonist.

☐ 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?

☐ NA → Patient is not using anticholinergic.

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: ☐☐☐ 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 : ☐☐

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials		Visit 8 Week 16
207499/156	[redacted]			

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes → *If 'Yes' please record details below. If the patient has had more than three Level 2 or 3 exacerbations since the start of double-blind medication, patient may be withdrawn after consultation with the Medical Monitor. If withdrawing, complete the assessments scheduled at this visit and the Assessments for Patients Withdrawing at Visit 8. The SGRQ and SF-36 should be completed before any additional assessments.*

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

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

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

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of excerbation (maximum level)	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1
	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2
	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations, including an increase in usual COPD medications, must be recorded in the COPD Medications or Procedures pages.

RESOURCE UTILIZATION

If the patient has received any COPD exacerbation-related medical care since the last visit, record details in the Resource Utilization section at the back of this module.

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Protocol	Patient Number	Patient Initials	Visit 8 Week 16
207499/156	[redacted]		

INDIRECT COST

Does the patient work?

☐ No

☐ Yes → *If 'Yes'*, has the patient missed work due to COPD-related symptoms, excluding scheduled protocol visits, since the last visit?

☐ No

☐ Yes → *If 'Yes', please record lost work days below:*

Start Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence

How many days since your last visit have you been restricted in performing your leisure activities, due to your COPD-related symptoms? *(please enter number of days below, if not restricted, enter 0)*

☐☐ Days

Since your last visit, how many hours per week did you require paid or unpaid assistance by a relative, friend or professional with your daily activities such as dressing, bathing, cooking, etc., due to your COPD-related symptoms? *(please enter number of hours below, if no paid or unpaid assistance, enter 0 in each instance)*

☐☐☐ Hours per week of **paid** assistance

☐☐☐ Hours per week of **unpaid** assistance

ADVERSE EXPERIENCES

If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

CONCOMITANT MEDICATION

If there has been any change in the patient's concomitant medication excluding treatment for COPD exacerbations (this is recorded in the COPD Exacerbations section) since the last visit, please record details in the Concomitant Medication section at the back of this module.

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 8 Week 16
207499/156		[redacted]			

"AS NEEDED" ALBUTEROL USE

Record the patient's evaluation of their 'as needed' albuterol use since the last visit.

[1] ☐ Much less than usual
[2] ☐ Less than usual
[3] ☐ About the same as usual
[4] ☐ More than usual
[5] ☐ Much more than usual

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	Patient Initials	Visit 8 Week 16
207499/156	[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. bid)

Date and time of last dose of study medication prior to the study visit ____ Day Month Yr ____ 24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
70					

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance < 80% or >120%?

☐ No

☐ Yes → *If 'Yes' please check the percent compliance at the previous visit. If compliance was <80% or >120% at the last visit, please contact the Medical Monitor to discuss patient withdrawal. If the patient is to be withdrawn, complete the assessments scheduled at this visit and the Assessments for Patients Withdrawing at Visit 8. The SGRQ and SF-36 should be completed before any additional assessments.*

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials	Visit 8 Week 16
207499/156	[redacted]		

OVERALL BREATHLESSNESS ASSESSMENT

Give the patient a copy of the following scale when assessing breathlessness.

Please ask the patient the following question and record the answer below.

"Generally speaking, how has your breathlessness been during the previous week when you carried out tasks that usually cause you to be short of breath (e.g. walking, carrying shopping, climbing stairs, etc)?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Overall breathlessness score ☐☐.☐

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 Exercise Tolerance Test) must be performed greater than 4 hours after the patient's last albuterol administration.

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials	Visit 8 Week 16
207499/156	[redacted]		

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
☐☐☐/☐☐☐	☐☐☐

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes.

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant changes noted at this examination compared to the last visit?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of this module.*

EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted? The distance walked should be entered even if the patient did not walk for 6 minutes.

☐ No

☐ Yes → *If 'Yes', Distance walked* ☐☐☐ Meters ☐

Yards ☐

Record any adverse experiences which occur during the exercise tolerance test in the Adverse Experience section at the back of this module.

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials	Visit 8 Week 16
207499/156	[redacted]		

POST-EXERCISE ASSESSMENTS *(Immediately after the patient completes the exercise tolerance)*

Heart Rate ☐☐☐ beats/min

SaO_2 ☐☐☐ %

Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

"How short of breath do you feel right now?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Post-exercise breathlessness score ☐☐.☐

INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise test (rest for at least 10 minutes) before performing the pulmonary function tests.

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials	Visit 8 Week 16
207499/156	[redacted]		

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 confirm that the pulmonary function tests were performed

[1] ☐ Not Performed

[2] ☐ Performed

PREGNANCY TEST

Is the patient a female of child-bearing potential?

☐ No

☐ Yes → *If 'Yes' please perform a urine pregnancy test locally.*

Urine Sample Date ☐☐ ☐☐☐ ☐☐
Day Month Yr

Is the patient pregnant?

☐ No

☐ Yes → *If 'Yes' please withdraw the patient from the study, complete the Serious Adverse Experiences form and forward it to SB within 24 hours. Complete the assessments scheduled at this visit and the Assessments for Patients Withdrawing at Visit 8. The SGRQ and SF-36 should be completed before any additional assessments.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 8 Week 16
207499/156		[redacted]			

STUDY MEDICATION LABEL

Issue the patient a 35 day supply of study medication (1 bottles, 70 tablets). Attach the tear-off label from the study medication bottle dispensed at this visit in the space below. Record the start date in the Study Medication Record section in the next visit section. Issue the patient an albuterol inhaler and retrieve their old inhaler for 'as-required' use.

Attach study medication label here

Enter 6-digit Code as it appears on the study medication label | | | | | | |

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 | | | | | |

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 8

- *If the patient **is not continuing** in the study, please complete the assessments for Visit 8 and the Assessments for Patients Withdrawing at Visit 8.*
- *If the patient **is continuing** in the study, please:*
  - *Issue the patient a diary card and and remind the patient to use the card to record if they feel differently since starting the study.*
  - *Ask the patient to return for the next visit in 28 +/- 6 days at the same time of day as at Visit 3.*
  - ***Remind the patient:***
    - i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after breakfast.*
    - ii ***not** to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).*
    - iii *to refrain from using albuterol or anticholinergic agents during the **4 hours** immediately preceding the 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 albuterol inhaler and spacer, and the diary card.*
    - vi *to continue to take the anticholinergic medication, if prescribed, at a constant dose.*
    - 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, diarrhea, 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.*

PATIENT ACTIVITY POSTCARD

Please complete the patient activity postcard for ***Visit 8*** located in the postcard section of this CRF. Detach the postcard and mail promptly. Postage has been prepaid.

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Pharmaceuticals

Protocol		Patient Number	Patient Initials		Withdrawal at Visit 8 Week 16
207499/156		[redacted]			

ASSESSMENTS FOR PATIENTS WITHDRAWING AT VISIT 8

Complete the assessments below only for patients who are withdrawing from the study.

ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

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

INVESTIGATOR GLOBAL ASSESSMENT

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

PATIENT GLOBAL ASSESSMENT

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

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Protocol		Patient Number	Patient Initials		Withdrawal at Visit 8 Week 16
207499/156		[redacted]			

COUGH AND SPUTUM PRODUCTION ASSESSMENTS

*Please ask the patient the following questions and record the answers below (Mark **one** box per section only.)*

COUGH

How troubled have you been by cough today?

[0] ☐ No symptoms at all

[1] ☐ Some symptoms, but hardly noticeable

[2] ☐ Symptoms noticeable and a little uncomfortable

[3] ☐ Symptoms definitely noticeable and uncomfortable

[4] ☐ Symptoms very bad and extremely uncomfortable

SPUTUM PRODUCTION

How much sputum have you produced today?

[0] ☐ No sputum at all

[1] ☐ Some sputum, but not as much as usual

[2] ☐ As much as usual

[3] ☐ More than usual

[4] ☐ A lot more than usual

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a **clinically significant worsening** in the patient's physical condition since the previous examination?

☐ No

☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of this module.*

SmithKline Beecham
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Protocol	Patient Number	Patient Initials	Withdrawal at Visit 8 Week 16
207499/156	[redacted]		

LABORATORY TESTS

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 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.

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes', please record the findings and/or diagnosis in the Adverse Experiences section (If a re-test is necessary, please use the Repeat Lab page at the end of this book)*

FECAL OCCULT BLOOD TEST

Issue the patient the fecal occult blood test kit. Instruct the patient to follow the Patient Instructions provided with the kit. Samples should be collected as specified on three consecutive bowel movements or three bowel movements closely spaced in time and returned to the clinic as soon as possible.

