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- *Aggregate data will be included; with any direct reference to individual patients excluded*

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A 13-week randomised, double-blind, parallel group, multicentre study to compare the bronchial anti-inflammatory activity of oral cilomilast (15 mg bd) with placebo twice daily in subjects with Chronic Obstructive Pulmonary Disease (COPD)

Clinical Study Report for Study SB-207499/181 (Development Phase IIIb)

Document Number: GM2004/00090/00 **Compound Number: SB-207499**

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

Indication Studied: Chronic Obstructive Pulmonary Disease

Initiation Date:	10 March 2003
Completion Date:	29 April 2004
Date of Report:	23 April 2007

Sponsor Signatory: [redacted]
Department Respiratory Medicine Development Center, Clinical
GlaxoSmithKline

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

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Synopsis

Document Number: GM2004/00090/00 Study Number: SB-207499/181

Title: A 13-week randomised, double-blind, parallel group, multicentre study to compare the bronchial anti-inflammatory activity of oral cilomilast (15 mg bd) with placebo twice daily in subjects with Chronic Obstructive Pulmonary Disease (COPD)	
Investigators: Multicentre study.	
Study centres: Multicentre study conducted in 27 centres in Australia, Canada, Finland, Ireland, Lithuania, Norway, Romania, Slovakia, Slovenia, South Africa, Sweden and the UK.	
Publication(s): None at the time of this report.	
Study period: 10 March 2003 - 29 April 2004	Phase of Development: IIIb
Objectives: The primary objective was to compare the numbers of inflammatory cells of distinct immuno and ultrastructural phenotypes after treatment with cilomilast 15 mg twice daily (bd) and with placebo bd in subjects with COPD, using bronchial biopsy. The secondary objective was to compare the relative numbers (i.e. percentage) of distinct inflammatory cells after treatment with cilomilast 15mg bd and with placebo bd in sputum induced from subjects with COPD.	
Methodology: This was a randomised, double-blind, placebo-controlled, parallel-group multicentre study in subjects with moderate to severe COPD. Subjects completed a four-week single-blind placebo run-in period before randomisation to either cilomilast 15 mg bd or placebo bd for 13 weeks. The treatment period was followed by a one-week follow-up period. Each subject visited the clinic on 8 occasions over the 18-week study period. Bronchial biopsies were performed (provided specified safety criteria were met) one week before randomisation for the baseline sample (i.e. at Week -1, Visit 2) and at the end of 12 weeks' treatment at Visit 6, or one week after early withdrawal. If safety criteria were not met, the biopsy procedure was rescheduled for 1 to 7 days time (Visit 2A and Visit 6A, respectively). An induced sputum sample was collected at Visit 3 (Week 0), at Visit 7 (at the end of 13 weeks' treatment), and at early withdrawal if the biopsy was not done. Pulmonary function tests (FEV_1, FVC, and SVC) were conducted at Visit 1 before and after administration of salbutamol 400 μg via an MDI and a Volumatic spacer. At Visits 2-8, and at the Early Withdrawal Visit (EWV), SVC (only) was measured before and after administration of salbutamol 400 μg via an MDI and a Volumatic spacer.	
Number of subjects: Approximately 116 subjects (58 subjects per treatment group) were to be recruited to achieve 86 treated subjects for the per-protocol analysis. In total, 127 subjects were randomised to treatment and took study medication (62 cilomilast; 65 placebo).	

Title: A 13-week randomised, double-blind, parallel group, multicentre study to compare the bronchial anti-inflammatory activity of oral cilomilast (15 mg bd) with placebo twice daily in subjects with Chronic Obstructive Pulmonary Disease (COPD)

Diagnosis and main criteria for inclusion: Male or female subjects aged 40-80 years (inclusive) with a clinical diagnosis of COPD, a post-salbutamol FEV_1 of ≥40 and ≤80% of predicted normal and a smoking history of ≥10 pack years. Subjects were to have a pre-bronchodilator FEV_1:FVC ratio of ≤0.7 and poor reversibility after administration of salbutamol 400 μg (i.e. ≤10% of predicted normal FEV_1 or ≤200 mL increase).

Treatment administration: Subjects took one tablet of study medication twice daily, in the morning immediately after breakfast and in the evening immediately after a meal. During the run-in period, all subjects received placebo; during the double-blind treatment phase subjects were randomised to receive either cilomilast 15 mg or placebo. Batch numbers: [redacted] (cilomilast) and [redacted] (placebo).

Criteria for evaluation: Efficacy: biopsy samples, induced sputum samples, slow vital capacity (SVC). The primary efficacy variables were the numbers of sub-epithelial CD68+ (macrophages) and CD8+ (cytotoxic T-lymphocytes) per unit area of biopsy tissue after 12 weeks of treatment. Safety: monitoring of adverse events (AEs), including a structured assessment of gastrointestinal (GI) adverse events of concern, and serious adverse events, clinical laboratory tests and vital signs.

Statistical methods: Treatment differences for the primary efficacy variables (CD68+ and CD8+ counts per area of tissue) were assessed using an analysis of variance model with effects for centre and treatment group. Least squares means with associated 95% confidence intervals (CIs) were calculated for each treatment group and for the treatment difference. Differences between treatment groups were assessed using T-tests on the least square means. Since there were two primary endpoints of interest, the modified Bonferroni procedure of Hochberg was used to adjust for primary endpoints.

Summary: Primary Efficacy Variables: The mean changes from baseline in the number of sub-epithelial CD68+ macrophages and CD8+ T-lymphocytes per unit area of biopsy tissue at endpoint are shown in the following table for the per-protocol population.

Variable		Placebo	Cilomilast
Sub-epithelial CD68+ macrophages (cells/mm^2)		n=49	n=54
Baseline	Mean (SEM)	143.6 (11.9)	121.4 (10.5)
Endpoint	Mean (SEM)	93.6 (8.6)	100.6 (7.6)
	Mean change from baseline (95% CI)	-50.0 (-77.4, -22.6)	-20.8 (-45.0, 3.4)
	Mean difference (95% CI)	-	29.2 (-5.0, 63.3)
	P value vs. placebo	-	0.093
Sub-epithelial CD8+ T-lymphocytes (cells/mm^2)		n=49	n=54
Baseline	Mean (SEM)	213.5 (10.9)	201.9 (9.6)
Endpoint	Mean (SEM)	143.7 (11.2)	126.6 (9.9)
	Mean change from baseline (95% CI)	-69.8 (-96.8, -42.7)	-75.3 (-99.2, 51.4)
	Mean difference (95% CI)	-	-5.5 (-39.3, 28.2)
	P value vs. placebo	-	0.744

Title: A 13-week randomised, double-blind, parallel group, multicentre study to compare the bronchial anti-inflammatory activity of oral cilomilast (15 mg bd) with placebo twice daily in subjects with Chronic Obstructive Pulmonary Disease (COPD)
The numbers of inflammatory cells were reduced in both groups, but there were no statistically significant differences between treatments. The analysis in which a Poisson model was fitted to the data supported the main results for both endpoints, and showed no significant differences between treatments ($p>0.29$). Results were similar in the ITT population.
Secondary Efficacy Variables (biopsy endpoints): There was a reduction from baseline in the number of sub-epithelial neutrophils (ne+) per unit area of biopsy tissue at endpoint in the cilomilast and placebo groups (2.2 and 21.6 cells/mm^2 respectively). The reduction was larger in the placebo group with a p value of 0.019. Reduction in cell numbers per area of biopsy tissue were seen for CD4+ lymphocytes, IL-8 mRNA positive cells, TNFα mRNA positive cells and CD45 positive cells in both treatment groups. There are no statistically significant differences between the treatments, although in most cases the reduction in cell numbers were smaller in the cilomilast group. Epithelial and sub-mucosal mucin expression showed reductions in MUC5AC and MUC5B cells in the epithelium and, mainly, increases in MUC5AC and MUC5B cells in the sub-mucosa, although submucosal MUC5B cells were reduced in the placebo group. None of the differences between the treatment groups was statistically significant.
Secondary Efficacy Variables (sputum endpoints) These include measurement of total cells per unit volume of sputum, macrophages, eosinophils, lymphocytes, neutrophil elastase and IL-8. There were reductions in total cell count in both groups (cilomilast: $5.3x10^6$/mL; placebo: $8.0x10^6$/mL), but the difference was not statistically significant. Other results were generally similar in both groups and there were no statistically significant differences between treatments.
Tertiary Efficacy Variables: During double-blind treatment there were no statistically significant differences between the treatment groups in the mean changes from baseline in SVC. At week 4 there the treatment difference reached 0.15L in favour of cilomilast although this was just outside the level of statistical significance ($p=0.054$). At endpoint there was a small improvement in both treatment groups of 0.03 and 0.04L for cilomilast and placebo respectively. The difference is not statistically significant ($p=0.900$).
Adverse Events: The overall incidence of AEs was similar in the cilomilast and placebo treatment groups (63.1% vs. 58.1%) and most events were of mild or moderate intensity. AEs occurring in at least 5% of subjects in either group are shown in the following table. The most frequently reported events in both groups were headache and nasopharyngitis. Gastrointestinal adverse events (GIAEs), such as nausea, diarrhoea and vomiting, occurred more frequently in the cilomilast group (31% vs.16% of subjects).

Title: A 13-week randomised, double-blind, parallel group, multicentre study to compare the bronchial anti-inflammatory activity of oral cilomilast (15 mg bd) with placebo twice daily in subjects with Chronic Obstructive Pulmonary Disease (COPD)

Adverse Event (Preferred Term)	Placebo (N = 62)	Cilomilast 15 mg bd (N = 65)
Subjects with at least one AE	36 (58.1%)	41 (63.1%)
Headache	12 (19.4%)	9 (13.8%)
Nasopharyngitis	8 (12.9%)	8 (12.3%)
Nausea	4 (6.5%)	6 (9.2%)
Diarrhoea	2 (3.2%)	5 (7.7%)
Pharyngolaryngeal pain	2 (3.2%)	5 (7.7%)
Vomiting	1 (1.6%)	5 (7.7%)

Gastrointestinal Adverse Events: Three subjects had GIAEs of concern, two in the cilomilast group (nausea and enteritis) and one in the placebo group (nausea/abdominal pain). Both subjects in the cilomilast group had severe GIAEs of concern and one was withdrawn following the event (severe enteritis). There were no serious GIAEs of concern. There was no evidence for a treatment effect of cilomilast on changes in orthostatic vital signs or on faecal occult blood results in subjects experiencing GIAEs of concern. Of all the subjects who had on-therapy faecal occult blood tests, 7.3% of those receiving cilomilast (3 of 41, one of whom had a positive test at baseline) and 12.5% of those receiving placebo (5 of 40, two of whom had a positive test at baseline) had a positive test result during the double blind period.

Serious Adverse Events/Deaths: There were no fatalities during the double-blind treatment period or within 30 days of completing double-blind study treatment. Two subjects (3.1%) who received cilomilast (anxiety and atrial flutter) and one subject (1.6%) who received placebo (COAD exacerbated) had serious, non-fatal AEs during treatment with double-blind medication. None of the serious AEs was considered by the investigator to be possibly related to study treatment.

Withdrawals due to Adverse Events: Five subjects were withdrawn from double-blind treatment due to AEs, four (6.2%) in the cilomilast group and one (1.6%) in the placebo group. The events leading to withdrawal were: atrial flutter, gastritis, gastro-oesophageal reflux disease, nausea and enteritis (cilomilast), and COAD exacerbated (placebo).

Laboratory Tests: Mean changes from baseline in clinical laboratory parameters were small and generally similar in both treatment groups.

Vital Signs: Mean changes in vital signs values were small with no clinically relevant changes from baseline in either group. During the double-blind treatment period, the percentages of subjects with transitions in sitting vital signs from normal at baseline to outside normal range on-therapy were similar in both the cilomilast and placebo groups. There were no subjects who had transitions from normal at baseline to potential clinical concern during treatment.

Title: A 13-week randomised, double-blind, parallel group, multicentre study to compare the bronchial anti-inflammatory activity of oral cilomilast (15 mg bd) with placebo twice daily in subjects with Chronic Obstructive Pulmonary Disease (COPD)

Conclusions:

- The present study demonstrated a mean reduction in inflammatory cell and mediator profiles in subjects with COPD for both treatment groups over the 13 week study interval. No significant changes compared with placebo were found in the primary endpoints and these findings were confirmed in an analysis using a Poisson regression model.

- Secondary endpoints showed reductions in both groups for an array of biopsy and sputum inflammatory markers. Reductions were variable relative to baseline values and more commonly larger in the placebo group. Differences failed to reach statistical significance in the majority of cases. Only sub-epithelial neutrophils showed a statistical difference in favour of placebo.

- The large placebo group reductions in a range of inflammatory cells and mediators remain unexplained. Such a placebo response may result from a combination of stability problems at baseline, inflammatory drivers which are not balanced between treatment arms, processing inconsistencies, or natural intra-patient variation in inflammatory profile.

- Lung function results of SVC did not show a significant difference between treatment groups, although the study was not powered on this endpoint.

- Cilomilast 15 mg bd was generally well tolerated. The incidence of on-therapy adverse events was similar to placebo and the majority of adverse events were of mild or moderate intensity.

- The incidence of gastrointestinal events was higher than placebo. GIAEs occurred in subjects receiving both cilomilast and placebo, but all resolved during study treatment.

- There were no consistent clinically significant effects on vital signs or laboratory results. The safety profile of cilomilast is in line with the previous development program and no new safety concerns were observed.

Date of Report: April 2007

TABLE OF CONTENTS

Page

TITLE PAGE 1

SYNOPSIS 2

ABBREVIATIONS 14

1. ETHICS 16
   1.1. Independent Ethics Committee (IEC) or Institutional Review Board (IRB) 16
   1.2. Ethical Conduct of the Study 16
   1.3. Subject Information and Consent 16

2. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE 16

3. INTRODUCTION 18

4. STUDY OBJECTIVES 19
   4.1. Primary Objective 19
   4.2. Secondary Objective 20

5. INVESTIGATIONAL PLAN 21
   5.1. Study Design 21
      5.1.1. Overall Study Design – Description 21
      5.1.2. Discussion of Study Design, Including the Choice of Control Group(s) 24
   5.2. Protocol Amendments 24
   5.3. Selection of Study Population 25
      5.3.1. Inclusion Criteria 25
      5.3.2. Exclusion Criteria 26
      5.3.3. Randomisation Criteria at Visit 3 27
      5.3.4. Other Eligibility Criteria Considerations 27
      5.3.5. Predetermined Criteria for Subject Withdrawal 27
   5.4. Investigational Product 29
      5.4.1. Description of Investigational Product 29
      5.4.2. Dosages and Administration 30
      5.4.3. Dose Rationale 31
      5.4.4. Blinding 31
      5.4.5. Treatment Assignment 31
      5.4.6. Assessment of Compliance 32
      5.4.7. Treatment of Investigational Product Overdose 33

5.5. Prior and Concomitant Medications and Non-Drug Therapies 33
5.5.1. Permitted Medications 33
5.5.2. Prohibited Medications 33
5.5.3. Medical Devices 34
5.5.4. Non-drug Therapies 34
5.6. Study Assessments and Procedures 34
5.6.1. Demographic and Baseline Assessments 34
5.6.2. Efficacy Assessment 36
5.6.3. Safety Assessments 41
5.7. Data Quality Assurance 51
5.8. Data Analysis Methods 52
5.8.1. Timings of Planned Analyses 52
5.8.2. Sample Size Considerations 52
5.8.3. Analysis Populations 52
5.8.4. Treatment Comparisons 54
5.8.5. General Considerations for Data Analyses 55
5.8.6. Data Handling Conventions 55
5.8.7. Study Population 60
5.8.8. Efficacy Analyses 60
5.8.9. Safety Analyses 61

6. STUDY POPULATION RESULTS 63
6.1. Disposition of Subjects 63
6.1.1. Number and Distribution of Subjects 63
6.2. Protocol Deviations 64
6.3. Populations Analysed 65
6.4. Demographics and Other Baseline Characteristics 65
6.4.1. Demographic Characteristics 65
6.4.2. Baseline Characteristics 66
6.4.3. Baseline Signs and Symptoms 70
6.4.4. Previous Medications 70
6.5. Concomitant Medications 71
6.5.1. All Concomitant Medications 71
6.5.2. Medications for COPD Exacerbations 73
6.6. Treatment Compliance 74

7. EFFICACY RESULTS 75
7.1. Primary Efficacy Results 75
7.1.1. Sub-epithelial CD68+ Macrophages per Unit Area of Tissue . 75

7.1.2. Sub-epithelial CD8+ T-Lymphocytes per Unit Area of Tissue . 81
7.1.3. Results of Covariate Analyses 87
7.2. Secondary Efficacy Results 87
7.2.1. Sub-epithelial Neutrophils (ne+) per Unit Area of Tissue 88
7.2.2. Sub-epithelial CD4+ Lymphocytes per Unit Area of Tissue . . . 90
7.2.3. Sub-epithelial IL-8 mRNA+ Cells per Unit Area of Tissue 90
7.2.4. Sub-epithelial TNFα mRNA+ Cells per Unit Area of Tissue 93
7.2.5. Sub-epithelial CD45+ Cells per Unit Area of Tissue 93
7.2.6. Mucin Expression 96
7.2.7. Sputum Total Cell Count per Unit Volume 99
7.2.8. Sputum Macrophages as Percentage of Total Cells 99
7.2.9. Sputum Eosinophils as Percentage of Total Cells 102
7.2.10. Sputum Lymphocytes as Percentage of Total Cells 102
7.2.11. Sputum Neutrophil Elastase per Unit Volume 105
7.2.12. Sputum IL-8 per Unit Volume 105
7.3. Other Efficacy Results 108
7.4. Efficacy Conclusions 110