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

Are these findings clinically significant?

☐ No

☐ Yes → *If 'Yes' please record the details in the Adverse Experience section at the back of this module.*

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Protocol		Patient Number	Patient Initials		Withdrawal at Visit 8 Week 16
207499/156		[redacted]			

VITAL SIGNS - ORTHOSTATIC CHANGE

1st Measurement: After 5 Minutes Supine

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
☐☐☐ / ☐☐☐	☐☐☐

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
☐☐☐ / ☐☐☐	☐☐☐

Are there any **clincially significant worsenings** since Baseline?

☐ No

☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of this module.*

INVESTIGATOR INSTRUCTIONS

Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return for the Safety Follow-Up Visit in 7 +/- 3 days.

VISIT 9, WEEK 20

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Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	
207499/156		[redacted]			Visit 9 Week 20

PRESENTATION TO CLINIC

Record time of presentation to clinic ☐☐ 24hr:min

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?

☐ NA → Patient is not using beta$_2$ agonist.

☐ 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?

☐ NA → Patient is not using anticholinergic.

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: ☐☐☐ 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 : ☐☐

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Visit 9 Week 20
207499/156		[redacted]			

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes → *If 'Yes' please record details below. If the patient has had more than three Level 2 or 3 exacerbations since the start of double-blind medication, patient may be withdrawn after consultation with Medical Monitor. If withdrawing, complete the assessments scheduled at this visit and the Assessments for Patients Withdrawing at Visit 9. The SGRQ and SF-36 should be completed before any additional assessments.*

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

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

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

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of excerbation (maximum level)	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1
	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2
	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations, including an increase in usual COPD medications, must be recorded in the COPD Medications or Procedures pages.

RESOURCE UTILIZATION

Please complete the Resource Utilization section at the back of this module. If the patient has received any COPD exacerbation-related medical care since the last visit, record details in the Resource Utilization section at the back of this module.

SmithKline Beecham
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Protocol		Patient Number	Patient Initials		Visit 9 Week 20
207499/156		[redacted]			

INDIRECT COST

Does the patient work?

☐ No

☐ Yes → *If 'Yes'*, has the patient missed work due to COPD-related symptoms, excluding scheduled protocol visits, since the last visit?

☐ No

☐ Yes → *If 'Yes', please record lost work days below:*

Start Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence

How many days since your last visit have you been restricted in performing your leisure activities, due to your COPD-related symptoms? *(please enter number of days below, if not restricted, enter 0)*

☐☐ Days

Since your last visit, how many hours per week did you require paid or unpaid assistance by a relative, friend or professional with your daily activities such as dressing, bathing, cooking, etc., due to your COPD-related symptoms? *(please enter number of hours below, if no paid or unpaid assistance, enter 0 in each instance)*

☐☐☐ Hours per week of **paid** assistance

☐☐☐ Hours per week of **unpaid** assistance

ADVERSE EXPERIENCES

Please complete the Adverse Experience section at the back of this module. If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

SmithKline Beecham
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Protocol	Patient Number	Patient Initials	Visit 9 Week 20
207499/156	[redacted]		

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.

"AS NEEDED" ALBUTEROL USE

Record the patient's evaluation of their 'as needed' albuterol use since the last visit.

[1] ☐ Much less than usual
[2] ☐ Less than usual
[3] ☐ About the same as usual
[4] ☐ More than usual
[5] ☐ Much more than usual

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	Patient Initials	
207499/156	[redacted]		Visit 9 Week 20

STUDY MEDICATION RECORD

Record the exact start and end dates of study medication dispensed at the previous visit. The start date should be the date of the previous visit and the end date should be when the last dose of study medication was taken. Record interruptions or changes in dose on separate lines.

Start Date Day Mth Yr	End Date Day Mth Yr	Number of tablets per dose	Frequency (e.g. bid)

Date and time of last dose of study medication prior to the study visit ____ Day Month Yr ____ 24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
70					

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance < 80% or >120%?

☐ No

☐ Yes → *If 'Yes' please check the percent compliance at the previous visit. If compliance was <80% or >120% at the last visit, please contact the Medical Monitor to discuss patient withdrawal. If the patient is to be withdrawn, complete the assessments scheduled at this visit and the Assessments for Patients Withdrawing at Visit 9. The SGRQ and SF-36 should be completed before any additional assessments.*

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials	Visit 9 Week 20
207499/156	[redacted]		

OVERALL BREATHLESSNESS ASSESSMENT

Give the patient a copy of the following scale when assessing breathlessness.

Please ask the patient the following question and record the answer below.

"Generally speaking, how has your breathlessness been during the previous week when you carried out tasks that usually cause you to be short of breath (e.g. walking, carrying shopping, climbing stairs, etc)?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Overall breathlessness score ☐☐.☐

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 Exercise Tolerance Test) must be performed greater than 4 hours after the patient's last albuterol administration.

SmithKline Beecham Pharmaceuticals

Protocol	Patient Number	Patient Initials	Visit 9 Week 20
207499/156	[redacted]		

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
☐☐☐/☐☐☐	☐☐☐

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes.

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant changes noted at this examination compared to the last visit?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of this module.*

EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted? The distance walked should be entered even if the patient did not walk for 6 minutes.

☐ No

☐ Yes → *If 'Yes', Distance walked* ☐☐☐ Meters ☐

Yards ☐

Record any adverse experiences which occur during the exercise tolerance test in the Adverse Experience section at the back of this module.

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials	Visit 9 Week 20
207499/156	[redacted]		

POST-EXERCISE ASSESSMENTS *(Immediately after the patient completes the exercise tolerance)*

Heart Rate ☐☐☐ beats/min

SaO_2 ☐☐☐ %

Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

"How short of breath do you feel right now?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Post-exercise breathlessness score ☐☐.☐

INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise test (rest for at least 10 minutes) before performing the pulmonary function tests.

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials	Visit 9 Week 20
207499/156	[redacted]		

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 confirm that the pulmonary function tests were performed

[1] ☐ Not Performed

[2] ☐ Performed

PREGNANCY TEST

Is the patient a female of child-bearing potential?

☐ No

☐ Yes → *If 'Yes' please perform a urine pregnancy test locally.*

Urine Sample Date ☐☐ ☐☐☐ ☐☐
Day Month Yr

Is the patient pregnant?

☐ No

☐ Yes → *If 'Yes' please withdraw the patient from the study, complete the Serious Adverse Experiences form and forward it to SB within 24 hours. Complete the assessments scheduled at this visit and the Assessments for Patients Withdrawing at Visit 9. The SGRQ and SF-36 should be completed before any additional assessments.*

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials	Visit 9 Week 20
207499/156	[redacted]		

STUDY MEDICATION LABEL

Issue the patient a 35 day supply of study medication (1 bottle, 70 tablets). Attach the tear-off label from the study medication bottle dispensed at this visit in the space below. Record the start date in the Study Medication Record section in the next visit section. Issue the patient an albuterol inhaler and retrieve their old inhaler for 'as-required' use.

Attach study medication label here

Enter 6-digit Code as it appears on the study medication label | | | | | | |

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

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 9

- *If the patient **is not continuing** in the study, please complete the assessments for Visit 9 and the Assessments for Patients Withdrawing at Visit 9.*
- *If the patient **is continuing** in the study, please:*
  - *Issue the patient a diary card and and remind the patient to use the card to record if they feel differently since starting the study.*
  - *Issue the patient the fecal occult blood test kit. Instruct the patient to follow the Patient Instructions provided with the kit. Samples should be collected as specified and returned by the next visit.*
  - *Ask the patient to return for the next visit in 28 +/- 6 days at the same time of day as at Visit 3.*
  - ***Remind the patient:***

    i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after breakfast.*

    ii ***not** to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).*

    iii *to refrain from using albuterol or anticholinergic agents during the **4 hours** immediately preceding the 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 albuterol inhaler and spacer, and the diary card.*

    vi *to continue to take the anticholinergic medication, if prescribed, at a constant dose.*

    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, diarrhea, 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.*

PATIENT ACTIVITY POSTCARD

Please complete the patient activity postcard for ***Visit 9*** located in the postcard section of this CRF. Detach the postcard and mail promptly. Postage has been prepaid.

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Withdrawal at Visit 9 Week 20
207499/156		[redacted]			

ASSESSMENTS FOR PATIENTS WITHDRAWING AT VISIT 9

Complete the assessments below only for patients who are withdrawing from the study.

ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

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

INVESTIGATOR GLOBAL ASSESSMENT

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

PATIENT GLOBAL ASSESSMENT

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	Patient Initials		Withdrawal at Visit 9 Week 20
207499/156		[redacted]			

COUGH AND SPUTUM PRODUCTION ASSESSMENTS

*Please ask the patient the following questions and record the answers below (Mark **one** box per section only.)*

COUGH

How troubled have you been by cough today?

[0] ☐ No symptoms at all

[1] ☐ Some symptoms, but hardly noticeable

[2] ☐ Symptoms noticeable and a little uncomfortable

[3] ☐ Symptoms definitely noticeable and uncomfortable

[4] ☐ Symptoms very bad and extremely uncomfortable

SPUTUM PRODUCTION

How much sputum have you produced today?

[0] ☐ No sputum at all

[1] ☐ Some sputum, but not as much as usual

[2] ☐ As much as usual

[3] ☐ More than usual

[4] ☐ A lot more than usual

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a **clinically significant worsening** in the patient's physical condition since the previous examination?

☐ No

☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of this module.*

SmithKline Beecham
Pharmaceuticals

Protocol	Patient Number	Patient Initials	Withdrawal at Visit 9 Week 20
207499/156	[redacted]		

LABORATORY TESTS

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 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.

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes', please record the findings and/or diagnosis in the Adverse Experiences section (If a re-test is necessary, please use the Repeat Lab page at the end of this book)*

FECAL OCCULT BLOOD TEST

Issue the patient the fecal occult blood test kit. Instruct the patient to follow the Patient Instructions provided with the kit. Samples should be collected as specified on three consecutive bowel movements or three bowel movements closely spaced in time and returned to the clinic as soon as possible.

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

Are these findings clinically significant?

☐ No

☐ Yes → *If 'Yes' please record the details in the Adverse Experience section at the back of this module.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Withdrawal at Visit 9 Week 20
207499/156		[redacted]			

VITAL SIGNS - ORTHOSTATIC CHANGE

1st Measurement: After 5 Minutes Supine

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
___ / ___	___

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
___ / ___	___

Are there any **clincially significant worsenings** since Baseline?

☐ No

☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of this module.*

INVESTIGATOR INSTRUCTIONS

Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return for the Safety Follow-Up Visit in 7 +/- 3 days.

ADVERSE EXPERIENCES (Non-serious)

DEFINITIONS

INTENSITY (Maximum)

MILD	*Adverse experience which is easily tolerated*
MODERATE	*Adverse experience sufficiently discomforting to interfere with daily activities*
SEVERE	*Adverse experience which prevents normal everyday activities*

RELATIONSHIP TO INVESTIGATIONAL DRUG

NOT RELATED	*The adverse experience is definitely not related to the test drug*
UNLIKELY	*There are other more likely causes and the drug is not suspected as a cause*
SUSPECTED (REASONABLE POSSIBILITY)	*A direct cause and effect relationship between the drug and the adverse experience has not been demonstrated but there is a reasonable possibility that the experience was caused by the drug*
PROBABLE	*There probably is a direct cause and effect relationship between the adverse experience and the study drug*

SERIOUS ADVERSE EXPERIENCE (SAE)

An SAE is any 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	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

ADVERSE EXPERIENCES (Non-serious)

*Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Have you felt different in any way since starting the treatment or since the previous 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).

If no adverse experiences occured since the previous module (i.e., since Visit 7), please mark this box. ☐

Adverse Experience *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***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) *See definitions page for Adverse Experience*	[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 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	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

ADVERSE EXPERIENCES (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 previous 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).

If no adverse experiences occured since the previous module (i.e., since Visit 7), please mark this box. ☐

Adverse Experience *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***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) *See definitions page for Adverse Experience*	[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 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	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

ADVERSE EXPERIENCES (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 previous 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).

If no adverse experiences occured since the previous module (i.e., since Visit 7), please mark this box. ☐

Adverse Experience *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***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) *See definitions page for Adverse Experience*	[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 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)

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

CONCOMITANT MEDICATION

Record any changes in concomitant medication taken since the previous module (i.e., since Visit 7). (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 (albuterol) use, using the date the study inhaler was returned.

☐ No concomitant medication changes since the previous module (i.e., since Visit 7)

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 Route, see General Instructions for acceptable abbreviations.*

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 (albuterol) 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 Route, see General Instructions for acceptable abbreviations.*

MEDICAL PROCEDURES
excluding treatment for COPD Exacerbations
(These are recorded in the COPD Exacerbations section)

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 (i.e., since Visit 7)?

☐ 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			

COPD EXACERBATION SECTION

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 previous module (i.e., since Visit 7) should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages***

If no COPD Exacerbations since previous module (i.e., since Visit 7), please mark this box. ☐

Adverse Experience	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***If patient died, STOP: go to SAE COPD Exacerbation pages.***	[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) *See definitions page for Adverse Experience form*	[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 COPD Medications and/or Medical Procedures page*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

DETAILS OF COPD EXACERBATIONS - CONTINUED

*An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy.*
*All exacerbations of COPD since the previous module (i.e., since Visit 7) should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages***

If no COPD Exacerbations since previous module (i.e., since Visit 7), please mark this box. ☐

Adverse Experience	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***If patient died, STOP: go to SAE COPD Exacerbation pages.***	[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) *See definitions page for Adverse Experience form*	[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 COPD Medications and/or Medical Procedures page*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

DETAILS OF COPD EXACERBATIONS - CONTINUED

*An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy.*
*All exacerbations of COPD since the previous module (i.e., since Visit 7) should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages***

If no COPD Exacerbations since previous module (i.e., since Visit 7), please mark this box. ☐

Adverse Experience	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***If patient died, STOP: go to SAE COPD Exacerbation pages.***	[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) *See definitions page for Adverse Experience form*	[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 COPD Medications and/or Medical Procedures page*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No

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	Center Number	Patient Number	Patient Initials	SB Receipt Date Day Month Year
207499/156		[redacted]		

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation

Person Reporting SAE *(Please print clearly)* _____

AEGIS Number

Serious Adverse Experience *(Please print clearly)*: **COPD Exacerbation**

Specify reason(s) for considering this a serious AE. Mark all that apply.

- [1] ☐ fatal
- [2] ☐ life threatening
- [3] ☐ disabling/incapacitating
- [4] ☐ results in hospitalization (excluding elective surgery or routine clinical procedures)
- [5] ☐ hospitalization 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 COPD Medication or Medical Procedures section*: ☐ Yes ☐ No

Was patient withdrawn due to this specific SAE ?: ☐ Yes ☐ No

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Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation (cont)

Relevant Laboratory Data
Please provide relevant abnormal laboratory data below

Test	Date	Value	Units	Normal Range
	Day Month Yr			
	Day Month Yr			
	Day Month Yr			
	Day Month Yr			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomization code broken at investigational site? ☐ No ☐ Yes

Randomization 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

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Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

SERIOUS ADVERSE EXPERIENCE - COPD EXACERBATION (Cont.) PHARMACOKINETIC EVALUATION

If the patient presents to the clinic within 24 hours of the onset of a serious adverse experience (SAE) COPD Exacerbation or with an ongoing SAE COPD Exacerbation, please collect a blood sample (5mL) for pharmacokinetic evaluation.

Was a pharmacokinetic sample taken?

☐ No

☐ Yes → *If 'Yes',* 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 taken prior to the onset of the serious adverse experience - COPD exacerbation

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 serious adverse experience - COPD exacerbation?

☐ No

☐ Yes → *If 'Yes',* record date and time of last dose of study medication taken prior to collection of the pharmacokinetic sample.

Day Month Yr 24hr:min

Was this dose taken with food?

☐ No

☐ Yes

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Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

MEDICATION FOR COPD EXACERBATIONS

Has the patient taken any medication for COPD exacerbations since the previous module (i.e., since Visit 7)?

☐ No

☐ Yes → *If 'Yes', please record details below*

Drug Name (Trade Name Preferred)	Unit Dose (eg 500mg)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible) Day Mth Yr	End Date (or if Continuing mark box) Day Mth Yr	
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							

** For Route, see General Instructions for acceptable abbreviations.*

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Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

MEDICAL PROCEDURES FOR COPD EXACERBATIONS

Have any non-medication, therapeutic, diagnostic or surgical procedures been performed for COPD exacerbations since the previous module (i.e., since Visit 7)?

☐ 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		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			

RESOURCE UTILIZATION

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Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

RESOURCE UTILIZATION

Has the patient utilized any COPD Exacerbation-related medical care since the previous module (i.e., since Visit 7)?