8. SAFETY RESULTS 111
8.1. Extent of Exposure 111
8.2. Adverse Events 111
8.2.1. Incidence of On-therapy Adverse Events 111
8.2.2. Adverse Events by Relationship to Study Medication 112
8.2.3. Adverse Events by Intensity 113
8.2.4. Adverse Events by Time of First Occurrence 114
8.2.5. Adverse Events Requiring Corrective Treatment 117
8.3. Serious Adverse Events 117
8.3.1. Fatal Events 117
8.3.2. Non-Fatal Events 117
8.4. Adverse Events Leading to Premature Discontinuation of Investigational Product and/or Study 118
8.5. COPD Exacerbations 121
8.6. Gastrointestinal Adverse Events of Concern 121
8.7. Pregnancies 124
8.8. Clinical Laboratory Evaluations 124
8.8.1. Laboratory Values Over Time 124
8.8.2. Adverse Events Related to Laboratory Results 126

8.9. Vital Signs 128
8.10. Medical Device Incidents, Near-Incidents, Malfunctions and Remedial Action 129
8.11. Safety Conclusions 129
9. DISCUSSION AND CONCLUSIONS 131
9.1. Discussion 131
9.2. Conclusions 135
10. REFERENCES 137
11. CASE NARRATIVES 140
STUDY POPULATION DATA SOURCE TABLES 148
EFFICACY DATA SOURCE TABLES 205
SAFETY DATA SOURCE TABLES 300

LIST OF TABLES

Page

Table 1 Outline of study assessments 22
Table 2 Laboratory values of potential clinical concern 59
Table 3 Vital signs values of potential clinical concern 60
Table 4 Subject distribution (number of subjects) 63
Table 5 Reason for study conclusion (number (%) of subjects): all randomised subjects 64
Table 6 Protocol violations (number (%) of subjects): intent-to-treat population 64
Table 7 Summary of study populations 65
Table 8 Summary of demographic characteristics: all randomised subjects and per-protocol population 66
Table 9 Summary of pulmonary and smoking history: all randomised subjects and per-protocol population 67
Table 10 Summary of pulmonary function measures: all randomised subjects and per-protocol population 69
Table 11 Most commonly occurring (at least 2% of subjects in either group) baseline signs and symptoms (number (%) of subjects): all randomised subjects 70
Table 12 Most commonly received (by least 5% of subjects in either group) prior medications (number (%) of subjects): all randomised subjects . . . 71
Table 13 Most commonly received (by least 5% of subjects in either group) concomitant medications (number (%) of subjects): all randomised subjects 72
Table 14 Medications taken for COPD exacerbations (number (%) of subjects): all randomised subjects 73
Table 15 Overall compliance with double-blind medication (number (%) of subjects): all randomised subjects 74
Table 16 Mean change from baseline in sub-epithelial CD68+ macrophages per area of tissue (cells/mm2): per-protocol population 76
Table 17 Mean change from baseline in sub-epithelial CD68+ macrophages per area of tissue (cells/mm2) for smoker and non-smokers: per-protocol population 78
Table 18 Mean change from baseline in sub-epithelial CD68+ macrophages per area of tissue (cells/mm2): intent-to-treat population 80
Table 19 Mean change from baseline in sub-epithelial CD8+ T-lymphocytes per area of tissue (cells/mm2): per-protocol population 82

Table 20 Mean change from baseline in sub-epithelial CD8+ T-lymphocytes per area of tissue (cells/mm2) for smoker and non-smokers: per-protocol population 84
Table 21 Mean change from baseline in sub-epithelial CD8+ T-lymphocytes per area of tissue (cells/mm2): intent-to-treat population 86
Table 22 Mean change from baseline in sub-epithelial neutrophils (ne+) per area of tissue (cells/mm2): per-protocol population 89
Table 23 Mean change from baseline in sub-epithelial CD4+ lymphocytes per area of tissue (cells/mm2): per-protocol population 91
Table 24 Mean change from baseline in sub-epithelial IL-8 mRNA+ cells per area of tissue (cells/mm2): per-protocol population 92
Table 25 Mean change from baseline in sub-epithelial TNFα mRNA+ cells per area of tissue (cells/mm2): per-protocol population 94
Table 26 Mean change from baseline in sub-epithelial CD45+ cells per area of tissue (cells/mm2): per-protocol population 95
Table 27 Mean change from baseline in mucin expression (MUC5AC) cells per area of tissue (cells/mm2): per-protocol population 97
Table 28 Mean change from baseline in mucin expression (MUC5B) cells per area of tissue (cells/mm2): per-protocol population 98
Table 29 Mean change from baseline in sputum total cell count per unit volume (x106/mL): per-protocol population 100
Table 30 Mean change from baseline in sputum macrophages as a percentage of total cells: per-protocol population 101
Table 31 Mean change from baseline in sputum eosinophils as a percentage of total cells: per-protocol population 103
Table 32 Mean change from baseline in sputum lymphocytes as a percentage of total cells: per-protocol population 104
Table 33 Mean change from baseline in sputum neutrophil elastase per unit volume (ng/mL): per-protocol population 106
Table 34 Mean change from baseline in sputum IL-8 per unit volume (ng/mL): per-protocol population 107
Table 35 Mean change from baseline in SVC (L) by week: per-protocol population 109
Table 36 Duration of exposure (number (%) of subjects): all randomised subjects 111
Table 37 Most frequently reported (by least 5% of subjects in either group) adverse events (number (%) of subjects): all randomised subjects 112

Table 38 Most frequently reported (by least 2% of subjects in either group) adverse events considered possibly related to study medication (number (%) of subjects): all randomised subjects 113
Table 39 Number (%) of subjects with on-therapy adverse events by intensity: all randomised subjects 114
Table 40 Number (%) of subjects with severe adverse events: all randomised subjects 114
Table 41 Most frequently reported on-therapy adverse events by initial time of onset (number (%) of subjects): all randomised subjects 116
Table 42 Non-fatal Serious Adverse Events 118
Table 43 Adverse events leading to withdrawal (number (%) of subjects): all randomised subjects 119
Table 44 Withdrawals due to on-therapy adverse events 120
Table 45 Number (%) of subjects with GIAEs of concern: all randomised subjects 121
Table 46 Subjects with GIAEs of concern 123
Table 47 Summary of mean changes in selected clinical laboratory variables 124
Table 48 Subjects with on-therapy laboratory values reported as adverse events 127
Table 49 Summary of mean changes in vital signs variables 128
Table 50 Number (%) of subjects with transitions from normal range at baseline for sitting vital signs – timepoint: on-therapy 129
Table 51 Comparison of change from baseline in biopsy and sputum data between current study (SB207499 181) and previous placebo group responses in biopsy studies SB207499 076 and SCO30005 132

Abbreviations

AE	adverse event
ALP	alkaline phosphatase
ALT (SGPT)	alanine aminotransferase
ANOVA	analysis of variance
APTT	activated partial thromboplastin time
AST (SGOT)	aspartate aminotransferase
BAL	bronchoalveolar lavage
bd	twice daily
BP	blood pressure
bpm	beats per minute
BTPS	Body Temperature and Pressure Standard
BUN	blood urea nitrogen
CI	confidence interval
cm	centimetre
COAD	chronic obstructive airway disease
COPD	chronic obstructive pulmonary disease
CRF	case report form
cyclic AMP	cyclic adenosine monophosphate
DBP	diastolic blood pressure
dL	decilitre
DRC	daily record card
EWV	early withdrawal visit
FEV_1	forced expiratory volume in 1 second
FOB	faecal occult blood
FVC	forced vital capacity
g	gram
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GIAE	gastrointestinal adverse event
GSK	GlaxoSmithKline
HCG	human chorionic gonadotrophin
HR	heart rate
ICH-GCP	International Conference for the Harmonisation of Good Clinical Practice
ICS	inhaled corticosteroid
IL	Interleukin
ITT	intent-to-treat
IU	international unit
IUD	intrauterine device
IVRS	Interactive Voice Response System
kg	kilogram
L	litre
LLN	lower limit of normal
LTOT	long-term oxygen therapy

µg	microgram
MDI	metered dose inhaler
MedDRA	Medical Dictionary for Regulatory Activities
mEq	milliequivalent
mg	milligram
mL	millilitre
mmHg	millimetres of mercury
mmol	millimole
mRNA	messenger ribonucleic acid
NAC	N-acetyl cysteine
NCS	not clinically significant
ng	nanogram
PDE4	phosphodiesterase 4
PFT	pulmonary function test
PP	per-protocol
prn	pro re nata (as needed)
PT	prothrombin time
PTT	partial thromboplastin time
QA	quality assurance
QC	quality control
RAMOS	Registration and Medication Ordering System
RBC	red blood cell count
SAE	serious adverse event
SaO_2	transcutaneous oxygen saturation
SB	SmithKline Beecham
SBP	systolic blood pressure
SD	standard deviation
SEM	standard error of the mean
SIN	sample identification number
SVC	slow vital capacity
TNF	tumour necrosis factor
TT	thrombin time
ULN	upper limit of normal
WBC	white blood cell count
WHO	World Health Organisation
wks	weeks
y	years

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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 centre ethics committee or institutional review board.

1.2. Ethical Conduct of the Study

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

1.3. Subject Information and Consent

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

2. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This was a multicentre study conducted in 27 centres in Australia, Canada, Finland, Ireland, Lithuania, Norway, Romania, Slovakia, Slovenia, South Africa, Sweden and the UK.

Monitoring of the study was undertaken by GSK personnel. Monitoring clinic visits were made on a frequent basis at a mutually convenient time with advanced notification to study personnel prior to the clinic visit.

Data Management was performed by Quintiles, Dublin, Ireland.

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

The complete blood counts (to include platelets, thrombin time, prothrombin time and partial thromboplastin time) were provided by local hospital laboratories. Pregnancy testing was undertaken using equipment provided by Quest Diagnostics, Heston, Middlesex, UK. Quest Diagnostics also handled transport of sputum and biopsy samples from each study centre to the central laboratory.

The central laboratory for sputum analysis (fixed slides and frozen supernatants) and counting was John Hunter Hospital, Newcastle, Australia, and for Biopsy sectioning and

counting was the Meakins-Christie Laboratory, McGill University, Canada. The work on mucin was undertaken by Professor [redacted] at the Brompton Hospital, London, UK.

The clinical study report was written by [redacted] MSc (Broadway Medical Limited) and edited by [redacted] PhD (Respiratory Medicines Development Centre), [redacted] MSc (Respiratory, European Clinical Operations), [redacted] PhD (Biomedical Data Sciences, Statistics) and [redacted] BSc (Biomedical Data Sciences, Data Management).

3. INTRODUCTION

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

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

The distinctive nature of the inflammation underlying COPD has recently been established, and differs from that of asthma in a number of respects, in particular in the predominance of CD8+ cells [Jeffery, 2000]. A predominance of CD8+ T-lymphocytes and CD68+ macrophages has been demonstrated in the airway and alveolar tissues of smokers with COPD [O'Shaughnessy, 1997].

It has previously been demonstrated that CD8+ T-lymphocytes are increased in the blood [Miller, 1982] and BAL [Costabel, 1986] of heavy smokers and in the airways and alveolar walls of subjects with COPD [Saetta, 1999, Lams, 2000]. Furthermore, CD8+ cell numbers in all lung compartments have been shown to correlate inversely with FEV_1 percent of predicted normal [Saetta, 2001; Baraldo, 2004] and to the degree of air trapping as determined by CT scanning [Berger 2003]. CD8+ T-lymphocytes are involved in the lysis of infected host cells particularly in response to viral infection [Cannon, 1988]. Inappropriate activation of CD8+ T-lymphocytes can induce apoptosis and cause tissue damage [Smyth, 1995]. Therefore in COPD, both the increased numbers of CD8+ T-lymphocytes and their activation (possibly during infection) may be an important part of the tissue damage that is known to occur in this condition. .

Macrophages are the key resident host defence cell of the alveolus with pleuripotential pro-inflammatory capabilities, their precise role in the inflammatory response in COPD is not clear. However these cells are involved with release of a range of inflammatory mediators, activation of other inflammatory cells and amplification of the immune response [Janeway, 1996]. Numbers of CD68+ cells (i.e. monocyte/macrophages) also correlate with the severity of airflow limitation [Di Stefano, 1998].

Increased numbers of neutrophils have been reported in bronchoalveolar lavage (BAL) and sputum [Lacoste, 1993] and correlate with a decline in FEV_1 over a 15 year follow-up period [Stanescu, 1996]. The cytokines interleukin (IL)-8 and tumour necrosis factor (TNF) α are increased in induced sputum [Keatings, 1996] and play a role in the selective recruitment of the inflammatory cells into the airways in subjects with COPD [Pauwels, 2001].

Stopping smoking is the single most effective means of improving prognosis in subjects with COPD [Doll, 1994], and is associated with a reduction in the accelerated rate of decline in FEV_1 [Fletcher, 1977]. None of the existing medications for COPD has been

shown to modify the long-term decline in lung function. Therefore, pharmacotherapy for COPD is used predominantly to decrease symptoms and minimise number and severity of exacerbations. The vast majority of subjects are treated with inhaled or oral bronchodilators alone, including anticholinergics, short- and long-acting β_2-agonists and theophyllines. Regular treatment with inhaled corticosteroids (ICS) is recommended for symptomatic subjects with a spirometric response to ICS or those with $FEV_1 < 50\%$ predicted normal value and repeated exacerbations requiring treatment with antibiotics or oral corticosteroids [GOLD, 2001].

Cilomilast is a potent and selective phosphodiesterase type 4 (PDE4) inhibitor currently under development for the treatment of COPD. The rationale for the use of PDE4 inhibitors in the treatment of COPD is based upon the role of cyclic adenosine monophosphate (cyclic AMP) as a second messenger that mediates a broad suppression of immune and inflammatory cell activities, along with the knowledge that PDE4 is the major cyclic AMP-hydrolysing isozyme in these cells [Torphy, 1991].

A previous, multicentre study (207499/076) of similar design evaluating the anti-inflammatory effects of cilomilast has been successfully completed [GlaxoSmithKline document number SB-207499/RSD-100J6D/1]. A total of 59 subjects, with a diagnosis of COPD, were randomised to receive cilomilast 15 mg bd or placebo for a period of 12 weeks. The study aimed to evaluate the anti-inflammatory effects of cilomilast by quantification of the key inflammatory cells in biopsies. Compared with placebo, analysis of change from baseline values demonstrated significant reductions in counts of bronchial biopsy CD8+ ($p=0.001$) and CD68+ ($p=0.04$) cells in the cilomilast group. Poisson regression analysis confirmed the reductions in the cilomilast group compared with the placebo group for CD8+ (48%, $p=0.004$) and CD68+ (55%, $p<0.001$). Additionally there were reductions in sub epithelial CD4+ cells (42%, $p=0.025$) and neutrophils (37%, $p=0.049$). There were no significant treatment related effects seen in the numbers of epithelial neutrophils, IL-8mRNA or TNFα mRNA+ cells. Sputum neutrophil % did not change significantly from baseline in either group. There were no significant changes in sputum macrophage %, total cell counts, IL-8 or neutrophil elastase concentrations.

The purpose of this clinical study was to explore further the potential for cilomilast to demonstrate anti-inflammatory effects in subjects with COPD.

4. STUDY OBJECTIVES

4.1. Primary Objective

The primary objective of the study was to compare the numbers of inflammatory cells of distinct immuno and ultrastructural phenotypes after treatment with cilomilast 15 mg twice daily (bd) and with placebo bd in subjects with COPD, using bronchial biopsy.

4.2. Secondary Objective

The secondary objective of the study was to compare the relative numbers (i.e. percentage) of distinct inflammatory cells after treatment with cilomilast 15mg bd and with placebo bd in sputum induced from subjects with COPD.

5. INVESTIGATIONAL PLAN

5.1. Study Design

5.1.1. Overall Study Design – Description

This was a randomised, double-blind, placebo-controlled, parallel-group multicentre study in subjects with moderate to severe COPD. Subjects completed a four-week single-blind placebo run-in period before randomisation to either cilomilast 15 mg bd or placebo bd for 13 weeks. The treatment period was followed by a one-week follow-up period.

Bronchial biopsies were performed one week before randomisation for the baseline sample (i.e. at Week -1, Visit 2) and at the end of 12 weeks' treatment at Visit 6, or one week after early withdrawal. The baseline and end-of-treatment bronchial biopsies were only to be performed if the safety criteria were met (see Section 5.6.2.4); otherwise the biopsy procedure was to be rescheduled within 1 to 7 days (Visit 2A and Visit 6A for the two biopsies, respectively). An induced sputum sample was to be collected at Visit 3 (Week 0), at Visit 7 (at the end of 13 weeks' treatment), and at early withdrawal if the biopsy was not done.

At Visit 1, pulmonary function tests (FEV_1, FVC, and SVC) were conducted before and after administration of salbutamol 400 μg via an MDI and a Volumatic spacer. At Visits 2-8, and including the Early Withdrawal Visit (EWV), SVC was measured before and after administration of salbutamol 400 μg via an MDI and a Volumatic spacer, and the results recorded in the CRF.

In addition, at Visits 2/2A and 6/6A, and at EWV (if applicable), before the biopsy procedures, FEV_1 (before and after the administration of salbutamol 400 μg via an MDI and a Volumatic spacer) was measured and the results recorded in the Biopsy Safety Form. At Visits 3 and 7, FEV_1 (before and after the administration of salbutamol 400 μg via an MDI and a Volumatic spacer) was measured as part of the sputum induction procedure.

Each subject was to visit the clinic on 8 occasions over the 18-week study period. Clinic visits were to take place within ± 3 days of the scheduled visit date and visits were to be scheduled at the same time of day (± 2 hours) and conducted preferably in the morning. Smoking was to be avoided for at least 2 hours before the clinic visit and the use of salbutamol and anticholinergic agents was to be avoided for at least 6 hours before the clinic visit. At each visit, study procedures were carried out according to the schedule in shown in Table 1.

Table 1 Outline of study assessments

Procedure	Screening	Baseline	Treatment					Follow-up	EWV[1]
Visit	V1	V2/2A	V3	V4	V5	V6/6A	V7	V8	
Week	-4	-1	0	4	8	12	13	14	
Signed written informed consent	x								
Inclusion/Exclusion criteria	x		x						
Demography	x								
Medical & surgical history	x								
Physical examination[2]	x							x	x[3]
Smoking history	x						x		x
Pulmonary history & symptoms	x								
Concurrent medication history	x								
Current medical conditions	X								
Resting SaO_2	X								
Posterio-anterior chest radiograph[4]	X								
Exacerbation assessment	X	X	X	X	X	X	X	X	X
Concomitant medication/Medical procedures	X	X	X	X	X	X	X	X	X
Adverse events[5]	X	X	X	X	X	X	X	X	X
Pre- and post-bronchodilator PFTs[6]	X	X	X	X	X	X	X	X	X
Salbutamol reversibility[7]	X								
Clinical laboratory & pregnancy testing	X						X		X
Blood clotting tests	X				X				X
Vital signs (BP, HR, temperature)		X	X			X	X	X	X
Faecal occult blood test		X					X	X[8]	X[8]
Bronchial biopsy & sample preparation[9]		X				X			X[10]
Sputum induction & sample preparation			X				X		X[10]
Dispense double-blind medication			X	X	X	X			
Collect study medication				X	X	X	X	X	X
Compliance with study medication				X	X	X	X	X	X

1. Early withdrawal visit for subjects who withdrew between clinic visits.
2. To include a respiratory examination.
3. If abnormalities were present at the previous visit.
4. To be available to the investigator by Visit 2 before taking the biopsy.
5. Only serious adverse events occurring from screening were to be collected. Serious adverse events occurring before study participation were not to be reported.
6. FEV_1, FVC and SVC measured at Visit 1; SVC only at Visits 2-8 and EWV.
7. Measured before and after administration of 400 μg salbutamol via MDI and spacer to determine %predicted normal FEV_1, and FVC.
8. If applicable.
9. Baseline (V2) and end-of-treatment (V6) biopsies performed only if safety criteria were met, otherwise biopsy rescheduled for 1-7 days later (V2A and V6A, respectively).
10. Bronchial biopsy performed one week after EWV; sputum induction performed, if possible, 7 days post-biopsy.

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

The dose of cilomilast selected for this study was based on results from previous phase II and III randomised, double-blind, placebo-controlled studies which investigated a dose of cilomilast 15 mg bd and found it to be efficacious at improving FEV_1 relative to placebo, reducing exacerbations and reducing inflammatory mediators such as CD8+ and CD68+ cells. A total treatment period of 13 weeks was chosen to assess the efficacy using biopsy and sputum samples as this allowed a repeat of the treatment period used for biopsy sampling in study number SB207499/076 (which previously demonstrated an apparent anti-inflammatory activity for cilomilast over 12 weeks) [GlaxoSmithKline document number SB-207499/RSD-100J6D/1]. The sputum sampling was undertaken one week after biopsy sampling within this study rather than prior to biopsy sampling in study 076 so that this process would be guaranteed not to have any affect on the inflammatory profile of the lung. The week delay between biopsy sampling and sputum induction was to allow recovery post biopsy

Subjects in the control group received placebo tablets twice daily, blinded to match the cilomilast tablets. A placebo control was regarded as most appropriate as the anti-inflammatory activity of other comparable drugs is poorly known and had not been investigated by a study of a similar nature.

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

The study was carried out only at specialist centres where there was expertise in taking biopsies and induced sputum samples.

5.2. Protocol Amendments

The protocol was initially approved on 16 October 2002 and was amended twice, on 6 November 2002 and 25 November 2002. Brief details of the protocol amendments are given below.

Amendment of 6 November 2002

- Faecal occult blood (FOB) testing between Visits 1 and 2, between Visits 7 and 8, or at early withdrawal was introduced. FOB testing was also to be performed in subjects who experienced gastrointestinal symptoms of concern or which interfered with daily activities.
- Urinalysis and pregnancy testing for women of childbearing potential was also introduced at Visit 8.
- The requirement for measuring all pulmonary function tests (i.e. FEV_1, FVC and SVC) at visits after Visit 1 was reduced to require only SVC to be measured.
- The inclusion criteria were amended to require women of childbearing potential to use effective contraceptive measures.

- The exclusion criteria at the randomisation visit (Visit 3) were amended to remove the requirement that subjects with clinically significant orthostatic changes in blood pressure be excluded if required by regulatory agencies.
- The requirement that subjects who failed to demonstrate stability in clinic trough FEV_1 between Visits 1 and 2 be withdrawn from the study was removed.
- Other amendments concerned more minor clarifications to wording of study procedures.

Amendment of 25 November 2002

- The timing of the FOB testing was clarified to specify that it be carried out at Visits 2 and 7, and, if applicable, at Visit 8 and the EWV.
- Other amendments concerned clarifications of discrepancies and inconsistencies in the original protocol and in the protocol amendment of 6 November 2002.

5.3. Selection of Study Population

Subjects who fulfilled all inclusion and exclusion criteria at Screening (described in Section 5.3.1 and Section 5.3.2) were eligible to enter the single-blind placebo run-in phase of the study.

5.3.1. Inclusion Criteria

Subjects 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[1], an IUD, a diaphragm with spermicide, a condom with spermicide or Depo-Provera[2]) for at least one month prior to Visit 1 (Screening) and were required to continue using the same contraceptive measure during the study.
2. Subjects with a clinical diagnosis of COPD, as defined by GOLD guidelines [GOLD, 2001]. (A diagnosis of COPD was to be considered in any subject who had symptoms of cough, sputum production or dyspnoea, and/or a history of exposure to risk factors for the disease. Post-bronchodilator FEV_1/FVC was to be ≤70% predicted at Visit 1.)
3. Subjects with a smoking history (current or ex-smoker) of ≥10 pack years (1 pack year = 20 cigarettes smoked per day for 1 year or the equivalent). (Ex-smokers were defined as those who had stopped smoking for at least 6 months prior to Visit 1. Ex-

[1] Norplant is a registered trademark for levonorgestrel.

[2] Depo-Provera is a registered trademark for medroxyprogesterone acetate manufactured by Pharmacia.

smokers were eligible to enter the study provided they had at least 10 pack years smoking history.)

4. Subjects with a pre-bronchodilator FEV_1 to FVC ratio (FEV_1:FVC) ≤0.7 at Visit 1.
5. Subjects with poor reversibility of airway obstruction, defined by ≤10% increase in FEV_1 as % of predicted normal, or ≤200 mL (or both) increase in FEV_1 after the administration of salbutamol 400 μg via MDI with a spacer at Visit 1 (Screening).
6. Subjects with a post-salbutamol FEV_1 of ≥40 and ≤80% of predicted normal for height, age and sex at Visit 1. Subjects were assessed 30 minutes after administration of salbutamol 400 μg via MDI and spacer.
7. Subjects without hypoxaemia (all subjects were to have an O_2 saturation ≥88% on room air).
8. Subjects who gave their signed and dated written informed consent to participate.

5.3.2. Exclusion Criteria

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

1. Women who were pregnant or lactating.
2. Subjects with asthma and/or atopy as the main component of their obstructive airways disease.
3. Subjects with poorly controlled COPD, defined as the occurrence of any of the following in the 4 weeks prior to Visit 1 (Screening): acute worsening of COPD that was managed by the subject at home by self-treatment with corticosteroids or antibiotics, or that required treatment prescribed by a physician, or for which the subject was hospitalised.
4. Subjects with known active tuberculosis, lung cancer, clinically overt bronchiectasis or other known specific pulmonary disease; any other condition known to be associated with inflammation (sarcoidosis and arthritis).
5. Subjects with a chest X-ray indicating a diagnosis other than COPD that might have interfered with the study (the chest X-ray was to be taken at entry to the run-in period or in the 9 weeks prior to entry to the run-in period).
6. Subjects with clinically significant cardiovascular, neurological, renal, endocrine or haematological abnormalities that were uncontrolled on permitted therapy.
7. Subjects with clinically significant gastrointestinal or hepatic abnormalities.
8. Subjects with a history of bleeding diathesis.
9. Subjects with a history of hypersensitivity to PDE4 inhibitors.
10. Subjects with suspected abuse of alcohol or any other recreational substance.
11. Subjects receiving treatment with inhaled cromolyn sodium or nedocromil, inhaled long-acting β_2-agonists, and/or oral β_2-agonists, long acting anticolinergics (e.g. tiotropium bromide), xanthines, leukotriene modifiers, mucolytics, oral/inhaled corticosteroids or NACs (N-acetyl cysteine). All COPD medication, except short-

acting anticholinergic medication (ipratropium bromide) and/or salbutamol or Combivent, was to be withdrawn prior to or at Visit 1 (Screening). All oral/inhaled corticosteroids, long-acting anticolinergics (e.g. tiotropium bromide) and xanthines were to be withdrawn at least four weeks prior to Visit 1.

12. Subjects receiving treatment with long term oxygen therapy (LTOT) or those subjects who required supplemental oxygen more often than on an occasional (prn) basis.
13. Subjects who had received an investigational drug within 30 days of entry into this study (Visit 1), or within 5 drug half-lives of the investigational drug (whichever was the longer).
14. Subjects who were unable or unwilling to comply with all protocol specified procedures.

5.3.3. Randomisation Criteria at Visit 3

Subjects who fulfilled the randomisation criteria described below at end of the 4 week single-blind, placebo-controlled run-in period (i.e. at Visit 3) were eligible to enter the double-blind treatment phase of the study.

Subjects who fulfilled any of the following criteria at Visit 3 were not eligible for continuation in the study.

1. Subjects who had had any changes to their COPD medication (other than salbutamol, ipratropium bromide or Combivent), had received corticosteroids (oral or inhaled) for respiratory disease, or had been hospitalised for COPD/lower respiratory tract infections during the run-in period.
2. Subjects receiving any other medication during the run-in period which, in the opinion of the investigator, was judged likely to affect baseline assessments.
3. Subjects unable to tolerate withdrawal of medications during the run-in period.
4. Subjects unable to tolerate or comply with the protocol procedures.

All subjects were stratified before treatment, according to their smoking habit (i.e. current smokers or ex-smokers):

5.3.4. Other Eligibility Criteria Considerations

In order to assess any potential impact on subject eligibility with regard to safety, the investigator was to refer to the Clinical Investigator Brochure for detailed information regarding warnings, precautions, contraindications, adverse events and other significant data pertaining to the investigational product being used in this study.

5.3.5. Predetermined Criteria for Subject Withdrawal

Subjects were defined as having completed the study if they completed the run-in, treatment and follow-up phases of the study as defined in the protocol. Subjects who

entered the study (i.e. gave written, informed consent) but did not, for any reason, complete the study as defined were considered as withdrawals, whether or not they had received any study medication.

5.3.5.1. Subject withdrawal from the investigational product

Subjects randomised to treatment who did not complete the 13-week treatment period and/or who did not attend all required clinic visits up to and including Visit 7 were defined as having withdrawn from the investigational product. The investigator recorded the primary reason for the subject's withdrawal in the CRF. Reasons for withdrawal included the following.

- Adverse events
- Lack of efficacy of study medication
- COPD exacerbations requiring hospitalisations or the use of oral corticosteroids
- Loss to follow-up
- Failure to meet entry criteria
- Protocol violation
- Withdrawal of consent
- Other reasons

Subjects could be withdrawn from study treatment at any time by the investigator if it was considered detrimental for them to continue in the study. Subjects were also free to withdraw themselves from the study at any time, although every effort was to be made to persuade them to return to the clinic for a follow-up visit and to return all study-related materials. Subjects who experienced a severe COPD exacerbation during the treatment period (see Section 5.6.3.2) were to be withdrawn from the study, as were subjects who experienced a moderate COPD exacerbation requiring the use of oral corticosteroids. Subjects who experienced one moderate COPD exacerbation requiring the use of antibiotics during the treatment period, were allowed to continue. Subjects experiencing more than one moderate COPD exacerbation requiring the use of antibiotics during the treatment period, however, were to be withdrawn from the study, and the withdrawal procedures followed as described below. The reason for withdrawal was to be recorded as COPD exacerbation. Subjects who changed their smoking status (i.e. started or stopped smoking) were to be excluded from the per-protocol population.

At withdrawal, all study medication and rescue medication were to be collected from the subject and drug accountability records or logs completed. If possible, the following assessments were to be completed and the data recorded in the CRF.

- Review of adverse events
- Review of concurrent medications
- Clinic pulmonary function tests

- Review of exacerbations
- Physical examination
- Clinical laboratory tests (chemistry, haematology, urinalysis, FOB test and pregnancy testing for females of childbearing potential)

A follow-up visit or telephone call was to be made 1 week ±3 days after the withdrawal visit when the 'End of Study Record' in the CRF was to be completed.

5.3.5.2. Subject withdrawal from the study

Once randomised to treatment, subjects were considered to have withdrawn from the study if they were withdrawn from the investigational product or if they did not complete the follow-up contact at Visit 8.

Subjects who entered the run-in period but did not meet the eligibility criteria for entry to the treatment period and were therefore not randomised to treatment, or subjects who discontinued the study during the run-in period, were to have the following information recorded in the CRF.

- All Visit 1 data
- Adverse events (including exacerbations if any)
- Concurrent medication (if any)
- 'End of Study' record in the CRF (including reason for withdrawal and date of withdrawal)

No follow-up contact was required for subjects withdrawn prior to randomisation at Visit 3, unless they experienced a serious adverse event (see Section 5.6.3.4) or were withdrawn due to an adverse event. For such subjects, a follow-up visit (phone call) was to be carried out two weeks after the date of withdrawal when the follow-up visit forms in the CRFs were to be completed.

5.4. Investigational Product

5.4.1. Description of Investigational Product

Cilomilast (SB 207499) was provided as yellow, round, convex tablets containing 15 mg 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. Batch numbers: [redacted] (cilomilast) and [redacted] (placebo).

For the single-blind placebo run-in phase, cilomilast-matched placebo tablets were provided in bulk and labelled as for the double-blind phase (see below) except that there was no protocol number on the bottle.

For the 13-week double-blind treatment phase, bottles contained either 70 tablets of cilomilast 15 mg or matching placebo (see Section 5.4.4 for blinding method). Each bottle provided a 35-day supply of study medication to allow for 7 days overage. Subjects were allocated four double-blind treatment bottles, each bottle labelled with a 6-digit Container Number (see Section 5.4.5). The investigator was advised to give the subject one bottle at each of the visits during treatment period, rather than dispense all 4 bottles at Visit 3. If the subject were to delay his/her next visit for some reason, an additional bottle could be dispensed at the discretion of the investigator. If more than one bottle was dispensed at any visit, the subject was reminded to use the bottles sequentially.

Bottles were labelled in accordance with all applicable regulatory requirements and labels included the following:

- Container number (for double-blind study medication)
- Space to enter subject initials, date dispensed and visit number (run-in medication only)
- Quantity statement
- Protocol number
- Packaging (job) number
- Dosing directions
- Storage conditions (room temperature)
- "Keep out of reach of children" statement
- Appropriate caution statements
- Company address.

Before dispensing, all study medication was kept safely locked, in a dry place at room temperature 20-25°C.

5.4.2. Dosages and Administration

For the single-blind placebo run-in phase, subjects took one cilomilast-matched placebo tablet twice daily, in the morning immediately after breakfast and in the evening immediately after a meal.

Subjects who fulfilled the randomisation criteria at Visit 3 entered the 13-week double-blind treatment phase and were randomised to receive either cilomilast 15 mg or placebo. One tablet of study medication was taken twice daily, in the morning immediately after breakfast and in the evening immediately after a meal. For days when subjects visited the clinic, they were reminded not to take their morning dose of study medication at home, but to bring their study medication with them to the clinic.

5.4.3. Dose Rationale

A recent randomised, double-blind, 24-week study provided evidence for the efficacy for cilomilast 15 mg bd over placebo in subjects with COPD [GlaxoSmithKline document number SB-207499/RSD-100J4D/1]. Cilomilast was shown to have statistically significant effects on the co-primary endpoints of change from baseline averaged over 24 weeks in trough FEV_1 and in the total score of the St. George's Respiratory Questionnaire (SGRQ).