☐ No

☐ Yes → *If 'Yes', please record details below*

Has the patient had any **Physician Visits** (COPD care excluding scheduled protocol visits) since the previous module (i.e., since Visit 7)?

☐ No

☐ Yes → *If 'Yes', please record details below*

Date of Visit Day Mth Yr	Reason for Visit

Has the patient had any **Emergency Room (ER)/Urgent Care Visits/Procedures (i.e., lung surgery)** between since the previous module (i.e., since Visit 7)?

☐ No

☐ Yes → *If 'Yes', please record details below*

Date of Visit Day Mth Yr	Reason for Visit	Patient Admitted from ER? Yes	No
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐

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Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

RESOURCE UTILIZATION - (cont)

Has the patient had any **Hospitalizations** since the previous module (i.e., since Visit 7)?

☐ No

☐ Yes → *If 'Yes', please record details below* ***(also record details of any hospitalization in the Serious Adverse Experience - COPD Exacerbation section)***

Name of Hospital & City	Date of Admission Day Mth Yr	Date of Discharge Day Mth Yr	Reason for Admission

Has the patient had any **Intensive Care Unit (ICU) stays** ***(did the patient stay in the ICU during any of the above hospitalizations?)*** since the previous module (i.e., since Visit 7)?

☐ 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

VISIT 10, WEEK 24

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Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

MOD6

Please do not split modules

Module 6 : Visit 10, Adverse Experiences, Concomitant Medications, Medical Procedures, COPD Exacerbations, Resource Utilization

CRF Pages 241 - 280

Unprocessed Forms : Within this module the following occur which will generate attachments that need to be brought in-house.

None

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Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	
207499/156		[redacted]			Visit 10 Week 24

PRESENTATION TO CLINIC

Record time of presentation to clinic ☐☐ 24hr:min

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?

☐ NA → Patient is not using beta$_2$ agonist.

☐ 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?

☐ NA → Patient is not using anticholinergic.

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: ☐☐☐ 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 : ☐☐

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes

ST. GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

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

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Protocol		Patient Number	Patient Initials		Visit 10 Week 24
207499/156		[redacted]			

ST. GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE (PAGE 1 OF 5)

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Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day / Month / Year)	
207499/156		[redacted]			Visit 10 Week 24

SF - 36 (HEALTH STATUS QUESTIONNAIRE) (Page 1 of 5)

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Protocol		Patient Number	Patient Initials		Visit 10 Week 24
207499/156		[redacted]			

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes → *If 'Yes' please record details below.*

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

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

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

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of excerbation (maximum level)	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1
	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2
	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations, including an increase in usual COPD medications, must be recorded in the COPD Medications or Procedures pages.

RESOURCE UTILIZATION

Please complete the Resource Utilization section at the back of this module. If the patient has received any COPD exacerbation related medical care since the previous visit, please complete the COPD Resource Utilization section at the back of this module.

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Protocol		Patient Number	Patient Initials		Visit 10 Week 24
207499/156		[redacted]			

INDIRECT COST

Does the patient work?

☐ No

☐ Yes → *If 'Yes'*, has the patient missed work due to COPD-related symptoms, excluding scheduled protocol visits, since the last visit?

☐ No

☐ Yes → *If 'Yes', please record lost work days below:*

Start Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence

How many days since your last visit have you been restricted in performing your leisure activities, due to your COPD-related symptoms? *(please enter number of days below, if not restricted, enter 0)*

☐☐ Days

Since your last visit, how many hours per week did you require paid or unpaid assistance by a relative, friend or professional with your daily activities such as dressing, bathing, cooking, etc., due to your COPD-related symptoms? *(please enter number of hours below, if no paid or unpaid assistance, enter 0 in each instance)*

☐☐☐ Hours per week of **paid** assistance

☐☐☐ Hours per week of **unpaid** assistance

ADVERSE EXPERIENCES

Please complete the Adverse Experience section at the back of this module. If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

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Protocol	Patient Number	Patient Initials	Visit 10 Week 24
207499/156	[redacted]		

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.

"AS NEEDED" ALBUTEROL USE

Record the patient's evaluation of their 'as needed' albuterol use since the last visit.

[1] ☐ Much less than usual
[2] ☐ Less than usual
[3] ☐ About the same as usual
[4] ☐ More than usual
[5] ☐ Much more than usual

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.

FECAL OCCULT BLOOD TEST

The fecal occult blood test should be performed on three consecutive bowel movements or on bowel movements closely spaced in time between Visits 9 and 10.

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

Are these findings clinically significant?

☐ No

☐ Yes → *If 'Yes' please record the details in the Adverse Experience section at the back of this module.*

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Protocol		Patient Number	Patient Initials		Visit 10 Week 24
207499/156		[redacted]			

INVESTIGATOR GLOBAL ASSESSMENT

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PATIENT GLOBAL ASSESSMENT

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

COUGH AND SPUTUM PRODUCTION ASSESSMENTS

*Please ask the patient the following questions and record the answers below (Mark **one** box per section only.)*

COUGH

How troubled have you been by cough today?

[0] ☐ No symptoms at all

[1] ☐ Some symptoms, but hardly noticeable

[2] ☐ Symptoms noticeable and a little uncomfortable

[3] ☐ Symptoms definitely noticeable and uncomfortable

[4] ☐ Symptoms very bad and extremely uncomfortable

SPUTUM PRODUCTION

How much sputum have you produced today?

[0] ☐ No sputum at all

[1] ☐ Some sputum, but not as much as usual

[2] ☐ As much as usual

[3] ☐ More than usual

[4] ☐ A lot more than usual

SmithKline Beecham
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Protocol	Patient Number	Patient Initials	Visit 10 Week 24
207499/156	[redacted]		

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a **clinically significant worsening** in the patient's physical condition since the previous examination?

☐ No

☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of this module.*

OVERALL BREATHLESSNESS ASSESSMENT

Give the patient a copy of the following scale when assessing breathlessness.

Please ask the patient the following question and record the answer below.

"Generally speaking, how has your breathlessness been during the previous week when you carried out tasks that usually cause you to be short of breath (e.g. walking, carrying shopping, climbing stairs, etc)?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Overall breathlessness score ☐☐.☐

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 Exercise Tolerance Test) must be performed greater than 4 hours after the patient's last albuterol administration.

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Protocol		Patient Number	Patient Initials		Visit 10 Week 24
207499/156		[redacted]			

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
☐☐☐ / ☐☐☐	☐☐☐

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

VITAL SIGNS - ORTHOSTATIC CHANGE

1st Measurement: After 5 Minutes Supine

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
☐☐☐ / ☐☐☐	☐☐☐

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
☐☐☐ / ☐☐☐	☐☐☐

Are there any clinically significant worsenings since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

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Protocol	Patient Number	Patient Initials		Visit 10 Week 24
207499/156	[redacted]			

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes.

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant changes noted at this examination compared to the last visit?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of this module.*

RESTING SaO_2

Measure Resting SaO_2 by pulse oximetry for all patients with an FEV_1 < 40% of predicted for age, height and gender at Visit 1.

[1] ☐ Measurement not required (patient's FEV_1 at Visit 1 ≥ 40% of predicted)

[2] ☐ Measurement required but not performed

[3] ☐ Measurement taken, *please record value below:*

Resting SaO_2 ☐☐☐ %

EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted? The distance walked should be entered even if the patient did not walk for 6 minutes.

☐ No

☐ Yes → *If 'Yes', Distance walked* ☐☐☐ [M] Meters ☐

[YD] Yards ☐

Record any adverse experiences which occur during the exercise tolerance test in the Adverse Experience section at the back of this module.

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Protocol		Patient Number	Patient Initials		Visit 10 Week 24
207499/156		[redacted]			

POST-EXERCISE ASSESSMENTS *(Immediately after the patient completes the exercise tolerance)*

Heart Rate ☐☐☐ beats/min

SaO_2 ☐☐☐ %

Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

"How short of breath do you feel right now?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Post-exercise breathlessness score ☐☐.☐

INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise tolerance test (rest for at least 10 minutes) before performing the pulmonary function tests.

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Protocol	Patient Number	Patient Initials	Visit 10 Week 24
207499/156	[redacted]		

PULMONARY FUNCTION TESTS (PRE-ALBUTEROL)

Pulmonary function tests will be assessed at least 4 hours after the last dose of inhaled beta-$_2$ agonist or anticholinergic agent.
NOTE: Additional pulmonary function tests will be performed after a dose of study albuterol is given in the clinic (see next page).

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 confirm that the pulmonary function tests were performed

[1] ☐ Not Performed

[2] ☐ Performed

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. If the pregnancy test is positive, complete the Serious Adverse Experiences form and forward it to SB within 24 hours.