In a 6 week double-blind, placebo-controlled, dose-ranging study, cilomilast at doses of 5, 10 and 15 mg bd were compared to determine its safety, tolerability and efficacy in out-subjects with COPD [GlaxoSmithKline document number SB-207499/RSD-100TFS/1]. At a dose of 15 mg bid, cilomilast was statistically superior to placebo with respect to improvements in pulmonary function. The superiority of the 15 mg bd regimen was supported by positive trends in symptoms (dyspnoea), quality of life and a significant reduction in β_2-agonist use. Although a greater degree of benefit was observed with 15 mg bd than with the other dosages of cilomilast, no clear dose ordering was observed.

5.4.4. Blinding

Cilomilast and placebo tablets were identical in appearance and the double-blind medication drug labels identified only the container number. All medication for randomised subjects was blinded to both the investigator and the subject. The blind was maintained by GSK who maintained an updated copy of the master randomisation code.

Individual subject code breaks, identifying the container number and the corresponding treatment allocation, were provided to the investigator with the study medication. Only in the case of an emergency, when knowledge of the investigational product was essential for the clinical management or welfare of the subject, could the investigator unblind a subject's treatment assignment. If the blind was broken for any reason, the investigator was to notify GSK immediately without revealing the subject's study treatment assignment.

If a serious adverse event was reported to GSK, Global Clinical Safety and Pharmacovigilance (GCSP) staff were permitted to unblind the treatment assignment for an individual subject. If an expedited regulatory report to one or more regulatory agencies was required, the report was to identify the subject's treatment assignment. When applicable, a copy of the regulatory report could be sent to investigators in accordance with relevant regulations, GSK policy, or both.

5.4.5. Treatment Assignment

At Visit 3, eligible subjects were assigned to a study treatment in accordance with the central randomisation schedule with randomisation balanced at site level. GSK's Registration and Medication Ordering System (RAMOS), using an Interactive Voice Response System (IVRS) was used to allocate the dispensing packs.

Medication was allocated by use of three numbers as follows:

- Each subject screened was allocated a CRF Number (Subject Number). This number was unique to each subject and was assigned from a list provided to the site in chronological order.
- Each subject who satisfied the randomisation criteria was assigned a unique Random Number by IVRS. Once a Random Number had been assigned to a subject, it could not be reassigned to any other subject. Neither the subject nor the investigator knew which treatment had been allocated to the subject.
- At Visit 3, following randomisation, RAMOS allocated four double-blind treatment bottles via the IVRS system. Each bottle labelled with a 6 digit Container Number was unique and corresponded to the study medication pack to be dispensed to the subject.

The procedures and times at which the investigator was to call RAMOS were as follows:

- At Visit 1, the investigator or designee telephoned RAMOS, specified the Subject Number (the number shown on the CRF) and RAMOS registered the subject.
- At Visit 3, the investigator or designee telephoned RAMOS, specifying the subject number and the smoking status of the subject (based on the criteria listed in Section 6.1.3 of the Protocol: Smoking History) for RAMOS to stratify the subject.
- RAMOS then randomised the subject, assigned the treatment number and assigned the study medication by reading the appropriate Container Numbers of the four treatment bottles to be dispensed to the subject.
- If the subject was withdrawn from the study at any time between Visits 3 and 7, the investigator or designee telephoned RAMOS, specified the subject number and logged the subject as withdrawn.
- At the follow-up visit (Visit 8), the investigator or designee telephoned RAMOS, specified the subject number and recorded the follow-up visit.
- On each call to the IVRS, the minimum information required was the unique centre number (allocated to each centre prior to centre approval) and the CRF number.

Although study medication was stored at each site, the investigator (or designee) was required to telephone RAMOS to obtain the Container Numbers of the treatment bottles to be dispensed to each subject. All calls to RAMOS were confirmed with faxes, which were sent to the investigator upon completion of each call.

5.4.6. Assessment of Compliance

At each treatment visit (from Visit 3 to Visit 7), including any unscheduled visits where medication was returned, the number of remaining doses was to be counted. Percentage compliance was calculated using the following formula and entered on the CRF:

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

Subjects were required to show ≥80% and ≤120% compliance in taking study medication at each treatment visit to continue in the study.

5.4.7. Treatment of Investigational Product Overdose

In the event of an overdose, general symptomatic and supportive measures were to be initiated promptly and maintained for as long as necessary. The investigator was to consult the approved product labels for further information on treatment of overdose.

5.5. Prior and Concomitant Medications and Non-Drug Therapies

5.5.1. Permitted Medications

All concomitant medications taken during the study were recorded in the CRF with indication, dosage and dates of administration. Any changes in concomitant medication were also to be recorded in the CRF.

The following concomitant medications were permitted.

- Treatment for smoking cessation, although changes in smoking status (i.e. starting or stopping smoking) resulted in the subject's exclusion from the per-protocol population.
- Salbutamol (prn) and/or ipratropium bromide or Combivent for use as relief medication was provided throughout the study. In addition, salbutamol and/or ipratropium bromide or Combivent for use via the nebuliser was provided for use before the bronchial biopsy and sputum induction procedures. The use of this medication was to be recorded in the CRF. At each visit, investigators were to ensure that the subject had sufficient rescue medication to last at least until the following visit.
- Between Visits 1 and 7, subjects were not permitted to take any additional bronchodilators that they possessed at home, with the exception of the salbutamol and/or ipratropium bromide or Combivent provided as relief medication. If the subject experienced symptoms that did not respond adequately to salbutamol and/or ipratropium bromide or Combivent, he/she was to contact the investigator.

5.5.2. Prohibited Medications

Except for the short-term management of exacerbations of COPD, the following medications were prohibited between Visit 1 and Visit 8.

- Inhaled, oral and systemic corticosteroids (treatment with these agents was to be stopped 4 weeks before Visit 1)
- Long-acting β_2-agonists (e.g. salmeterol and formoterol; treatment with these agents was to be stopped two weeks before Visit 1)

- Oral β_2-agonists (e.g. bambuterol) and nebulised β_2-agonists (except as part of the biopsy or sputum induction procedures)
- Long-acting anticholinergics e.g. tiotropium bromide (treatment with these agents was to be stopped 4 weeks before Visit 1)
- Xanthines (treatment with these agents was to be stopped 4 weeks before Visit 1)
- Leukotriene modifiers
- Sodium cromoglycate and nedocromil sodium
- N-acetyl cysteine (NAC)

5.5.3. Medical Devices

The following medical devices were provided by GSK for this study.

- MDI inhaler
- Volumatic spacer

5.5.4. Non-drug Therapies

Non-drug therapies for conditions other than COPD were permitted during the study provided that their use was not considered to have an impact on the subject's COPD.

5.6. Study Assessments and Procedures

For each scheduled study visit, subjects were required to attend the clinic at the same time of day (±2 hours), preferably in the morning, and after breakfast (except on the days when biopsies were taken when they were not to have had breakfast before the biopsy). Subjects were to refrain from smoking and using medication during the clinic stay if at all possible.

Each subject was provided with Run-In and Treatment Daily Record Cards on which to record any exacerbations experienced. During the Treatment period, subjects were also asked to record their compliance with study medication. Relevant information from the Daily Record Card about exacerbations and compliance was recorded in the CRF.

A summary of the assessments and procedures conducted at all visits is provided in the outline of study procedures in Table 1.

5.6.1. Demographic and Baseline Assessments

At Visit 1, the following demographic and baseline information was recorded.

- Written informed consent was obtained before the subject was asked to stop taking medication specified in the study exclusion criteria (see Section 5.3.2).

- Any adverse events were recorded that the subject might have experienced from the time of giving consent. Adverse events could include pre- or post-treatment events that occurred as a result of protocol specified procedures (i.e. invasive procedures, modifications of the subject's previous therapeutic regimen).
- Demographic details (sex, ethnic origin and date of birth) were recorded.
- A full medical and surgical history was obtained, including history of myocardial infarctions. A physical examination including height and weight, and a respiratory examination, as well as a full examination of major organ systems was performed.
- Cigarette smoking history and smoking status were recorded. Ex-smokers, defined as those who had stopped smoking for at least 6 months prior to Visit 1, were eligible to enter the study provided they had at least 10 pack years smoking history.
- COPD history and duration, including history and duration of chronic bronchitis, were recorded.
- Current medical conditions were recorded.
- All medication for COPD taken during the 12 weeks preceding Visit 1 were recorded, together with all other medication taken during the previous 4 weeks.
- Resting SaO_2 was measured by pulse oximetry.
- The investigator reviewed a current (carried out within 9 weeks before Visit 1) posterio-anterior chest X-ray. If a current film was not available for review, a new film was obtained and results made available at Visit 2 prior to the biopsy.
- An assessment of COPD exacerbations in the 12 months before Visit 1 was made. Subjects with poorly controlled COPD in the previous 4 weeks, defined as acute worsenings that required oral corticosteroids or antibiotics, or changes in COPD medication, were not eligible to participate in the study.
- Pulmonary function tests (PFTs): FEV_1, FVC and SVC, including reversibility after administration of 400 μg of salbutamol, were carried out at least 6 hours after the subject's last administration of a β_2-agonist.
- The inclusion and exclusion criteria checklist was completed once the procedures above had been carried out.
- Samples were taken for clinical laboratory tests (chemistry, haematology, urinalysis and pregnancy testing for females of childbearing potential). All clinically significant abnormal laboratory findings were to be repeated until the values returned to normal.
- A blood sample was taken for the blood clotting test. Samples were to be processed at the site, where possible, and results were to be available before the biopsy procedure was conducted at Visit 2.

At Visit 2, the following baseline information was recorded.

- Vital signs (blood pressure and heart rate) and temperature were measured after the subject had been sitting for 5 minutes.

- The results of the faecal occult blood (FOB) test, which the subject had carried out at home, were reviewed.
- A bronchial biopsy was performed, but only if the safety criteria (see Section 5.6.2.4) were met, otherwise the biopsy procedure was rescheduled for 1 to 7 days time (Visit 2A).

At Visit 3, the following baseline information was recorded.

- Sputum induction and sample preparation was performed.

5.6.2. Efficacy Assessment

5.6.2.1. Primary efficacy endpoints

The primary efficacy endpoints were to measure the following inflammatory cells in biopsy tissue and compare the results from subjects treated with cilomilast 15 mg bd with those from subjects treated with placebo bd.

- Sub-epithelial CD68+ (macrophages) per unit area of tissue
- Sub-epithelial CD8+ (cytotoxic T-lymphocytes) per unit area of tissue

5.6.2.2. Secondary efficacy endpoints

The secondary efficacy endpoints concerned the comparison of cell numbers in biopsy tissue and sputum from subjects treated with cilomilast and from subjects treated with placebo, as detailed below.

Biopsy tissue: number of sub-epithelial cells per unit area

- Neutrophil elastase positive cells (neutrophils)
- CD4+ lymphocytes
- IL-8 mRNA positive cells
- TNFα mRNA positive cells
- CD45 positive cells
- Mucin expression

Sputum: number of cells per unit volume

- Sputum total cell count
- Macrophages as a percentage of total cells
- Eosinophils as a percentage of total cells
- Lymphocytes as a percentage of total cells

- Neutrophil elastase
- IL-8

5.6.2.3. Tertiary efficacy endpoint

The tertiary efficacy endpoint was comparison of SVC measured in subjects treated with cilomilast and subjects treated with placebo.

5.6.2.4. Methodology

Bronchial Biopsy

The bronchial biopsy was performed by a physician experienced in the use of this technique in subjects with COPD, and the procedure was standardised across all participating centres according to a detailed protocol. Before screening the first subject at each study site, the physician conducting biopsies was to take a pilot sample biopsy for submission to the central laboratory (Meakins-Christie Laboratories, McGill University, Canada) for confirmation of sample size and quality, and logistics.

Bronchial biopsies were performed prior to randomisation (Visit 2/2A) and after 12 weeks of treatment (Visit 6/6A), or 7 days after early withdrawal from the study (if possible). Specific safety criteria on the day of bronchoscopy had to be met by each subject in order for the test to proceed:

- Pre-salbutamol FEV_1 40-80% predicted normal value
- No history of bleeding diathesis
- Normal platelet count
- Ability to be collected by a friend/relative at the end of the biopsy procedure.

If the subject was unsuitable for bronchoscopy on the scheduled day (Visits 2 and 6), the procedure was re-scheduled for 1 to 7 days times (Visits 2A and 6A, respectively).

Experienced bronchoscopists in dedicated bronchoscopy units performed the procedure with facilities available for the management of medical emergencies and resuscitation. A similarly experienced nurse or inhalation therapist assisted the bronchoscopist. The procedures were scheduled for 10.00 am ± 2 hours. No food or drink was to be consumed by the subject from midnight before the bronchoscopy ("nil by mouth"). On arrival in the unit, the following procedures were carried out: evaluation of pulmonary symptoms; respiratory examination; measurement of heart rate, blood pressure and temperature; spirometry with documentation of FEV_1, FVC and SVC. A complete blood count with platelets, thrombin time (TT), prothrombin time (PT) and partial thromboplastin time (PTT) was to be available, performed within 4 weeks of the day of bronchoscopy. In addition, all subjects over the age of 45 years were to have a recent electrocardiogram available for review by the physician.

Subjects were premeditated with midazolam (2.5-7.5 mg) via an intravenous line and salbutamol (2.5 mg) via a nebuliser. Sufficient midazolam was given in order to achieve mild sedation; intravenous flumazenil was to be available as an antagonist to midazolam if needed. Topical lignocaine was administered to the nose, tongue and pharynx with lignocaine gel to facilitate entry of the bronchoscope via the subject's nose or mouth (using a mouthpiece). After insertion of the bronchoscope, topical anaesthesia of vocal cords and trachea was to be achieved with a total dose of <400 mg of lignocaine (4% above the vocal cords, 2% below). Six biopsies of adequate size (2 mm) were to be performed on the right side beginning at the subcarinae in the right lower lobe (2 biopsies), then the right middle lobe (2 biopsies) and finally the right upper lobe (2 biopsies). Biopsy size and overall quality free of blood was to be macroscopically inspected by the bronchoscopist/assistant. Bronchoscopies were performed at each centre using an Olympus BF fibreoptic bronchoscope (type IT40, 2.8 mm channel or similar) or equivalent, and the bronchoscope was provided for each centre participating in the study. Use of any other type of bronchoscope was to be pre-agreed with GSK. Cup forceps (FB-35C-1, 2.8 mm (fenestrated forceps)) or equivalent were to be used for all subjects, and each set of forceps replaced after every 5 biopsy occasions. Use of any other type of forceps was to be pre-agreed with GSK.

To prevent the potential for reader bias based on knowledge of visit number, the biopsy tissue blocks for each subject were identified by a unique number, generated by the Meakins-Christie Laboratory. Personnel involved in the counting of the cells were blind to the code.

Full details of the procedure are provided in the Bronchial Biopsy Procedures Document, which also describes the immunohistological and in-situ hybridisation techniques used to analyse the samples.

Sputum Induction

The procedure for sputum collection and processing was standardised across all participating centres according to a detailed protocol. At each centre, an induced sputum sample was to be taken as a pilot sample (fixed slides and frozen supernatants) for submission to the central laboratory (John Hunter Hospital, Australia) to confirm sputum sample quality and logistics. Sputum samples were only to be processed by appropriately qualified laboratory staff that had been trained in conducting the procedure.

Sputum induction was carried out at baseline (Visit 3) and after 13 weeks of treatment (Visit 7), and, if applicable after early withdrawal from the study, a week after taking the early withdrawal biopsy sample. If the sputum sample taken at Visit 3 was unsatisfactory, no further sputum samples were to be taken for the subject, but he/she was to continue in the study with biopsy procedures performed at the scheduled visits.

No longer than 60 minutes of beginning the induction procedure, baseline FEV_1 was measured, followed by administration of bronchodilator (Ventolin 400 µg via spacer), and post-bronchodilator FEV_1 and FVC measurements performed following American Thoracic Society guidelines [American Thoracic Society, 1995b]. The induction process was not continued if the post-salbutamol FEV_1 was less than 0.8 L or <40% predicted.

Subjects continuing with the induction procedure were asked to inhale a mist of 0.9% bacteriostatic saline generated with a low output Medix ultrasonic nebuliser or high output Devilbiss ultrasonic nebuliser. The nebuliser was supplied by GSK. After 30 seconds nebulisation, the subject was asked to expectorate the sputum into a specimen container using a cough. FEV_1 was measured after 1 minute in order to ensure that significant bronchoconstriction had not occurred, i.e. >10% change from baseline. After each nebulisation period, if the subject's FEV_1 had changed by <10%, the induction was repeated using a nebulisation time of 1 minute, then 2 minutes and 4 minutes to a total cumulative time of 7.5 minutes.

If, after 7.5 minutes cumulative nebulisation time, an adequate sample had been obtained, the procedure was stopped. If an adequate sample had yet to be obtained, subjects were asked to inhale a mist of 4.5% hypertonic saline, assuming their FEV_1 still showed <10% change from baseline. The procedures as for the 0.9% bacteriostatic saline were repeated.