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes', please record the findings and/or diagnosis in the Adverse Experiences section (If a re-test is necessary, please use the Repeat Lab page at the end of this book)*

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Protocol		Patient Number	Patient Initials		Visit 10 Week 24
207499/156		[redacted]			

ARTERIAL BLOOD GASES

If a resting SaO2 test was required at this visit AND the patient's resting SaO2 < 88% OR the patient lives at a high altitude, please take an arterial blood gas sample for analysis if feasible. The patient should be rested (5 to 10 minute rest) after pulmonary function tests.

☐ Not required

☐ Sample required but not taken

PO_2 (mmHg)	PCO_2 (mmHg)	HCO_3- (mEq/L)	pH	SaO_2 %
☐☐☐	☐☐	☐☐	☐.☐☐	☐☐☐

POST-ALBUTEROL PULMONARY FUNCTION TESTS

Administer 180mcg (2 puffs) of albuterol via MDI with a spacer using the study inhaler provided for "as required" rescue-medication use.

Record the time of albuterol inhalation ☐☐ 24hr:min

Wait 30 minutes *(+/-5 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 manuals).*** *For each set of three FEV_1 measurements, one FEV_1 must be within 10% of the highest.*

Please confirm that the pulmonary function tests were performed

[1] ☐ Not Performed

[2] ☐ Performed

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Protocol	Patient Number	Patient Initials	Visit 10 Week 24
207499/156	[redacted]		

PHARMACOKINETIC EVALUATIONS - PRE-DOSE BLOOD SAMPLE

Record the date and time of the previous two doses of study medication.

Study Medication Taken	Date Day Mth Yr	Time 24hr:min	Did the patient take this dose with food ?	
Yesterday's Morning Dose			☐ Yes	☐ No
Yesterday's Evening Dose			☐ Yes	☐ No

Collect a pre-dose blood sample (5mL) for pharmacokinetic evaluation.

Was a pharmacokinetic sample taken?

☐ No

☐ Yes → *If 'Yes',* 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)

Did the patient accidentally take this morning's dose prior to attending the clinic?

☐ No

☐ Yes → *If 'Yes', check that the Study Medication Record for this visit is recorded correctly.*

ADMINISTRATION OF STUDY MEDICATION

Give the patient their dose of study medication (from the bottle dispensed at Visit 9) with food and record the date and time of administration below.

Date and time of administration ☐☐ ☐☐☐ ☐☐ Day Month Yr ☐☐ 24hr:min

Note: If this is a morning visit, patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

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Protocol		Patient Number	Patient Initials		Visit 10 Week 24
207499/156		[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 (and should reflect the date of the dose given in the clinic at Visit 10). Record interruptions or changes in dose on separate lines.

Start Date Day Mth Yr	End Date Day Mth Yr	Number of tablets per dose	Frequency (e.g. bid)

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
70					

Note: Include the dose of study medication given to the patient at this visit.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance < 80% or > 120%?

☐ No

☐ Yes

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Protocol		Patient Number	Patient Initials		Visit 10 Week 24
207499/156		[redacted]			

POST-DOSE PULMONARY FUNCTION TESTS

Pulmonary function tests will be completed every hour in the 4-hour period following administration of the dose of study medication.

Ask the patient to avoid using their albuterol or anticholinergic medication and to refrain from smoking if at all possible.

If the patient uses their albuterol or anticholinergic medication during this period, the tests should be abandoned.

Time post-dose	Completed?	
	Yes	No
1 Hour	☐	☐
2 Hours	☐	☐
3 Hours	**Perform ECG**	
3 Hours	☐	☐
4 Hours	☐	☐

Record any adverse experiences which occur during the pulmonary function tests in the Adverse Experience section at the back of this module.

12 LEAD ELECTROCARDIOGRAM - 3 HOURS POST DOSE

The ECG should be performed before the 3-hour post-dose pulmonary function test and after the patient has been semi-supine for 5 minutes.

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant changes noted at this examination compared to the ECG performed earlier in this visit?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of this module.*

INSTRUCTIONS TO THE INVESTIGATOR AT VISIT 10

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 previous COPD medications as appropriate.*
- ***Remind the patient:***

  i *to refrain from using albuterol or anticholinergic agents during the **4 hours** immediately preceding the visit.*

  ii *to refrain from smoking for **2 hours** immediately preceding the visit.*

  iii *to bring the study albuterol inhaler and spacer to the visit.*

  iv *to call the investigator as soon as possible to report any gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhea, 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.*

PATIENT ACTIVITY POSTCARD

Please complete the patient activity postcard for ***Visit 10*** located in the postcard section of this CRF. Detach the postcard and mail promptly. Postage has been prepaid.

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	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

ADVERSE EXPERIENCES (Non-serious)

*Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Have you felt different in any way since starting the treatment or since the previous 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).

If no adverse experiences occured since the last visit, please mark this box. ☐

Adverse Experience *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***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) *See definitions page for Adverse Experience*	[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 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	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

ADVERSE EXPERIENCES (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 previous 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).

If no adverse experiences occured since the last visit, please mark this box. ☐

Adverse Experience *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***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) *See definitions page for Adverse Experience*	[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 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	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

ADVERSE EXPERIENCES (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 previous 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).

If no adverse experiences occured since the last visit, please mark this box. ☐

Adverse Experience *(please print clearly)*		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***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) *See definitions page for Adverse Experience*	[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 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)

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

CONCOMITANT MEDICATION

Record any changes in concomitant medication taken since the last 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 (albuterol) use, using the date the study inhaler was returned.

☐ No concomitant medication changes since the last visit

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 Route, see General Instructions for acceptable abbreviations.*

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 (albuterol) 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 Route, see General Instructions for acceptable abbreviations.

MEDICAL PROCEDURES
excluding treatment for COPD Exacerbations
(These are recorded in the COPD Exacerbations section)

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 visit?

☐ 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			

COPD EXACERBATION SECTION

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[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 visit should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages***

If no COPD Exacerbations since the last visit, please mark this box. ☐

Adverse Experience	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***If patient died, STOP: go to SAE COPD Exacerbation pages.***	[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) *See definitions page for Adverse Experience*	[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 COPD Medication 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	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

DETAILS OF COPD EXACERBATIONS - CONTINUED

*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 since the last visit should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages***

If no COPD Exacerbations since the last visit, please mark this box. ☐

Adverse Experience	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***If patient died, STOP: go to SAE COPD Exacerbation pages.***	[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) *See definitions page for Adverse Experience*	[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 COPD Medication 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	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

DETAILS OF COPD EXACERBATIONS - CONTINUED

*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 since the last visit should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages***

If no COPD Exacerbations since the last visit, please mark this box. ☐

Adverse Experience	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time *(If ongoing please leave blank)*	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome ***If patient died, STOP: go to SAE COPD Exacerbation pages.***	[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) *See definitions page for Adverse Experience*	[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 COPD Medication and/or Medical Procedures section if appropriate*	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No

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	Center Number	Patient Number	Patient Initials	SB Receipt Date (Day Month Year)
207499/156		[redacted]		

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation

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 hospitalization (excluding elective surgery or routine clinical procedures)
[5] ☐ hospitalization 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 COPD Medication or Medical Procedures section* ←
☐ Yes ☐ No

Was patient withdrawn due to this specific SAE ?
☐ Yes ☐ No

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation (cont)

Relevant Laboratory Data
Please provide relevant abnormal laboratory data below

Test	Date	Value	Units	Normal Range
	Day Month Yr			
	Day Month Yr			
	Day Month Yr			
	Day Month Yr			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomization code broken at investigational site? ☐ No ☐ Yes

Randomization 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 _____

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

SERIOUS ADVERSE EXPERIENCE - COPD EXACERBATION (Cont.) PHARMACOKINETIC EVALUATION

If the patient presents to the clinic within 24 hours of the onset of a serious adverse experience (SAE) COPD Exacerbation or with an ongoing SAE COPD Exacerbation, please collect a blood sample (5mL) for pharmacokinetic evaluation.

Was a pharmacokinetic sample taken?

☐ No

☐ Yes → *If 'Yes'*, 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 taken prior to the onset of the serious adverse experience - COPD exacerbation

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 serious adverse experience - COPD exacerbation?

☐ No

☐ Yes → *If 'Yes'*, record date and time of last dose of study medication taken prior to collection of the pharmacokinetic sample.

Day Month Yr 24hr:min

Was this dose taken with food?

☐ No

☐ Yes

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

MEDICATION FOR COPD EXACERBATIONS

Has the patient taken any medication for COPD exacerbations since the previous visit?

☐ No

☐ Yes → *If 'Yes', please record details below*

Drug Name (Trade Name Preferred)	Unit Dose (eg 500mg)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible) Day Mth Yr	End Date (or if Continuing mark box) Day Mth Yr	
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							
				COPD EXACERBATION			
For SB							

* *For Route, see General Instructions for acceptable abbreviations.*

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

MEDICAL PROCEDURES FOR COPD EXACERBATIONS

Have any non-medication, therapeutic, diagnostic or surgical procedures been performed for COPD exacerbations since the previous visit?

☐ 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		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			
	COPD EXACERBATION		
For SB			

RESOURCE UTILIZATION

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

RESOURCE UTILIZATION

Has the patient utilized any COPD Exacerbation-related medical care since the last visit?

☐ No

☐ Yes → *If 'Yes', please record details below*

Has the patient had any **Physician Visits** (COPD care excluding scheduled protocol visits) since the last visit?

☐ No

☐ Yes → *If 'Yes', please record details below*

Date of Visit Day Mth Yr	Reason for Visit

Has the patient had any **Emergency Room (ER)/Urgent Care Visits/Procedures (i.e., lung surgery)** since the last visit?

☐ No

☐ Yes → *If 'Yes', please record details below*

Date of Visit Day Mth Yr	Reason for Visit	Patient Admitted from ER? Yes	No
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

RESOURCE UTILIZATION - (cont)

Has the patient had any **Hospitalizations** since the last visit?

☐ No

☐ Yes → *If 'Yes', please record details below* ***(also record details of any hospitalization in the Serious Adverse Experience - COPD Exacerbation section)***

Name of Hospital & City	Date of Admission Day Mth Yr	Date of Discharge Day Mth Yr	Reason for Admission

Has the patient had any **Intensive Care Unit (ICU) stays** ***(did the patient stay in the ICU during any of the above hospitalizations?)*** since the last visit?

☐ 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

EARLY WITHDRAWAL BETWEEN SCHEDULED VISITS

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

EW2

Please do not split modules

Module : Early Withdrawal Between Scheduled Visits

CRF Pages 281 - 291

Unprocessed Forms : Within this module the following occur which will generate attachments that need to be brought in-house.

Early Withdrawal:
SGRQ Quality of Life Assessment
SF-36 Quality of Life Assessment

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Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

Complete these assessments ONLY for patients who withdraw from the study between scheduled clinic visits. These assessments should be completed within 24 hours of stopping study medication.

PRESENTATION TO CLINIC

Record time of presentation to clinic ☐☐ 24hr:min

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?

☐ NA → Patient is not using $beta_2$ agonist.

☐ 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?

☐ NA → Patient is not using anticholinergic.

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: ☐☐☐ 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 : ☐☐

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

ST. GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

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

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes ⟶ *If 'Yes' please record details below.*

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

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

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

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of excerbation (maximum level)	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1
	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2
	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of the module which contains the visit (or visit interval) at which the patient withdrew, 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 UTILIZATION

If the patient has received any COPD exacerbation related medical care since the previous visit, record details in the Resource Utilization section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

INDIRECT COST

Does the patient work?

☐ No

☐ Yes → *If 'Yes'*, has the patient missed work due to COPD-related symptoms, excluding scheduled protocol visits, since the last visit?

☐ No

☐ Yes → *If 'Yes', please record lost work days below:*

Start Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence

How many days since your last visit have you been restricted in performing your leisure activities, due to your COPD-related symptoms? *(please enter number of days below, if not restricted, enter 0)*

☐☐ Days

Since your last visit, how many hours per week did you require paid or unpaid assistance by a relative, friend or professional with your daily activities such as dressing, bathing, cooking, etc., due to your COPD-related symptoms? *(please enter number of hours below, if no paid or unpaid assistance, enter 0 in each instance)*

☐☐☐ Hours per week of **paid** assistance

☐☐☐ Hours per week of **unpaid** assistance

ADVERSE EXPERIENCES

If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of the module which contains the visit (or visit interval) at which the patient withdrew. The patient should refer to the notes in their diary when answering this question.

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

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 the module which contains the visit (or visit interval) at which the patient withdrew.

"AS NEEDED" ALBUTEROL USE

Record the patient's evaluation of their 'as needed' albuterol use since the last visit.

[1] ☐ Much less than usual
[2] ☐ Less than usual
[3] ☐ About the same as usual
[4] ☐ More than usual
[5] ☐ Much more than usual

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 the module which contains the visit (or visit interval) at which the patient withdrew.

INVESTIGATOR GLOBAL ASSESSMENT

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

PATIENT GLOBAL ASSESSMENT

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	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

COUGH AND SPUTUM PRODUCTION ASSESSMENTS

*Please ask the patient the following questions and record the answers below (Mark **one** box per section only.)*

COUGH

How troubled have you been by cough today?

[0] ☐ No symptoms at all

[1] ☐ Some symptoms, but hardly noticeable

[2] ☐ Symptoms noticeable and a little uncomfortable

[3] ☐ Symptoms definitely noticeable and uncomfortable

[4] ☐ Symptoms very bad and extremely uncomfortable

SPUTUM PRODUCTION

How much sputum have you produced today?

[0] ☐ No sputum at all

[1] ☐ Some sputum, but not as much as usual

[2] ☐ As much as usual

[3] ☐ More than usual

[4] ☐ A lot more than usual

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a **clinically significant worsening** in the patient's physical condition since the previous examination?

☐ No

☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.*

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Pharmaceuticals

Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

FECAL OCCULT BLOOD TEST

Issue the patient the fecal occult blood test kit. Instruct the patient to follow the Patient Instructions provided with the kit. Samples should be collected as specified on three consecutive bowel movements or three bowel movements closely spaced in time and returned to the clinic as soon as possible.

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

Are these findings clinically significant?

☐ No

☐ Yes → *If 'Yes' please record the details in the Adverse Experience section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.*

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Pharmaceuticals

Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[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. bid)

Date and time of last dose of study medication prior to the study visit ____ ____ ____ (Day Month Yr) ____ ____ (24hr:min)

Did the patient take their last dose with food?

☐ No

☐ Yes

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance

Note: If this is a morning visit, patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance ≥ 80% and ≤120%?

☐ No

☐ Yes

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Pharmaceuticals

Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[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 and ECG) must be performed greater than 4 hours after the patient's last albuterol administration.

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
☐☐☐/☐☐☐	☐☐☐

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.*

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Pharmaceuticals

Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

VITAL SIGNS - ORTHOSTATIC CHANGE

1st Measurement: After 5 Minutes Supine

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
___ / ___	___

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
___ / ___	___

Are there any clinically significant worsenings since Baseline?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes.

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant changes noted at this examination compared to the last visit?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted? The distance walked should be entered even if the patient did not walk for 6 minutes.

☐ No

☐ Yes → *If 'Yes', Distance walked* ☐☐☐ [M] Meters ☐

[YD] Yards ☐

Record any adverse experiences which occur during the exercise tolerance test in the Adverse Experience section at the back of the module which contains the visit (or visit interval) at which the patient withdrew.

POST-EXERCISE ASSESSMENTS *(Immediately after the patient completes the exercise tolerance)*

Heart Rate ☐☐☐ beats/min

SaO_2 ☐☐☐ %

Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

"How short of breath do you feel right now?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

0	Nothing at all
1	Very, very slight (just noticeable)
2	Very slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Post-exercise breathlessness score ☐☐.☐

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Early Withdrawal between Scheduled Visits
207499/156		[redacted]			

INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise test (rest for at least 10 minutes) before performing the pulmonary function tests.

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 confirm that the pulmonary function tests were performed

[1] ☐ Not Performed

[2] ☐ Performed

LABORATORY TESTS

Please take blood samples for hematology, 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. If the pregnancy test is positive, please complete the Serious Adverse Experiences form and forward it to SB within 24 hours.

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes', please record the findings and/or diagnosis in the Adverse Experiences section (If a re-test is necessary, please use the Repeat Lab page at the end of this book)*

INSTRUCTION TO THE INVESTIGATOR

Please complete the Study Conclusion page at the end of this book.

Ask the patient to return for the Safety Follow-Up Visit in 7 +/- 3 days.

PATIENT ACTIVITY POSTCARD

Please complete the patient activity postcard for ***Early Withdrawal Between Scheduled Visits*** located in the postcard section of this CRF. Detach the postcard and mail promptly. Postage has been prepaid.