If FEV_1 fell by >10% but <20% from baseline after any nebulisation period, the induction procedure was paused and Ventolin 200-400 μg via spacer was administered. After a wait of 15 minutes, FEV_1 was reassessed and if the value had returned to within 5% of baseline, the induction procedure was re-started. If recovery was not complete the test was discontinued. If FEV_1 fell by >20% after any nebulisation period or if bothersome symptoms occurred, nebulisation was discontinued and treatment with inhaled bronchodilator given.

Preparation of Cytospins and Sputum Supernatants

Mucus clumps free of salivary contamination were selected using forceps, their volume recorded, and they were then dispersed in dithiothreitol, diluted with phosphate-buffered saline and filtered. Total cell count and cell viability were assessed using a haemocytometer and the trypan blue exclusion method. Cytospins were prepared (two with 70 μL) for the differential cell count.

To prevent the potential for reader bias based on knowledge of visit number, the slides produced for each subject visit were assigned a random code number generated by GSK (a Sample Identification Number, SIN) which corresponded to the visit number for each subject. All slides were labelled with the SIN which linked the slide to the subject number and visit number. Air-dried, unfixed slides and frozen samples of sputum supernatant were shipped from sites in batches to the central sputum laboratory (Quest) using the slide shipper boxes provided by GSK. The slides and three frozen supernatants were forwarded by Quest to the John Hunter Hospital, Newcastle, Australia where the slides were counted and the supernatants processed according to the methodology in the Sputum Procedure Document.

Pulmonary Function Tests (PFTs)

Throughout the study, it was recommended that the same pulmonologist, technician or nurse administer the pulmonary function tests for any individual subject at all study visits in order to ensure consistency of technique. Where possible, pulmonary function measurements were to be performed at the same time of day under BTPS (Body

Temperature and Pressure Standard) conditions using the same spirometer at each visit. The subject was also to be in the same position (i.e. sitting or standing) at each visit. It was mandatory to use spirometers that could print out a hard copy of the FEV_1 measurements which was stored in the subject's source notes.

Forced expiratory volume in 1 second (FEV_1) forced vital capacity (FVC), slow vital capacity (SVC) and FEV_1/FVC ratio were measured according to the BTPS convention. The spirometer was to be calibrated and maintained to acceptable respiratory function laboratory standards [ERS Consensus Statement, 1995; Standardisation of Lung Function Tests, 1993]. At each assessment, PFTs were to be performed three times. For each set of three FEV_1, FVC and SVC measurements, the highest measurement was to be taken.

Visit 1

At Visit 1, FEV_1, FVC and SVC were recorded before and 30 minutes after inhalation of 400 μg salbutamol delivered via an MDI inhaler and a Volumatic spacer. Subjects were to have refrained from taking short acting β_2-agonists and anticholinergics for at least 6 hours before the visit. The % predicted normal value for FEV_1 was also calculated and recorded in the CRF using the highest of the three measurements. All predicted normal values were taken from the ECCS tables provided [Standardisation of Lung Function Tests, 1993].

At Visit 1, reversibility was calculated as a percentage of predicted normal FEV_1 using the following formula:

$$\text{Reversibility} = \frac{(\text{Highest post-bronchodilator } FEV_1 - \text{Highest pre-bronchodilator } FEV_1)}{\text{Predicted normal } FEV_1} \times 100\%$$

Visit 3

Before randomisation to study treatment at Visit 3, subjects were to meet the following criterion: a reversibility defined as ≤10% increase in FEV_1 as a percentage of the predicted normal value or ≤200 mL absolute improvement, 30 minutes after inhalation of 400 μg salbutamol via the MDI inhaler and a Volumatic spacer, demonstrated at Visit 1.

All other visits

At all visits other than Visit 1, SVC (only) was assessed more than 6 hours after the last dose of salbutamol and/or ipratropium bromide or Combivent. Subjects were also asked to refrain from smoking in the two hours before SVC was recorded. SVC was measured both before and 30 minutes after inhalation of 400 μg salbutamol delivered via an MDI inhaler and a Volumatic spacer

PFTs for biopsy and sputum induction procedures

Before the biopsy procedure at Visits 2/2A and 6/6A, and at EWV (if applicable), FEV_1 was measured before and after the administration of salbutamol 400 μg via an MDI and a

Volumatic spacer. The results were recorded in the Biopsy Safety Form. FVC data generated while measuring FEV_1 were to be recorded in the subject's source notes.

At Visits 3 and 7, FEV_1 (before and after the administration of salbutamol 400 μg via an MDI and a Volumatic spacer) was measured as part of the sputum induction procedure. These results were not recorded in the CRF but were kept with the subject's source notes.

Hand held spirometers were to be used for the biopsy procedure and during the sputum induction process.

5.6.3. Safety Assessments

Safety was evaluated by monitoring adverse events, clinical laboratory tests, physical examinations, vital signs, oxygen saturation and pre-biopsy blood tests.

5.6.3.1. Adverse events

The investigator was responsible for the detection and documentation of events meeting the criteria and definition of an adverse event or serious adverse event as defined in the protocol.

Definition of an Adverse Event

An adverse event was defined as any untoward medical occurrence in a subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An adverse event could therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products this also included failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

Examples of adverse events included the following.

- Significant or unexpected worsening or exacerbation of the condition/indication under study (see 'Lack of Efficacy' below).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after investigational product administration even though they might have been present prior to the start of the study.
- Signs, symptoms or the clinical sequelae of a suspected interaction.
- Signs, symptoms or the clinical sequelae of a suspected overdose of either investigational product or a concurrent medication (overdose *per se* was not to be reported as an adverse event or serious adverse event).
- Significant failure of expected pharmacological or biological action (see 'Lack of Efficacy' below).

The following were not examples of adverse events.

- Medical or surgical procedure (e.g. endoscopy, appendectomy); the condition that led to the procedure was an adverse event.
- Situations where an untoward medical occurrence did not occur (e.g. hospital admission for social reasons and/or convenience).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that did not worsen.
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

For GSK clinical studies, adverse events could include pre- or post-treatment events that occurred as a result of protocol-mandated procedures (i.e. invasive procedures, modification of subject's previous therapeutic regimen).

Lack of Efficacy

"Lack of efficacy" *per se* was not to be reported as an adverse event. The signs and symptoms or clinical sequelae resulting from lack of efficacy were to be reported only if they fulfilled the definition of an adverse event or serious adverse event.

Abnormal Laboratory or Clinical Findings

Abnormal laboratory findings (e.g. clinical chemistry, haematology, urinalysis results) or other abnormal findings (e.g. X-rays, etc.) that were judged by the investigator to be clinically significant were to be recorded as adverse events or serious adverse events if they meet the appropriate definitions. Clinically significant abnormal laboratory findings or other abnormal assessments that were detected during the study or were present at baseline and significantly worsened following the start of the study were to be reported as adverse events or serious adverse events. However, such findings present or detected at the start of the study that did not worsen were not to be reported as adverse events. In addition, clinically significant abnormal laboratory findings or other abnormal assessments that were associated with the disease being studied were not to be reported as adverse events or serious adverse events unless judged by the investigator as being more severe than expected for the subject's condition.

Reporting of Adverse Events

The time period for reporting adverse events began at the time consent was obtained (when prohibited medication was withdrawn) to the end of the follow-up period.

At each visit or contact, the investigator was to inquire about adverse events by asking the following standard question:

- "Have you had any (other) medical problems since your last visit/assessment?"

When an adverse event occurred, it was the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory and diagnostics reports) relative to the event. The investigator was then to record all relevant information on the CRF. It was not acceptable for the investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the appropriate CRF pages. However, in the event that copies of medical records for certain cases were requested by GSK, all subject identifiers were to be blinded on the copies of the medical records prior to submission to GSK.

The investigator was to attempt to establish a diagnosis of the event based on signs, symptoms and/or other clinical information. In such cases, the diagnosis itself was to be documented as the adverse event rather than the individual signs/symptoms.

All adverse events documented at a previous visit/contact and designated as ongoing were to be reviewed at subsequent visits/contacts.

All adverse events were to be followed until resolution, until the condition stabilised, until the event was otherwise explained or until the subject was lost to follow-up. Once resolved, the appropriate CRF page was to be updated. The investigator was to ensure that follow-up included any supplemental investigations as might be indicated to elucidate the nature and/or causality of the adverse event. This might include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals.

GSK could request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the adverse event and the investigator was obligated to assist.

Evaluation of Adverse Events

Assessment of intensity

The interviewer was to make an assessment of intensity for each adverse event, according to the following categories.

Mild: An adverse event which was easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.

Moderate: An adverse event that was sufficiently discomforting to interfere with normal everyday activities.

Severe: An adverse event which prevented normal everyday activities.

Assessment of causality

The investigator was to use clinical judgement to determine the relationship between investigational product and adverse event. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors and the temporal relationship of the event to the investigational product were to be considered and

investigated. The investigator was also to consult the Investigator Brochure and/or Product Information in the determination of his assessment. Causality was assessed using the following question: was there a reasonable possibility that the AE may have been caused by the investigational product (Yes or No). Consequently the categories are divided into possibly and unlikely within this report.

Post-study Adverse Events

A post-study adverse event was defined as any event that occurred outside the detection period (the time the subject gave consent until the end of the follow-up period). Investigators were not obligated actively to seek adverse events in former study participants.

5.6.3.2. COPD Exacerbations

COPD exacerbations were defined as a worsening of COPD symptoms requiring changes to normal treatment, including antibiotic therapy, short courses of oral steroids and other bronchodilator therapy. Exacerbations of COPD were recorded as adverse events, or serious adverse events if appropriate, in the appropriate section of the CRF.

COPD exacerbations were categorised as follows.

- Mild exacerbation: Acute worsening of COPD that was self-managed by the subject at home by increasing usual COPD bronchodilator medications, but for which antibiotics were not taken (i.e. the subject did not see a doctor for this episode).
- Moderate exacerbation: Acute worsening of COPD that required additional treatment (e.g. a short course of oral steroids, antibiotics, etc.) prescribed by a primary care physician or as a result of a hospital out-subject visit (including a visit to the Emergency Room).
- Severe exacerbation: Acute worsening of COPD that required the subject to be admitted to the hospital for treatment.

Subjects who experienced moderate or severe exacerbations during the run-in period were not eligible to be randomised to the double-blind treatment period.

Subjects were provided with Daily Record Cards to record exacerbations that they might experience during the course of the study.

Subjects who experienced a severe exacerbation during the treatment period were to be withdrawn from the study, as were subjects who experienced a moderate exacerbation requiring the use of oral corticosteroids. However, subjects experiencing one moderate exacerbation requiring the use of antibiotics were allowed to continue in the study. Subjects experiencing more than one moderate exacerbation requiring the use of antibiotics were to be withdrawn from the study.

5.6.3.3. Gastrointestinal adverse events

In order to address concerns identified pre-clinically with cilomilast and drugs of a similar pharmacological class for their effect on the gut vasculature or on the heart, a gastrointestinal adverse event (GIAE) profile was defined. Particular attention was to be paid to collection of data on gastrointestinal adverse events, with extensive monitoring (physical examination, laboratory assessments, faecal occult blood, orthostatic heart rate and blood pressure) for events of potential concern. Gastrointestinal adverse events (i.e. bloody or black stool, abdominal discomfort such as pain or cramps, diarrhoea, vomiting) which caused the subject concern or interfered with daily activities (including eating and sleeping) were to be assessed by the investigator within 24 hours of occurrence. The investigator was to review the results of the initial assessment and arrange further follow-up as appropriate. All events were to be followed to resolution. The investigator recorded the GIAEs on the separate GIAE forms provided, and reported the GIAEs to the GSK monitor within 24 hours of the first assessment.

5.6.3.4. Serious adverse events

Definition of a Serious Adverse Event

A serious adverse event (SAE) was any untoward medical occurrence that:

i. resulted in death.

ii. was life-threatening.

iii. required hospitalisation or prolongation of existing hospitalisation.

iv. resulted in disability/incapacity.

v. was a congenital anomaly/birth defect.

vi. was an important medical event that, although not immediately life-threatening or resulting in death or hospitalisation, might jeopardise the subject or might require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events were invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that did not result in hospitalisation, or development of drug dependency or drug abuse.

Reporting of Serious Adverse Events

Serious adverse events that were possibly related to study participation (e.g. procedures, invasive tests, a change from existing therapy) or were related to a concurrent medication were collected and recorded from the time the subject consented to participation in the study until the subject withdrew from or completed the study. All other serious adverse events were collected from the time the subject gave consent until the end of the follow-up period.

Investigators were to record any serious adverse events on the CRF and transfer the report to GSK within 24 hours by facsimile transfer. In rare circumstances and in the

absence of facsimile equipment notification by telephone was acceptable, with a copy of the paper SAE form sent by overnight mail. The investigator was always to provide an assessment of causality (see above) at the time of the initial report.

In the case when an SAE had occurred and the investigator had minimal information to include in the initial report to GSK, it was still considered very important that the investigator make an assessment of causality prior to transmission of the serious adverse event CRF to GSK. The investigator could change his/her opinion of causality in the light of follow-up information, amending the serious adverse event CRF accordingly. The causality assessment was one of the criteria used when determining regulatory reporting requirements.

All serious adverse events documented at a previous visit/contact and designated as ongoing were to be reviewed at subsequent visits/contacts.

All serious adverse events were to be followed until resolution, until the condition stabilised, until the event was otherwise explained or until the subject was lost to follow-up. Once resolved, the appropriate CRF page was to be updated. The investigator was to ensure that follow-up included any supplemental investigations as might be indicated to elucidate the nature and/or causality of the serious adverse event. This might include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

GSK could request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the serious adverse event and the investigator was obligated to assist. If a subject died during participation in the study or during a recognised follow-up period, GSK was to be provided with a copy of any post-mortem findings, including histopathology.

Post-study Serious Adverse Events

A post-study serious adverse event was defined as any event that occurred outside the detection period (the time the subject gave consent until the end of the follow-up period). Investigators were not obligated actively to seek serious adverse events in former study participants. If, however, the investigator learned of any serious adverse event, including a death, at any time after a subject had been discharged from the study, and he considered that there was reasonable chance that the event was related to study treatment, the investigator was to notify GSK promptly.

5.6.3.5. Pregnancies

Pregnancy Testing

A urine or serum pregnancy test was conducted at Visits 1 and 7 in all women of childbearing potential. Subjects were asked to provide a urine sample of approximately 20 mL, and subjects with a positive pregnancy test at Visit 1 were to be excluded from entry to the study. If a subject became aware that she was pregnant during the course of the study, she was to be withdrawn.

Reporting of Pregnancy

The investigator or designee was to collect pregnancy information on any female subject who became pregnant while participating in the study. The time period for collecting information on the occurrence of a pregnancy was between Visits 1 and 7 and GSK was to be informed within two weeks of the investigator learning of a subject's pregnancy. The subject was to be followed-up to determine the outcome of the pregnancy and information of the status of mother and child forwarded to GSK. In general, follow-up was no longer than 6 to 8 weeks following the estimated date of delivery. Any premature termination of the pregnancy was to be reported to GSK.

While pregnancy itself was not considered to be an adverse event or serious adverse event, any complication of pregnancy or elective termination for medical reasons was to be recorded as an adverse event or serious adverse event as described in Section 5.6.3.1 and Section 5.6.3.4, and followed as described.

A spontaneous abortion was always considered to be a serious adverse event and was to be reported as described in Section 5.6.3.4. In addition, any serious adverse event occurring as a result of a post-study pregnancy and considered by investigator as having a reasonable possibility of relationship to study treatment was to be reported as described for post-study serious adverse events. While the investigator was not obligated actively to seek this information in former study participants, he/she might learn of a serious adverse event through spontaneous reporting.

5.6.3.6. Clinical laboratory evaluations

Blood and urine samples for clinical laboratory testing were collected at Visits 1, 7 and/or EWV for laboratory analyses. Subjects who completed the study or who withdrew from the study had blood and urine samples collected at the safety follow-up visit only if abnormalities had been observed at Visit 7 and/or EWV. Clotting parameters (PT, TT and APTT), haemoglobin concentration and platelet counts were also measured at the hospital's local laboratory (where possible) within 4 weeks of the bronchial biopsy.

The following variables were measured.

Haematology: Haemoglobin concentration, haematocrit, red cell count (RBC), white cell count (WBC) with differential, platelet count.

Clinical chemistry: Blood urea, creatinine, aspartate transaminase (ASAT/SGOT), alanine transaminase (ALAT/SGPT), gamma glutamyl-transferase (GGT), alkaline phosphatase (ALP), total protein, albumin, total bilirubin, sodium, potassium, chloride, glucose, uric acid.

Amylase was measured at Visit 1 (Screening), Visit 7 (end of treatment), and at early withdrawal, and also for subjects who reported gastrointestinal symptoms which were of concern to them or interfered with daily activities.

Faeces: Faecal occult blood (FOB) tests were carried out at Visits 2 and 7, and, if applicable, at Visit 8 (follow-up), EWV. Three tests were carried out on consecutive bowel movements. The tests were performed at home, before the designated clinic visit, according to the instructions provided with the FOB kits. FOB was also tested in subjects who reported gastrointestinal symptoms which were of concern to them or interfered with daily activities.

Urinalysis: Blood, glucose, protein and ketones.

Pregnancy: Urine/Serum β-HCG for women of childbearing potential at Visits 1 and 7 and at EWV, if appropriate.

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

All clinically significant abnormal laboratory findings were to be repeated until the values returned to normal. If such values did not return to normal within a period judged reasonable by the investigator, the aetiology was to be identified and the sponsor notified. Clinically significant worsenings in laboratory findings were to be recorded in the Baseline Signs and Symptoms or Adverse Events section of the CRF. Values outside the reference range, but not of clinical significance, were to be marked 'NCS' by the investigator on the printed laboratory report sheet. If the FOB test was positive, the test was to be repeated, and if the second test was also positive, the subject was to be followed-up by the primary care physician or referred to a gastroenterologist as appropriate.

5.6.3.7. Physical examination

A full physical examination (including respiratory examination) was carried out at Visit 1, to include measurement of height and body weight (light clothes, no shoes) and a full examination of the major organ systems. At Visit 8, or on early withdrawal, the investigator addressed the following question "Has there been a clinically significant worsening since the last assessment in the subject's physical condition?" Any changes were to be documented as adverse events.

5.6.3.8. Vital signs

Vital signs (blood pressure and heart rate) and temperature were recorded at Visits 2/2A, 3, 6/6A, 7, 8 and at EWV. Measurements of blood pressure and heart rate were made after the subject had been sitting for 5 minutes.

5.6.3.9. Chest radiograph

At Visit 1, the investigator reviewed a current (carried out within 9 weeks before Visit 1) posterio-anterior chest X-ray to exclude the possibility of any abnormality that might mimic or co-exist with COPD (e.g. pneumothorax, bronchial carcinoma or active

pulmonary TB). If a current film was not available for review, a new film was obtained and results made available at Visit 2 prior to the biopsy. A review of written reports without the accompanying films was not acceptable.

5.6.3.10. Resting SaO_2

Resting SaO_2 was measured by pulse oximetry at Visit 1. Subjects with SaO_2 values <88% in room air were not eligible for participation in the study.

5.6.3.11. Medical devices

GSK medical devices were provided for use in this study. In order to fulfil international reporting obligations the investigator was responsible for the detection and documentation of events meeting the definitions of incident, near-incident or malfunction that occurred during the study with such devices.

Definition of a Medical Device

A medical device was defined as any instrument, apparatus, appliance, material or other article, the principal intended action of which was typically fulfilled by physical means (including mechanical action, physical barrier, replacement of, or support to, organs or body functions). Examples of medical devices include measuring spoons, syringes, spacers and spring-loaded auto-injectors.

Definition of an Incident, Near-Incident, Malfunction and Remedial Action

Incident: any medical occurrence that occurred in a study subject, user, or other person with a GSK medical device provided for use in the study, which resulted in death or a serious deterioration in the state of health, whether or not due to a malfunction of the device.

Incidents included, for example:

- inhalation of an object that had accidentally entered a spacer device and resulted in tracheal obstruction.

Incidents did not include, for example:

- medical occurrences associated with metered-dose inhalers that did not fulfil the definition of a medical device (such events were to be reported as medicinal product adverse events),
- non-serious medical occurrences which had no further safety implications for the subject or the device.

Near-incident: any potential incident occurring with a GSK medical device provided for use in the study. Near-incidents were events that could have jeopardised the study subject, user, or other person, causing death or a serious deterioration of health if medical

intervention or other fortunate circumstances had not occurred. This included deficiencies or inaccuracies in the instructions for use of the device and/or malfunctions.

Near-incidents included, for example:

- discovery of caustic damage to the plastic parts of a device caused by contamination with an ointment, where no actual injury to a subject occurred but the reporter recognised that such an event could happen in normal medical use of the device and could kill or seriously harm a subject.

Malfunction: a failure of a device to perform in accordance with its intended purpose when used in accordance with the manufacturer's instructions.

Remedial action: any action other than routine maintenance or servicing of a device where such action was necessary to prevent recurrence of an incident or near-incident. This included any amendment to the design to prevent recurrence.

Reporting of Medical Device Incidents and Near-Incidents

The time period for reporting medical device incidents, near-incidents or malfunctions was all periods of the study during which GSK-provided medical devices were available for use.

Any medical device incident or near-incident occurring during the study was to be documented in the subject's medical records, in accordance with the investigator's normal clinical practice, and on the "Medical Device Incident Report Form". In addition, for incidents and near-incidents fulfilling the definition of an adverse event or serious adverse event, the appropriate pages of the CRF were to be completed.

Investigators were to transfer reports of any medical device incidents or near-incidents to GSK within 24 hours by facsimile transfer. In the absence of facsimile equipment notification by telephone was acceptable, with a copy of the paper "Medical Device Incident Report Form" form sent by overnight mail. The investigator was always to provide an assessment of causality at the time of the initial report, and describe any corrective or remedial actions taken to prevent recurrence of the incident.

All medical device incidents and near-incidents involving an adverse event were to be followed until resolution of the event, until the condition stabilised, until the condition was otherwise explained, or until the subject was lost to follow-up. The investigator was responsible for ensuring that follow-up included any supplemental investigations as might be indicated to elucidate as completely as practicable the nature and/or causality of the incident.

Post-study Medical Device Incidents and Near-Incidents

Investigators were not obligated actively to seek reports of medical device incidents or near-incidents in former study participants. If, however, the investigator learned of any incident or near-incident at any time after a subject had been discharged from the study,

and he considered that there was reasonable possibility that this was related to a GSK medical device, the investigator was to notify GSK promptly.

5.7. Data Quality Assurance

At the clinical study sites, the investigator or his designee recorded all required subject data in paper CRFs and subjects completed a Daily Record Card (DRC). A screening log with GSK-required information, created by the investigator at site, tracked subjects who were screened prior to entry into the study but were not randomised.

Monitors' meetings were held on 3-5 December 2002 for Australia, 16 December 2002 in the UK, 13-16 July 2003 in Toronto, Canada and 22 July 2003 in Cape Town, South Africa where the CRF and CRF completion guidelines were presented.

The completed original CRFs and a copy of DRCs were returned to Quintiles Data Management for processing. In addition, validated central laboratory data were transmitted electronically to Quintiles Data management. The investigator retained copies of the CRFs and any original subject-completed documents.

Data entry applications were designed and validated at Quintiles Data Management. Data values recorded on the CRF were entered using double data entry.

Computerised data validation was performed on CRF data using data validation checks. Validation discrepancies, if not covered by a Standard Clarification Agreement, were queried using the documented data query process for review and resolution by investigators, and, if appropriate, with reference to the Clinical Study Team members. Any necessary changes were made to both the CRF and the database by data management staff.

Quality Control (QC) tasks were conducted in accordance with existing data management standard operating procedures to ensure database accuracy against the data collected in the CRF. QC procedures are in alignment with the International Conference for the Harmonisation of Good Clinical Practice (ICH GCP). Adverse events and concomitant medications were coded by the autoencoder using company standard dictionaries MedDRA and GSK Drug.

Serious adverse event data, consistent with the data collected for other adverse events, was entered onto the database and quality assured, including reconciliation with the Global Clinical Safety and Pharmacovigilance database.

After all data management QC/QA procedures were completed the database was released on 6 August 2004. The database was frozen on 19 August 2004 at which time access to the data was also restricted (database lock).

The raw data (CRFs, etc.) will be archived according to company standard procedures.

5.8. Data Analysis Methods

5.8.1. Timings of Planned Analyses

5.8.1.1. Interim analyses and data monitoring

No interim analyses were planned or performed for this study.

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

The changes to the conduct of the study were those described in the protocol amendments (see Section 5.2).

There were no changes in methods of data analysis to those planned.

5.8.2. Sample Size Considerations

In order to obtain 86 subjects for the per-protocol analysis, it was planned to enrol 116 subjects to the cilomilast and placebo groups in an equal ratio.

The sample size estimates were based on the results of study 076 and ensured 90% power to detect an approximate difference of 175 (assumed common standard deviation 230) in CD8+ between cilomilast and placebo at significance level of 2.5%. The target sample size ensured more than 99% power to detect a difference of 80 (assumed common standard deviation 75) in CD68+ between cilomilast and placebo at significance level of 2.5%.

Sample size sensitivity was assessed with various standard deviations as illustrated below. It should be noted that sample sizes did not change greatly as standard deviation changed.

CD8+		CD68+	
Standard Deviation	Sample Size	Standard Deviation	Sample Size
210	36	55	12
220	40	65	17
230	43	75	22
240	47	85	29
250	51	95	36

5.8.3. Analysis Populations

5.8.3.1. Definitions

Three analysis populations were defined.

Randomised Population

The randomised population consisted of all subjects who had a randomisation number assigned and were confirmed as having received at least one dose of double-blind study medication. All safety variables were analysed for this population.

Intent-to-treat (ITT) Population

The intent-to-treat population included all subjects who received randomised study medication, 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.

Per-protocol (PP) Population

The primary analysis for efficacy in this study was based on the per-protocol population. Subjects with violations of eligibility criteria were entirely excluded entirely from this analysis. Subjects with violations occurring post-randomisation had only the data collected subsequent to the violation excluded. Because of their potential to confound measurement of the primary endpoint, any data collected subsequent to the onset of a subject's initial COPD exacerbation were also excluded from the per-protocol analysis. Protocol violations resulting in exclusion of data from the per-protocol analysis were documented in full prior to unblinding the study.

5.8.3.2. Protocol violations

Subject data were examined for evidence of protocol violations in order to assess how well the protocol was followed.

Violations of Eligibility Criteria

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

- Pre-bronchodilator FEV_1/FVC ratio >0.7 at Visit 1.
- Increase in FEV_1 of >10% of predicted normal and >200 mL following salbutamol at Visit 1.
- Post-salbutamol FEV_1 <40% or >80% of predicted value at Visit 1.
- O_2 saturation < 88%.

Excluded Medication

Unless stated otherwise any primary endpoint data collected after the initiation of an excluded medication (listed below) were excluded from the per-protocol analysis.

- Inhaled, oral and systemic corticosteroid use within 4 weeks prior to Visit 1.
- Concomitant oral or IV xanthine use within 4 weeks prior to Visit 1.

- Concomitant oral or inhaled long-acting beta-2 agonist use within 2 weeks prior to Visit 1.
- Oral beta-2 agonist and nebulised beta-2 agonists.
- Long-acting anticholinergic use that was discontinued within 4 weeks prior to Visit 1.
- Concomitant leukotriene modifiers.
- Sodium cromoglycate and nedocromil sodium.
- NAC (N-acetyl cysteine).

Visit Specific Protocol Violations

For these violations, data collected at the visit were excluded from the per-protocol analysis

- Study medication compliance <80% or >120% during active, on-therapy dosing.
- Salbutamol/albuterol and/or anticholinergic medication within 6 hours of pulmonary function testing. This protocol violation applied only to the pulmonary function tests.

Conduct of Study Deviations

For these deviations, no data were 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).
- Moderate or severe exacerbation of COPD within 6 weeks prior to Visit 3.
- Smoking within two hours of pulmonary function testing (at Visit 3 or later).

5.8.4. Treatment Comparisons

5.8.4.1. Primary comparisons of interest

For biopsy measures, the primary analysis was a comparison between groups in the per-protocol population at endpoint. Endpoint, for any measurement, was defined as the last evaluable (measured prior to occurrence of protocol violation) observation in the double-blind treatment period. The primary comparisons were based on separate analysis of variance (ANOVA) models, performed for the difference in change from baseline at endpoint between the cilomilast group and the placebo group in both CD68 and CD8 cell counts per area of tissue. The models controlled for centre effect as well as treatment. The primary comparisons were performed using Hochberg multiple comparison adjustment method [Hochberg, 1988] with an overall alpha level of 0.05.

5.8.4.2. Other comparisons of interest

Secondary comparisons of interest were the comparisons between treatment groups at Week 13 for sputum and Week 12 for biopsy measures.

For lung function measure, SVC, the comparison of interest between groups was in the intent-to-treat at all scheduled visits (Weeks 4, 8, 12 and 13) and endpoint (defined as the last on-therapy measurement in the double-blind treatment period for each subject).

5.8.5. General Considerations for Data Analyses

5.8.5.1. Multicentre studies

For the analysis of the primary endpoint, centres were not pooled.

5.8.5.2. Examination of subgroups

The statistical analysis for the primary efficacy variables (CD68+ and CD8+) was performed by smoking status (i.e. smoker and non-smoker). ANOVA models were used with the population subsetted by baseline smoking status. Multiplicity issues were not addressed.

5.8.5.3. Multiple comparison/multiplicity

The comparison between cilomilast and placebo, based on the per-protocol population for the primary endpoints; CD68+ and CD8+, was of primary interest. Since there were two primary endpoints of interest, the modified Bonferroni procedure of Hochberg was used [Hochberg, 1988].

5.8.6. Data Handling Conventions

5.8.6.1. Premature discontinuation and missing data

Missing data arising from subjects sporadically missing visits or assessments at visits were assumed to be missing completely at random. No attempts were to be made to assess the impact of such missing data.

5.8.6.2. Derived and transformed data

Baseline

In general, the last non-missing evaluation prior to the first dose was defined as baseline. The baseline bronchial biopsy was that performed prior to randomisation (Visit 2/2A, Week -1) and the baseline sputum induction was that conducted at Visit 3 (Week 0).

If the baseline biopsy sample was unevaluable (as ascertained by the central laboratory) the second biopsy was not performed. Similarly, if the baseline sputum was unevaluable, further sputum samples were not to be induced.

For vital signs and temperature, evaluations occurring within 15 minutes post-first dose of double-blind study medication were considered the baseline measurements.

For laboratory evaluations, only date was compared. Laboratory samples collected in association with gastrointestinal adverse events (GIAEs) of concern on the date of the randomisation visit or prior to the date of the randomisation visit were not to be considered for baseline.

Endpoint

Endpoint was defined as the last non-missing on-therapy assessment collected for a subject, regardless of the type of visit at which the assessment was collected. For bronchial biopsy, endpoint was defined as the assessment at Week 12 (Visit 6/6A) or one week after Early Withdrawal. The endpoint for sputum was defined as the assessment at Visit 7 (Week 13).

Duplicate or Repeated Observations

Multiple biopsy and sputum results for the efficacy endpoints for each subject at each visit were be provided. These observations were to be averaged. In all other cases where multiple observations were available, or where tests were repeated for a particular visit, the latest evaluation was used in the analysis. If the latest evaluation could not reasonably be determined, based on date and/or time, then the average of the multiple evaluations was used.

Study Medication Record

Date of first dose in the double-blind period: this was taken from the start date of double-blind medication field on the investigational product panel. If this date was missing then the visit date for Visit 3 was used instead.

Date of last dose in the double-blind period: this was taken from stop date of the treatment period double-blind medication field on the investigational product panel. If this date was missing then the visit date for Visit 7 was used instead, unless the subject withdrew. In that case the visit date from the Early Withdrawal visit was used.

Exposure to double-blind study medication: this was calculated according to the following formula.

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

A randomised subject whose date of first dose was not available, but was confirmed as having received a dose of double-blind study medication was taken as having an assumed exposure of one day.

Relative day was defined as follows.

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

For assessments and events occurring before the date of first dose of double-blind study medication, '1' was not added when calculating the relative day.

Compliance

The number of tablets consumed was defined as follows.

(no. tablets dispensed) – (no. tablets returned) – (no. tablets lost)

The number of days between visits was defined as follows.

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

Visit level compliance was defined as follows.

$$\frac{100\% \text{ x (number of tablets consumed at a visit)}}{2 \text{ x (number of days between visits)}}$$

Overall compliance was defined as follows.

$$\frac{100\% \text{ x } \Sigma \text{ (number of tablets consumed at a visit)}}{2 \text{ x } \Sigma \text{ (number of days between visits)}}$$

Visit Dates

The date for each visit was defined as the date recorded in the CRF for that visit. If this date was not available, the date from the COPD pulmonary function tests was used instead. If this date was also missing, the earliest visit date recorded for the visit was used.

Last Study Day

The last study day was defined as the last visit day regardless of withdrawal.

Prior, Concomitant and Post-therapy Medications

Prior medications: any medication used prior to the date of the first dose, including those which continued beyond the date of first dose of double-blind study medication.

Concomitant medications: any medications initiated after the date of the first dose of double-blind study medication and before the last dose of double-blind study medication. Medications initiated before the date of the first dose of double-blind study medication and continued on or after the date of the first dose of double-blind study medication were also considered concomitant.

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

COPD Exacerbation

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

Sputum Induction

If the sputum result was found to be below the lowest level of detection, one half of this value was used in the analysis.

Adverse Events

Baseline signs and symptoms: any event with an onset date prior to the initial dose of double-blind study medication.

On-therapy adverse events: any event with an onset date on or after the date of first dose of double-blind study medication and prior to two days after the last dose of double-blind study medication.

Post-therapy adverse events: any event with an onset date at least two days after the last dose of study medication.

Adverse events leading to withdrawal: any event for which the 'withdrawn' field in CRF was checked as 'Yes'.

Adverse events with missing onset date: these were assumed to have started on Day 1 of the double-blind period.

Clinical Laboratory Tests/Vital Signs/Orthostatic Vital Signs

On-therapy assessments: any assessment performed after the first dose of double-blind study medication and no later than one day after the last dose of double-blind study medication. Visit 3 laboratory data associated with GIAEs of concern were also considered on-therapy.

Worst-case on-therapy assessment: this was defined as the result with the highest concern level observed during the double-blind treatment period. Subjects with results beyond the normal range in both the high and low direction during the double-blind period were presented in both categories.