SAFETY FOLLOW-UP

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

SFU2

Please do not split modules

Module : Safety Follow-Up

CRF Pages 292 - 297

Unprocessed Forms : Within this module the following occur which will generate attachments that need to be brought in-house.

None

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Visit Date (Day Month Year)	Safety Follow-Up
207499/156		[redacted]			

INVESTIGATOR INSTRUCTIONS

Complete these assessments for those patients who withdrew early from the study or for patients who have completed Visit 10. These assessments should be completed within 7 +/- 3 days after discontinuation of study medication.

PRESENTATION TO CLINIC

Record time of presentation to clinic ☐☐ 24hr:min

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?

☐ NA → Patient is not using beta$_2$ agonist.

☐ 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?

☐ NA → Patient is not using anticholinergic.

☐ No

☐ Yes → Record date and time of patient's last dose of anticholinergic: ☐☐☐ 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 : ☐☐

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Safety Follow-Up
207499/156		[redacted]			

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes → *If 'Yes' please record details below.*

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

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

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

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of excerbation (maximum level)	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1	[1] ☐ Level 1
	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2	[2] ☐ Level 2
	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3	[3] ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of the module which contains the visit (or visit interval) at which the patient withdrew or after Visit 10, if applicable, 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 UTILIZATION

If the patient has received any COPD exacerbation related medical care since the previous visit, record details in the Resource Utilization section at the back of the module which contains the visit (or visit interval) at which the patient withdrew or after Visit 10, if applicable.

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Safety Follow-Up
207499/156		[redacted]			

INDIRECT COST

Does the patient work?

☐ No

☐ Yes → *If 'Yes'*, has the patient missed work due to COPD-related symptoms, excluding scheduled protocol visits, since the last visit?

☐ No

☐ Yes → *If 'Yes', please record lost work days below:*

Start Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence

How many days since your last visit have you been restricted in performing your leisure activities, due to your COPD-related symptoms? *(please enter number of days below, if not restricted, enter 0)*

☐☐ Days

Since your last visit, how many hours per week did you require paid or unpaid assistance by a relative, friend or professional with your daily activities such as dressing, bathing, cooking, etc., due to your COPD-related symptoms? *(please enter number of hours below, if no paid or unpaid assistance, enter 0 in each instance)*

☐☐☐ Hours per week of **paid** assistance

☐☐☐ Hours per week of **unpaid** assistance

ADVERSE EXPERIENCES

If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of the module which contains the visit (or visit interval) at which the patient withdrew or after Visit 10, if applicable.

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Safety Follow-Up
207499/156		[redacted]			

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 the module which contains the visit (or visit interval) at which the patient withdrew or after Visit 10, if applicable.

At the patient's final study visit, record the end date for prn study rescue medication (albuterol) use, using the date the study inhaler was returned.

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 the module which contains the visit (or visit interval) at which the patient withdrew or after Visit 10, if applicable.

PULMONARY REHABILITATION PROGRAM

Has the patient entered a Pulmonary Rehabilitation Program since the last visit?

☐ No

☐ Yes

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	**Heart Rate** (beats/min)
☐☐☐/☐☐☐	☐☐☐

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of the module which contains the visit (or visit interval) at which the patient withdrew or after Visit 10, if applicable.*

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		Safety Follow-Up
207499/156		[redacted]			

12 LEAD ELECTROCARDIOGRAM

If any abnormalities were observed at the last visit, please perform a 12-lead ECG. The ECG should be performed after the patient has been semi-supine for 5 minutes.

Was an ECG performed?

☐ No

☐ Yes

Were any clinically significant changes noted at this examination compared to the last visit?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of the module which contains the visit (or visit interval) at which the patient withdrew or after Visit 10, if applicable.*

LABORATORY TESTS

If abnormal laboratory results were reported at the previous visit, 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 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.

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes', please record the findings and/or diagnosis in the Adverse Experiences section at the back of the module which contains the visit (or visit interval) at which the patient withdrew or after Visit 10, if applicable. (If a re-test is necessary, please use the Repeat Lab page at the end of this book)*

SmithKline Beecham Pharmaceuticals

Protocol		Patient Number	Patient Initials		Safety Follow-Up
207499/156		[redacted]			

PREGNANCY TEST

Is the patient a female of child-bearing potential?

☐ No

☐ Yes → *If 'Yes' please perform a urine pregnancy test locally.*

Urine Sample Date ☐☐ ☐☐ ☐☐ Day Month Yr

Is the patient pregnant?

☐ No

☐ Yes → *If the pregnancy test is positive, complete the Serious Adverse Experiences form and forward it to SB within 24 hours.*

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

If any abnormalities were noted at the last visit, please perform a physical examination (including respiratory examination).

Were any clinically significant changes noted at this examination compared to the last visit?

☐ No

☐ Yes → [I] ☐ Improvement

[W] ☐ Worsening → *Enter details in the Adverse Experiences section at the back of the module which contains the visit (or visit interval) at which the patient withdrew or after Visit 10, if applicable.*

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 confirm that the pulmonary function tests were performed

[1] ☐ Not Performed

[2] ☐ Performed

PATIENT ACTIVITY POSTCARD

Please complete the patient activity postcard for ***Safety Follow-Up Visit*** located in the postcard section of this CRF. Detach the postcard and mail promptly. Postage has been prepaid.

STUDY CONCLUSION

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

CONC3

Please do not split modules

Module : Study Conclusion

CRF Pages 298

Unprocessed Forms : Within this module the following occur which will generate attachments that need to be brought in-house.

None

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

STUDY CONCLUSION

Did the patient complete the double-blind phase of the study as planned?

☐ Yes

☐ No → *If 'No' please mark the **PRIMARY** cause of withdrawal. (Mark one box only).*

[1] ☐ Adverse experience (complete AE form)

[2] ☐ Insufficient therapeutic effect

[3] ☐ Protocol deviation (including non-compliance)

[4] ☐ Lost to follow-up

[7] ☐ Other - specify: _____

Date of Final Visit ☐☐ ☐☐☐ ☐☐ (Day Month Yr)

Date of Final Dose ☐☐ ☐☐☐ ☐☐ (Day Month Yr)

INVESTIGATOR SIGNATURE

I certify that I have reviewed the data on this case report form, 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	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

SAE3

Please do not split modules

Module : Serious Adverse Experiences

CRF Pages 299 - 301

Unprocessed Forms : Within this module the following occur which will generate attachments that need to be brought in-house.

None

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	SB Receipt Date (Day Month Year)
207499/156		[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 hospitalization (excluding elective surgery or routine clinical procedures)
- [5] ☐ hospitalization 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 section* ☐ Yes ☐ No

Was patient withdrawn due to this specific SAE ? ☐ Yes ☐ No

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[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 randomization code broken at investigational site? ☐ No ☐ Yes

Randomization 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 _____

SmithKline Beecham
Pharmaceuticals

Protocol		Patient Number	Patient Initials		
207499/156		[redacted]			

SERIOUS ADVERSE EXPERIENCE (Cont.) PHARMACOKINETIC EVALUATION

If the patient presents to the clinic within 24 hours of the onset of a serious adverse experience (SAE) or with an ongoing SAE, please collect a blood sample (5mL) for pharmacokinetic evaluation.

Was a pharmacokinetic sample taken?

☐ No

☐ Yes → *If 'Yes'*, 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 taken prior to the onset of the serious adverse experience

☐☐☐ ☐☐
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 serious adverse experience?

☐ No

☐ Yes → *If 'Yes'*, record date and time of last dose of study medication taken prior to collection of the pharmacokinetic sample.

☐☐☐ ☐☐
Day Month Yr 24hr:min

Was this dose taken with food?

☐ No

☐ Yes

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

FORMD3

Please do not split modules

Module: Form D

CRF Pages: 302

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials
207499/156		[redacted]	

FORM D

Certified Cause of Death _____

Date of Death Day Month Yr → *Please complete Serious Adverse Experience section.*

Was a post-mortem examination carried out?

☐ No

☐ Yes → *If 'Yes' please summarize findings (include diagnosis):*

_____

_____

_____

_____

Reporting Physician's Signature _____ Date Day Month Yr

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		OPTIONAL Repeat Lab
207499/156		[redacted]			

RPLAB3

Please do not split modules

Module: Repeat Lab

CRF Pages: 303

Unprocessed Forms: Within this module, the following tests / procedures occur which may generate attachments.