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

5.8.6.3. Values of clinical concern

Laboratory values of potential clinical concern are shown in Table 2.

Table 2 Laboratory values of potential clinical concern

Variable	Low Value of Concern	Low	High	High Value of Concern
Haemoglobin	<0.8 x LLN	≥0.8 x LLN – <1 x LLN	>1 x ULN – ≤1.2 x ULN	>1.2 x ULN
Haematocrit	<0.8 x LLN	≥0.8 x LLN – <1 x LLN	>1 x ULN – ≤1.2 x ULN	>1.2 x ULN
WBC	≤3.0 x 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 x ULN
Creatinine	<0.5 x LLN	≥0.5 x LLN – <1 x LLN	>1 x ULN – ≤1.5 x ULN	>1.5 x ULN
BUN (SI units)	not defined	not defined	>1 x ULN – ≤17.85 mmol/L	>17.85 mmol/L
BUN (non-SI units)	not defined	not defined	>1 x ULN – ≤50 mg/dL	> 50 mg/dL
Urea	not defined	not defined	>1 x ULN – ≤17.85 mmol/L	> 17.85 mmol/L
Sodium (SI units)	≤130 mmol/L	130 mmol/L – <1 x LLN	>ULN – <150 mmol/L	≥150 mmol/L
Sodium (non-SI units)	≤130 mEq/L	130 mEq/L – <1 x LLN	>ULN – <150 mEq/L	≥150 mEq/L
Potassium (SI units)	≤3.0 mmol/L	3.0 mmol/L – <1 x LLN	>ULN – <5.5 mmol/L	≥5.5 mmol/L
Potassium (non-SI units)	≤3.0 mEq/L	3.0 mEq/L – <1 x LLN	>ULN – <5.5 mEq/L	≥5.5 mEq/L
Glucose	<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

NB LLN = lower limit of normal; ULN = upper limit of normal

Vital signs values of potential clinical concern are shown in Table 3.

Table 3 Vital signs values of potential clinical concern

Variable	Low Value of Concern	Low	High	High Value of Concern
Sitting Systolic BP	<75 mmHg	75 – 89 mmHg	140 – 180 mmHg	>180 mmHg
Sitting Diastolic BP	<50 mmHg	50 – 59 mmHg	90 – 110 mmHg	>110 mmHg
Sitting Heart Rate	<50 bpm	50 – 59 bpm	100 – 120 bpm	>120 bpm
Orthostatic Change[1] in Systolic BP	not defined	not defined	decrease of 10 – 19 mmHg	decrease ≥20 mmHg
Orthostatic Change[1] in Diastolic BP	not defined	not defined	not defined	decrease ≥10 mmHg
Orthostatic Change[1] in Heart Rate	not defined	not defined	not defined	increase of ≥10 bpm

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

5.8.7. Study Population

5.8.7.1. Demographic and baseline characteristicsd

Baseline and demographic characteristics have been summarised using descriptive statistics. No hypothesis testing was to be performed for treatment differences in subject baseline characteristics, demography or subject disposition.

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

5.8.7.2. Treatment compliance

Subject compliance was calculated at each visit. The numbers of subjects with compliance below 80% and above 120% have been presented. Descriptive statistics have also been presented.

5.8.8. Efficacy Analyses

5.8.8.1. Primary efficacy measures

All linear models to assess treatment effects for efficacy measures were performed using SAS procedure MIXED.

The assessment of treatment differences for the primary efficacy variables (CD68+ and CD8+ counts per area of tissue) was based on an analysis of variance model with effects for centre and treatment group. Least squares means along with associated 95% confidence intervals (CIs) were calculated for each treatment group. Least squares means

and 95% CIs were also calculated for the treatment difference. Differences between treatment groups were assessed using T-tests on the least square means. The primary endpoints were also analysed by smoking status.

The robustness of the inference from the analysis of variance model was explored with respect to inclusion/exclusion of covariates, treatment by centre interaction, and normality of the underlying data.

Testing for treatment-by-centre interaction was performed at a significance level of 0.10. The model for testing this interaction had all the effects specified in the primary model with the addition of the interaction term. No evidence for a treatment-by-centre interaction was observed.

The normality assumption of the underlying data was explored through graphical examination of the residuals. The degree and effects of departures from normality were assessed through normal probability plots of residuals and the use of Wilcoxon Sign tests. No evidence of an unacceptable departure from normality was observed.

5.8.8.2. Secondary efficacy measures

The response to treatment of CD8+ and CD68+ in biopsy tissue was also explored by fitting a Poisson model to the data, adjusting for centre, treatment, baseline smoking status and baseline value. These analyses were considered to be supportive, and the p-values obtained were not adjusted.

Continuous secondary efficacy variables were analysed using the main effects models described above for the primary measures.

5.8.8.3. Other efficacy measures

Descriptive statistics and a repeated measures model with treatment and baseline as effects were used to analyse SVC.

5.8.9. Safety Analyses

Evaluation of safety data included all randomised subjects and was based on comparisons of subject experience by assigned medication regiment. Clinical interpretation was based on review of adverse events, laboratory values and vital signs. The principal considerations in this evaluation were time-to-onset, severity and investigator-reported relationship to study medication for the adverse event. Descriptive statistics were also used in the evaluation of safety when appropriate.

5.8.9.1. Adverse events

All adverse events in the double-blind period have been presented for both treatment groups by body system, severity level (mild, moderate and severe), time of initial onset and action taken. No formal statistical hypothesis testing was performed for adverse events.

Adverse events leading to a subject's withdrawal from the study have been summarised by body system, preferred term and treatment group.

5.8.9.2. Deaths and serious adverse events

Serious adverse events (including deaths) have been summarised by body system, preferred term, treatment group and on-therapy status. Special attention has been given to GIAEs.

5.8.9.3. Clinical laboratory evaluations

Descriptive statistics for blood chemistry and haematology by visit/week and treatment group have been provided. Faecal occult blood (FOB) measurements have been summarised for all subjects, and separately for the population of subjects with GIAEs of concern. The number and percentage of subjects with positive results have been presented.

5.8.9.4. Other safety measures

Vital signs heart rate, systolic blood pressure, diastolic blood pressure and temperature have been summarised in a similar way to that used for clinical laboratory variables.

6. STUDY POPULATION RESULTS

6.1. Disposition of Subjects

6.1.1. Number and Distribution of Subjects

In total, 160 subjects were enrolled into the study; subject disposition by treatment group is summarised in Table 4.

Table 4 Subject distribution (number of subjects)

Study Stage	Treatment Group		Total
	Placebo	Cilomilast 15 mg bd	
Entered single-blind phase	-	-	160
Randomised	62	65	127
Completed double-blind phase	56	57	113

Data source: Table 13.1B

This was a multi-centre study carried out in 27 centres in Australia (4 centres), Canada (5 centres), Finland (one centre), Ireland (two centres), Lithuania (two centres), Norway (one centre), Romania (two centres), Slovakia (one centre), Slovenia (two centres), South Africa (one centre), Sweden (two centres) and the UK (5 centres). The number of subjects enrolled in each country ranged from 6 (Norway) to 26 (Canada) (Table 13.1B).

Reason for Withdrawal

Of the 160 subjects enrolled into the study, 33 withdrew during the placebo run-in period and were not randomised to study treatment (Table 13.3). The main reasons for withdrawal were COPD exacerbation (10 subjects, 6.3%) and withdrawal of consent (8 subjects, 5.0%). Subjects were also withdrawn due to failure to fulfil the entry criteria (4 subjects, 2.5%), adverse events and protocol violations (each three subjects, 1.9%), loss to follow-up (one subject, 0.6%) and other reasons (4 subjects, 2.5%).

At least 87% of randomised subjects in both treatment groups completed the study. Fourteen subjects discontinued the study prematurely and their reasons for withdrawal are summarised in Table 5.

Table 5 Reason for study conclusion (number (%) of subjects): all randomised subjects

Study Conclusion Reason	Treatment Group	
	Placebo (N = 62)	Cilomilast 15 mg bd (N = 65)
Completed study	56 (90.3%)	57 (87.7%)
Reason for withdrawal		
Adverse event[1]	3 (4.8%)	6 (9.2%)
Insufficient therapeutic effect	0	1 (1.5%)
Consent withdrawn	1 (1.6%)	1 (1.5%)
COPD exacerbation	2 (3.2%)	0
Total withdrawn	6 (9.7%)	8 (12.3%)

Data source: Table 13.4

1. Two subjects in each group withdrawn due to adverse events occurring during run-in.

The proportions of subjects withdrawn due to adverse events was higher in the cilomilast group than the placebo group (9.2% vs. 4.8%) but withdrawal due to COPD exacerbation occurred only in the placebo group (3.2% of subjects).

6.2. Protocol Deviations

Protocol violations that resulted in the exclusion of subject data from the per-protocol analysis are summarised in Table 6.

Table 6 Protocol violations (number (%) of subjects): intent-to-treat population

Study Conclusion Reason	Treatment Group	
	Placebo (N = 61)	Cilomilast 15 mg bd (N = 61)
Exclusionary Medication		
Corticosteroid (inhaled, oral, systemic) within 4 wks before Visit 1	3 (4.9%)	2 (3.3%)
Concomitant NACs	1 (1.6%)	0
Visit Specific Violations		
Study medication compliance <80% or >120% on-therapy	2 (3.3%)	1 (1.6%)
Salbutamol and/or anti-cholinergic within 6 hr of PFT	2 (3.3%)	2 (3.3%)
Total number of subjects completely excluded	2 (3.3%)	0
Total number of subjects with at least one PV	7 (11.5%)	4 (6.6%)

Data source: Table 13.6A

There were a lower proportion of subjects with a protocol violation in the cilomilast group than in the placebo group and no subject in the cilomilast group was completely excluded from the per-protocol analysis.

Protocol violations are summarised by visit in Table 13.6B.

Protocol violations that did not result in the exclusion of subjects from the per-protocol analysis were considered to be conduct of study deviations. Three subjects (one in the cilomilast group and two in the placebo group) failed to meet the compliance with study medication criteria during the placebo run-in period (Table 13.6C).

6.3. Populations Analysed

Three subject populations were defined: randomised population, intent-to-treat population and per-protocol population (see Section 5.8.3.1). A summary of the numbers of subjects in each population is shown in Table 7.

Table 7 Summary of study populations

Study Population	Treatment Group		Total
	Placebo	Cilomilast 15 mg bd	
All randomised subjects	62	65	127
Intent-to-treat efficacy	61	61	122
Per-protocol efficacy	58	61	119

Data source: Table 13.1B

Five subjects were excluded from the intent-to-treat population because they had no confirmed dose of double-blind study medication.

Three subjects (all in the placebo group) in the intent-to-treat population were excluded from the per-protocol population. Two subjects were excluded due to protocol violations (see Table 6), and one was excluded because the subject had no on-therapy efficacy data.

6.4. Demographics and Other Baseline Characteristics

6.4.1. Demographic Characteristics

The demographic characteristics for all randomised subjects and for the per-protocol population are summarised in Table 8.

Table 8 Summary of demographic characteristics: all randomised subjects and per-protocol population

Demographic Characteristic	All Randomised Subjects		Per-protocol Population	
	Placebo (N = 62)	Cilomilast 15 mg bd (N = 65)	Placebo (N = 58)	Cilomilast 15 mg bd (N = 61)
Sex n (%)				
Male	47 (75.8%)	47 (72.3%)	46 (79.3%)	46 (75.4%)
Female	15 (24.2%)	18 (27.7%)	12 (20.7%)	15 (24.6%)
Age (years) n (%)				
<50	5 (8.1%)	4 (6.2%)	4 (6.9%)	3 (4.9%)
50-65	30 (48.4%)	40 (61.5%)	29 (50.0%)	38 (62.3%)
>65	27 (43.5%)	21 (32.3%)	25 (43.1%)	20 (32.8%)
Mean (SD)	63.4 (9.1)	61.4 (8.4)	63.6 (8.9)	61.6 (8.4)
Range	45 – 79	47 – 78	45 – 79	49 – 78
Race n (%)				
White	60 (96.8%)	62 (95.4%)	56 (96.6%)	58 (95.1%)
Other	2 (3.2%)	3 (4.6%)	2 (3.4%)	3 (4.9%)
Weight[1] (kg)				
Mean (SD)	75.6 (14.5)	77.7 (17.8)	76.4 (13.6)	76.3 (16.9)
Range	40 – 120	36 – 123	50 – 120	36 – 118
Height (cm)				
Mean (SD)	169.8 (7.9)	170.2 (7.9)	170.1 (7.8)	170.3 (8.0)
Range	153 – 187	156 – 189	153 – 187	156 – 189

Data source: Table 13.7A, Table 13.7B

1. One subject in the cilomilast group with missing data for both all randomised subjects and per-protocol population.

Overall, there were no marked differences in the demographic characteristics of the two treatment groups for all randomised subjects. The mean ages of the two groups were similar and most subjects were of at least 50 years of age, although the proportion of subjects over the age of 65 was higher in the placebo group (43.5% vs. 32.3%). A majority of the subjects (approximately 75%) were male and almost all subjects (≥95%) were White.

The demographic characteristics of the per-protocol population were similar to those of the all randomised subject group.

6.4.2. Baseline Characteristics

6.4.2.1. Pulmonary and smoking history

A summary of pulmonary and smoking history is presented in Table 9 for all randomised subjects and for the per-protocol population.

Table 9 Summary of pulmonary and smoking history: all randomised subjects and per-protocol population

Characteristic	All Randomised Subjects		Per-protocol Population	
	Placebo (N = 62)	Cilomilast (N = 65)	Placebo (N = 58)	Cilomilast (N = 61)
Duration of COPD n (%)				
<5 years	32 (51.6%)	24 (36.9%)	30 (51.7%)	22 (36.1%)
≥5 – <10 years	14 (22.6%)	25 (38.5%)	13 (22.4%)	24 (39.3%)
≥10 – <15 years	9 (14.5%)	9 (13.8%)	9 (15.5%)	9 (14.8%)
≥15 – <20 years	4 (6.5%)	5 (7.7%)	3 (5.2%)	4 (6.6%)
≥20 – <25 years	2 (3.2%)	0	2 (3.4%)	0
≥25 years	0	1 (1.5%)	0	1 (1.6%)
Unknown	1 (1.6%)	1 (1.5%)	1 (1.7%)	1 (1.6%)
Type of COPD n (%)				
Chronic bronchitis	34 (54.8%)	35 (53.8%)	33 (56.9%)	32 (52.5%)
Emphysema	27 (43.5%)	29 (44.6%)	24 (41.4%)	28 (45.9%)
Unknown	1 (1.6%)	1 (1.5%)	1 (1.7%)	1 (1.6%)
Exacerbations[1] that were self-managed				
N (%)	8 (12.9)	6 (9.2)	6 (10.3)	6 (9.8)
Mean (SD)	1.0 (0.0)	1.0 (0.0)	1.0 (0.0)	1.0 (0.0)
Exacerbations[1] that required oral corticosteroids and/or antibiotics				
N (%)	13 (21.0)	10 (15.4)	10 (17.2)	8 (13.1)
Mean (SD)	1.0 (0.0)	1.0 (0.0)	1.0 (0.0)	1.0 (0.0)
Exacerbations[1] that required hospitalisation				
N (%)	7 (11.3)	5 (7.7)	6 (10.3)	4 (6.6)
Mean (SD)	1.0 (0.0)	1.0 (0.0)	1.0 (0.0)	1.0 (0.0)
Smoking status at baseline n (%)				
Former smoker	34 (54.8%)	33 (50.8%)	32 (55.2%)	30 (49.2%)
Current smoker	28 (45.2%)	32 (49.2%)	26 (44.8%)	31 (50.8%)
Smoking pack years				
Mean (SD)	41.3 (22.1)	46.3 (28.2)	42.1 (22.5)	47.3 (28.8)
Range	12.0 – 108.0	10.0 – 128.0	12.0 – 108.0	10.0 – 128.0
Cigarettes per day (all subjects)				
Mean (SD)	20.8 (11.5)	23.3 (12.3)	21.1 (11.5)	23.7 (12.6)
Range	4 – 60	1 – 60	5 – 60	1 – 60

Data source: Table 13.9A, Table 13.9B, Table 13.10A, Table 13.10B

1. Exacerbations in the last 12 months.

In general, there were no marked differences in the baseline characteristics of the two treatment groups for all randomised subjects. Most subjects (75%) had had their COPD for less than 10 years and very few subjects had a COPD history of more than 20 years. The proportions of subjects with chronic bronchitis as opposed to emphysema were similar (approximately 55% vs. 45%). In the previous 12 months, exacerbations of COPD were similar in both groups. The groups had a smoking history of 41 or 46 mean pack years and approximately 47% of subjects were current smokers. The groups were similar with respect to mean number of cigarettes per day.

The baseline characteristics of the per-protocol population were similar to those of the all randomised subject group.

Smoking status at each visit is summarised in Table 13.15. In general, there were only small changes in smoking status, i.e. non-smokers who had become smokers and vice versa, and no marked differences between the treatment groups

6.4.2.2. Pulmonary function

Pulmonary function measures at screening are summarised in Table 10 for all randomised subjects and for the per-protocol population.