None

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		OPTIONAL Repeat Lab
207499/156		[redacted]			

REPEAT 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, complete the Early Withdrawal between Scheduled Visits 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.*

REPEAT 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, complete the Early Withdrawal between Scheduled Visits 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	Center Number	Patient Number	Patient Initials	Investigator
207499/156		[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	
MOD5	V8, V9, AE, CM, MPro, COPD, RU	197 - 240	☐	☐	
MOD6	V10, AE, CM, Med Pro, COPD, RU	241 - 280	☐	☐	
EW2	Early Withdrawal	281 - 291	☐	☐	
SFU2	Safety Follow-Up	292 - 297	☐	☐	
CONC3	Conclusion	298	☐	☐	
SAE3	Serious Adverse Experiences	299 - 301	☐	☐	
FORMD3	Form D	302	☐	☐	
RPLAB3	Repeat Labs	303	☐	☐	

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	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

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

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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) which cause concern or interfere with usual activity (including eating and sleeping) at any time during the study.

Report this gastrointestinal symptom(s) to the SB Medical Monitor by telephone within 24 hours of the first assessment and fax the completed Supplemental Gastrointestinal Adverse Experience Report within 24 hours of the first assessment.

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.

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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 on page 3) specify: _____

☐ Back

☐ Groin

☐ Shoulder tip

☐ Other, specify: _____ _____

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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	☐	☐
Abdominal masses	☐	☐
Peritoneal signs	☐	☐

Other clinically significant GI physical examination findings, please specify: _ _ _ _ _ _ _ _ _ _ _ _ _ _

SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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: _____

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: _____

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report
207499/156		[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

_ _ _ _

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Investigator
207499/156		[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

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		
207499/156		[redacted]			

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

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[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:				
	☐	☐	☐	☐
	☐	☐	☐	☐
	☐	☐	☐	☐

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[redacted]			

SUPPLEMENTAL REPORT FOR GASTROINTESTINAL ADVERSE EXPERIENCE - FOLLOW UP

PHYSICAL EXAMINATION (*continued*)

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

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[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: _____

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: _____

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials		Supplemental Report Follow-Up
207499/156		[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.

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Investigator
207499/156		[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*
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- *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	Center Number				
207499/156					

PATIENT ASSIGNMENT SHEET

Investigator _____ **For SB** **Date** Day Month Yr

Directions: *Do not enter the patient on this form until he/she is randomized (starts double-blind medication).*

Final Status: C = *Completed study*
W = *Withdrawn from study*

	Patient Initials	Patient Number	Randomization Number	Date of Randomization Day Mth Yr	Status (C/W)	Ad Referral (for SB) Yes	No
1							
2							
3							
4							
5							
6							
7							
8							
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18							

SmithKline Beecham
Pharmaceuticals

Protocol	Center Number
207499/156	

PATIENT LOG

Investigator _____

Directions: *Enter **all** patients who have been considered for the study and who have been interviewed. Indicate if the patient was referred for the study through a study advertisement. For patients not entering the trial, note the reason for exclusion in the designated column.*

Patient Initials	Interview Date Day Mth Yr	Ad Referral		Reason for Exclusion
		Yes	No	

SB 207499/156

SmithKline Beecham

Pharmaceuticals

PATIENT DIARY

This diary is a **very important** part of the study.

Remember:

- Complete the diary card if you feel different since starting the study medication.
- All visits should be in the morning between 10am and 12 noon, therefore on the day of your next visit do NOT take your morning dose of study medication before attending the clinic. In the exceptional case that your appointment has to be in the afternoon, please contact your doctor for instructions regarding your morning dose of study medication.
- DO NOT use your inhaler during the 4 hours before your next appointment unless you really have to.
- DO NOT smoke 2 hours before your next appointment.
- Bring all empty study medication bottles, any unused study medication, and the study inhaler and spacer to your next appointment.
- Bring this diary with you to your next appointment.
- At your next appointment, you will be asked to recall the time at which you took your study medication on the day before the visit.
- If you experience gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhea, or vomiting) that interfere with your usual activities (including eating and sleeping) or cause concern, please telephone the number below as soon as possible.

In an emergency, telephone:

_____

name

at:_____

phone number

Date and time of next appointment | | | | | | | | | | |

Day Month Yr 24hr:min

If you feel different since starting the study medication, please write in the space below and include the date:

Date

Date

Patient has been assigned to the
EARLY
Pharmacokinetic sampling group

Patient has been assigned to the
LATE
Pharmacokinetic sampling group

Patient has been assigned to the
EARLY
Pharmacokinetic sampling group

Patient has been assigned to the
LATE
Pharmacokinetic sampling group

Patient has been assigned to the
EARLY
Pharmacokinetic sampling group

Patient has been assigned to the
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Patient has been assigned to the
EARLY
Pharmacokinetic sampling group

Patient has been assigned to the
LATE
Pharmacokinetic sampling group

Patient has been assigned to the
EARLY
Pharmacokinetic sampling group

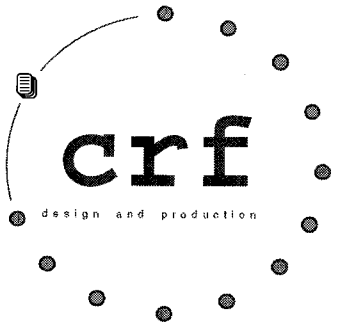
Patient has been assigned to the
LATE
Pharmacokinetic sampling group

Patient has been assigned to the
EARLY
Pharmacokinetic sampling group

Patient has been assigned to the
LATE
Pharmacokinetic sampling group

Patient has been assigned to the
EARLY
Pharmacokinetic sampling group

Patient has been assigned to the
LATE
Pharmacokinetic sampling group



CRF FINALIZATION FORM

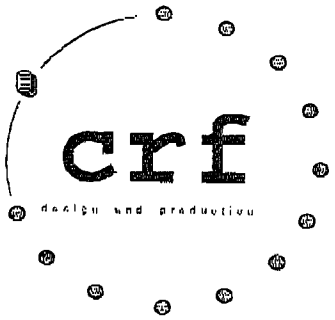
The signatures on this page belong to the CRF Review Team members for the following Protocol:

PROTOCOL NUMBER: 207499 / 156

I confirm that I have reviewed all books, diaries and associated forms required by the above Protocol and now consider them to be complete and final:

Project Co-ordinator / Clinical Scientist	[redacted]	20 NOV 00 Day Month Yr	
Statistician *		Day Month Yr	☐
Programmer *		Day Month Yr	☐
Global Database Manager (GDM)		Day Month Yr	
Data Co-ordinator		Day Month Yr	
Document Management Representative		Day Month Yr	
CRF Designer	[redacted]	20 NOV 00 Day Month Yr	

** In the absence of this team member the DART Leader may sign on their behalf and mark the box to indicate this.*



CRF FINALIZATION FORM

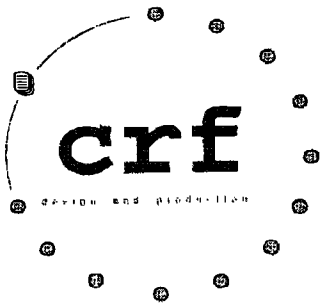
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Statistician *	[redacted]	20 NOV 00 Day Month Yr	☐
Programmer *	[redacted]	20 NOV 00 Day Month Yr	☐
Global Database Manager (GDM)	[redacted]	20 NOV 00 Day Month Yr	
Data Co-ordinator	_____	Day Month Yr	
Document Management Representative	_____	Day Month Yr	
CRF Designer	_____	Day Month Yr	

** In the absence of this team member the DART Leader may sign on their behalf and mark the box to indicate this.*



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Project Co-ordinator / Clinical Scientist	_____	Day Month Yr	
Statistician *	_____	Day Month Yr	☐
Programmer *	_____	Day Month Yr	☐
Global Database Manager (GDM)	_____	Day Month Yr	
Data Co-ordinator	[redacted]	20 NOV 00 Day Month Yr	
Document Management Representative	[redacted]	20 NOV 00 Day Month Yr	
CRF Designer	_____	Day Month Yr	

** In the absence of this team member the DART Leader may sign on their behalf and mark the box to indicate this.*

crf
design and production

CRF FINALIZATION FORM

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Project Co-ordinator / Clinical Scientist	_____	Day Month Yr	
Statistician *	[redacted]	20 NOV 00 Day Month Yr	☐
Programmer *	[redacted]	20 NOV 00 Day Month Yr	☐
Global Database Manager (GDM)	[redacted]	20 NOV 00 Day Month Yr	
Data Co-ordinator	_____	Day Month Yr	
Document Management Representative	_____	Day Month Yr	
CRF Designer	_____	Day Month Yr	

** In the absence of this team member the DART Leader may sign on their behalf and mark the box to indicate this.*

This section contained Principal Investigator's Curriculum Vitae and has been excluded to protect Principal Investigator privacy.