Table 10 Summary of pulmonary function measures: all randomised subjects and per-protocol population

Characteristic	All Randomised Subjects		Per-protocol Population	
	Placebo (N = 62)	Cilomilast 15 mg bd (N = 65)	Placebo (N = 58)	Cilomilast 15 mg bd (N = 61)
FEV_1[1] (L)				
n	62	65	58	61
Mean (SD)	1.61 (0.50)	1.70 (0.40)	1.61 (0.50)	1.69 (0.40)
Range	0.80 – 3.19	0.97 – 2.59	0.80 – 3.19	0.97 – 2.59
% Predicted FEV_1[2]				
n	62	65	58	61
Mean (SD)	59.8 (11.7)	62.0 (10.1)	59.7 (11.8)	61.5 (10.2)
Range	33.7 – 80.0	41.3 – 79.8	33.7 – 80.0	41.3 – 79.8
Reversibility (%)				
n	62	65	58	61
Mean (SD)	4.6 (3.8)	4.2 (3.3)	4.7 (3.9)	4.3 (3.4)
Range	-7.3 – 14.0	-5.1 – 9.4	-7.3 – 14.0	-5.1 – 9.4
FEV_1/FVC ratio[2]				
n	62	65	58	61
Mean (SD)	0.54 (0.10)	0.55 (0.10)	0.54 (0.10)	0.55 (0.10)
Range	0.30 – 0.70	0.33 – 0.72	0.32 – 0.70	0.33 – 0.72
FVC[1] (L)				
n	62	65	58	61
Mean (SD)	3.03 (0.78)	3.18 (0.93)	3.01 (0.80)	3.19 (0.96)
Range	1.63 – 4.71	1.61 – 5.87	1.63 – 4.71	1.61 – 5.87
% Predicted FVC[2]				
n	61	65	57	61
Mean (SD)	75.6 (28.3)	78.2 (33.8)	75.3 (26.5)	77.2 (34.6)
Range	2.6 – 126.9	3.5 – 132.4	2.6 – 110.9	3.5 – 132.4
SVC[1] (L)				
n	60	64	56	61
Mean (SD)	3.17 (0.86)	3.32 (0.95)	3.17 (0.88)	3.34 (0.96)
Range	1.63 – 4.99	1.10 – 6.25	1.63 – 4.99	1.10 – 6.25
% Predicted SVC[2]				
n	53	58	50	55
Mean (SD)	80.1 (26.7)	80.1 (36.1)	81.0 (25.0)	79.6 (36.9)
Range	2.9 – 122.9	3.5 (153.0)	3.4 – 122.9	3.5 (153.0)

Data source: Table 13.8A, Table 13.8B

1. FEV_1, FEV_1/FVC ratio, FVC and SVC are presented pre-salbutamol inhalation.
2. % predicted FEV_1, FVC and SVC are presented post-salbutamol inhalation

The treatment groups were similar with respect to pulmonary function at screening for all subjects randomised. Post-salbutamol FEV_1 was 62.0% of predicted for the cilomilast group and 59.8% of predicted for placebo. The pre-salbutamol FEV_1/FVC ratio was 0.55 in the cilomilast group and 0.54 in the placebo group. Reversibility was low; 4% in the

cilomilast group and 5% in the placebo group. SVC was 80.1% of predicted in both groups.

Pulmonary function at screening in the per-protocol population was similar to that in the all randomised subject group.

6.4.3. Baseline Signs and Symptoms

Baseline signs and symptoms were defined as any event with an onset date prior to the initial dose of double-blind study medication. The signs/symptoms most commonly occurring (in at least 2% of subjects in either treatment group) are summarised in Table 11.

Table 11 Most commonly occurring (at least 2% of subjects in either group) baseline signs and symptoms (number (%) of subjects): all randomised subjects

Baseline Sign/Symptom	Treatment Group	
	Placebo (N = 62)	Cilomilast 15 mg bd (N = 65)
Subjects with at least one sign/symptom	31 (50.0%)	34 (52.3%)
Nausea	1 (1.6%)	8 (12.3%)
Headache	7 (11.3%)	4 (6.2%)
Sore throat	2 (3.2%)	4 (6.2%)
Common cold	0	4 (6.2%)
Cough	3 (4.8%)	3 (4.6%)
Haemoptysis	2 (3.2%)	1 (1.5%)
Back pain	2 (3.2%)	0

Data source: Table 13.12

The incidence of baseline signs and symptoms were generally evenly distributed within the treatment groups. Nausea, however, was observed at baseline in a much higher number of subjects in the cilomilast group compared with the placebo group, 8 (12.1%) vs. 1 (1.6%). The distribution of other GIAEs such as abdominal pain, diarrhoea and vomiting was evenly matched within the treatments which suggests that the increased incidence of nausea was a chance occurrence.

6.4.4. Previous Medications

Almost all subjects had received prior medication before entry into the study. The medications most commonly used (by at least 5% of subjects in either treatment group) are presented in Table 12.

Table 12 Most commonly received (by least 5% of subjects in either group) prior medications (number (%) of subjects): all randomised subjects

Prior Medication	Treatment Group	
	Placebo (N = 62)	Cilomilast 15 mg bd (N = 65)
Subjects with at least one medication	61 (98.4%)	65 (100%)
Salbutamol	45 (72.6%)	45 (69.2%)
Ipratropium bromide	38 (61.3%)	44 (67.7%)
Paracetamol	22 (35.5%)	22 (33.8%)
Acetylsalicylic acid	12 (19.4%)	13 (20.0%)
Codeine	7 (11.3%)	9 (13.8%)
Fluticasone	5 (8.1%)	9 (13.8%)
Salmeterol	8 (12.9%)	7 (10.8%)
Fenoterol	9 (14.5%)	5 (7.7%)
Levothyroxine	2 (3.2%)	5 (7.7%)
Caffeine	1 (1.6%)	5 (7.7%)
Hydrochlorothiazide	1 (1.6%)	5 (7.7%)
Beclometasone	6 (9.7%)	4 (6.2%)
Theophylline	5 (8.1%)	4 (6.2%)
Tiotropium	4 (6.5%)	4 (6.2%)
Eformoterol	2 (3.2%)	4 (6.2%)
Fentanyl	2 (3.2%)	4 (6.2%)
Simvastatin	2 (3.2%)	4 (6.2%)
Budesonide	6 (9.7%)	3 (4.6%)
Ramipril	6 (9.7%)	2 (3.1%)
Terbutaline	7 (11.3%)	1 (1.5%)
Nifedipine	4 (6.5%)	1 (1.5%)

Data source: Table 13.13A

NB Total numbers may be marginally underestimated for some compounds as usage may be detailed under more than one salt.

In general, there were no marked differences between the treatment groups in the receipt of prior medication, although the proportions of subjects receiving some medications, e.g. terbutaline, showed differences between the groups which were not of clinical significance for interpretation of the study results. In both groups the prior medications most commonly received were salbutamol and ipratropium, and the proportions of subjects receiving these were similar in both groups.

6.5. Concomitant Medications

6.5.1. All Concomitant Medications

More than 95% of subjects in both treatment groups received concomitant medication during the double-blind phase of the study: concomitant medication includes continuing prior medications. During the study, salbutamol and/or ipratropium bromide was

supplied to all subjects for use as rescue medication. The medications most commonly used (by at least 5% of subjects in either treatment group) are presented in Table 13. Medications taken for COPD exacerbations are included in Table 13, but also discussed separately in Section 6.5.2.

Table 13 Most commonly received (by least 5% of subjects in either group) concomitant medications (number (%) of subjects): all randomised subjects

Concomitant Medication	Treatment Group	
	Placebo (N = 62)	Cilomilast 15 mg bd (N = 65)
Subjects with at least one medication	59 (95.2%)	63 (96.9%)
Ipratropium bromide	29 (46.8%)	43 (66.2%)
Salbutamol	42 (67.7%)	40 (61.5%)
Paracetamol	24 (38.7%)	24 (36.9%)
Acetylsalicylic acid	11 (17.7%)	12 (18.5%)
Codeine	5 (8.1%)	11 (16.9%)
Caffeine	2 (3.2%)	6 (9.2%)
Hydrochlorothiazide	2 (3.2%)	5 (7.7%)
Ibuprofen	4 (6.5%)	4 (6.2%)
Levothyroxine	2 (3.2%)	4 (6.2%)
Simvastatin	2 (3.2%)	4 (6.2%)
Omeprazole	1 (1.6%)	4 (6.2%)
Amoxycillin	3 (4.8%)	3 (4.6%)
Atorvastatin	3 (4.8%)	3 (4.6%)
Ramipril	6 (9.7%)	2 (3.1%)
Ascorbic acid	4 (6.5%)	2 (3.1%)
Nifedipine	4 (6.5%)	1 (1.5%)

Data source: Table 13.13B

NB Total numbers may be underestimated for some compounds as usage may be detailed under more than one salt.

In general, there were no marked differences between the treatment groups in the receipt of concomitant medication, although the proportions of subjects receiving some medications, e.g. codeine, showed differences between the groups which were not of clinical significance for interpretation of the study results. A majority of subjects received salbutamol and/or ipratropium bromide, supplied as rescue medication. Apart from this, the most frequently received concomitant medications in both groups were paracetamol, acetylsalicylic acid and codeine.

Post-therapy medications are summarised in Table 13.13C.

6.5.2. Medications for COPD Exacerbations

Approximately 15% of subjects received medication taken for COPD exacerbations during the double-blind treatment phase of the study. The medications received are presented in Table 14.

Table 14 Medications taken for COPD exacerbations (number (%) of subjects): all randomised subjects

COPD Medication	Treatment Group	
	Placebo (N = 62)	Cilomilast 15 mg bd (N = 65)
Subjects with at least one medication	9 (14.5%)	10 (15.4%)
Prednisolone	2 (3.2%)	3 (4.6%)
Doxycycline	0	3 (4.6%)
Amoxycillin	3 (4.8%)	2 (3.1%)
Clavulanate	3 (4.8%)	2 (3.1%)
Ipratropium	2 (3.2%)	2 (3.1%)
Clarithromycin	0	2 (3.1%)
Salbutamol	3 (4.8%)	1 (1.5%)
Hydrocortisone	0	1 (1.5%)
Ibuprofen	0	1 (1.5%)
Moxifloxacin	0	1 (1.5%)
Paracetamol	0	1 (1.5%)
Roxithromycin	0	1 (1.5%)
Acetylcysteine	1 (1.6%)	0
Beclometasone	1 (1.6%)	0
Betamethasone	1 (1.6%)	0
Budesonide	1 (1.6%)	0
Cefaclor	1 (1.6%)	0
Erythomycin	1 (1.6%)	0
Prednisone	1 (1.6%)	0
Terbutaline	1 (1.6%)	0
Tiotropium	1 (1.6%)	0

Data source: Table 13.13D

NB Total numbers may be underestimated for some compounds as usage may be detailed under more than one salt.

In general, there were no marked differences between the treatment groups in the receipt of medication for exacerbations of COPD. The most frequently received medications in the cilomilast group were prednisolone and doxycycline, and in the placebo group, amoxycillin (with clavulanate) and salbutamol.

6.6. Treatment Compliance

As stipulated by the protocol, subjects were to be withdrawn from the study if study medication compliance at each visit during the double-blind period was not ≥80% and ≤120%. Overall compliance is summarised in Table 15.

Table 15 Overall compliance with double-blind medication (number (%) of subjects): all randomised subjects

Overall Compliance[1]	Treatment Group	
	Placebo (N = 62)	Cilomilast 15 mg bd (N = 65)
n[2]	61	63
<80%	3 (4.9%)	3 (4.8%)
80-120%	57 (93.4%)	58 (92.1%)
>120%	1 (1.6%)	2 (3.2%)
Mean (SD) (%)	96.5 (10.3)	96.5 (14.1)
Range (%)	50.0 – 140.0	27.1 – 151.8

Data source: Table 13.14A, Table 13.14B

1. Compliance during double-blind treatment period.
2. Subjects with non-missing compliance data

Overall compliance with receipt of double-blind medication was more than 90% in both treatment groups.

Compliance during the single-blind run-in phase and at each visit during double-blind treatment is shown in Table 13.14A and Table 13.14B.

7. EFFICACY RESULTS

7.1. Primary Efficacy Results

There were two co-primary efficacy endpoints:

- Sub-epithelial CD68+ (macrophages) per unit area of tissue,
- Sub-epithelial CD8+ (cytotoxic T-lymphocytes) per unit area of tissue.

The primary analysis was performed in the per-protocol population, with the analysis in the intent-to-treat population being a supportive analysis. Additional supportive analysis was provided with the use of a Poisson regression model.

7.1.1. Sub-epithelial CD68+ Macrophages per Unit Area of Tissue

7.1.1.1. Primary analysis

The adjusted mean changes[3] from baseline in the number of sub-epithelial CD68+ macrophages per unit area of biopsy tissue at Week 12 and at endpoint are shown in Table 16 for the per-protocol population.

At endpoint there was a smaller reduction from baseline in the cilomilast group than in the placebo group: 20.8 cells/mm^2 vs. 50.0 cells/mm^2. The difference between the groups was not statistically significant. The level of reduction represented 17.1% and 34.8% of the baseline levels of CD68+ cells in the cilomilast and placebo groups, respectively.

Descriptive statistics for the change from baseline in the number of sub-epithelial CD68+ macrophages per unit area of tissue are provided in Table 14.1B.

[3] The adjusted mean change is the least square mean derived from an ANOVA model which adjusts for centre.

Table 16 Mean change from baseline in sub-epithelial CD68+ macrophages per area of tissue (cells/mm^2): per-protocol population

Week of Double-Blind Trt.	Treatment Group	n[1]	Assessment		Change from Baseline				Comparison with Placebo			
			Mean[2]	SEM	Mean[2]	SEM	Lower 95% CI	Upper 95% CI	Mean Difference	Lower 95% CI	Upper 95% CI	P-value
Baseline	Placebo	49	143.6	11.9								
	Cilomilast	54	121.4	10.5								
Week 12	Placebo	49	93.6	8.6	-50.0	13.7	-77.4	-22.6				
	Cilomilast	54	100.6	7.6	-20.8	12.2	-45.0	3.4	29.2	-5.0	63.3	0.093
Endpoint	Placebo	49	93.6	8.6	-50.0	13.7	-77.4	-22.6				
	Cilomilast	54	100.6	7.6	-20.8	12.2	-45.0	3.4	29.2	-5.0	63.3	0.093

Data source: Table 14.1A

1. Number of subjects with evaluation at baseline and the specified week.
2. Mean values are adjusted for centre.

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The adjusted mean changes from baseline in the number of sub-epithelial CD68+ macrophages per unit area of tissue at Week 12 and at endpoint for smokers and non-smokers are shown in Table 17 for the per-protocol population.

Reductions from baseline in the number of sub-epithelial CD68+ macrophages per unit area of tissue were larger among non-smokers than among smokers for both treatment groups. Although the reductions were larger in the placebo groups, there were no statistically significant treatment differences.

Descriptive statistics for the change from baseline in the number of sub-epithelial CD68+ macrophages per unit area of tissue for smokers and non-smokers are provided in Table 14.1G and Table 14.1H.

Table 17 **Mean change from baseline in sub-epithelial CD68+ macrophages per area of tissue (cells/mm^2) for smoker and non-smokers: per-protocol population**

Week of Double-Blind Trt.	Treatment Group	n[1]	Assessment		Change from Baseline				Comparison with Placebo			
			Mean[2]	SEM	Mean[2]	SEM	Lower 95% CI	Upper 95% CI	Mean Difference	Lower 95% CI	Upper 95% CI	P-value
Smokers												
Baseline	Placebo	21	116.4	16.4								
	Cilomilast	26	109.1	13.3								
Week 12	Placebo	21	84.6	14.9	-31.8	15.9	-64.6	1.0				
	Cilomilast	26	112.7	12.1	3.6	12.9	-23.0	30.3	35.4	-7.7	78.5	0.103
Endpoint	Placebo	21	84.6	14.9	-31.8	15.9	-64.6	1.0				
	Cilomilast	26	112.7	12.1	3.6	12.9	-23.0	30.3	35.4	-7.7	78.5	0.103
Non-Smokers												
Baseline	Placebo	28	162.7	14.8								
	Cilomilast	28	116.8	15.3								
Week 12	Placebo	28	98.6	11.2	-64.0	18.0	-100.6	-27.4				
	Cilomilast	28	92.6	11.6	-24.3	18.7	-62.2	13.7	39.8	-10.8	90.3	0.119
Endpoint	Placebo	28	98.6	11.2	-64.0	18.0	-100.6	-27.4				
	Cilomilast	28	92.6	11.6	-24.3	18.7	-62.2	13.7	39.8	-10.8	90.3	0.119

Data source: Table 14.1E, Table 14.1F

1. Number of subjects with evaluation at baseline and the specified week.
2. Mean values are adjusted for centre.

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7.1.1.2. Supportive analysis

The results of the intent-to-treat analysis closely mirrored those seen for the per-protocol analysis. The adjusted mean changes from baseline in the number of sub-epithelial CD68+ macrophages per unit area of biopsy tissue at Week 12 and at endpoint are shown in Table 18 for the intent-to-treat population.

At endpoint there was a smaller reduction from baseline in the cilomilast group than in the placebo group: 19.7 cells/mm^2 vs. 44.6 cells/mm^2. The difference between the groups was not statistically significant.

Descriptive statistics for the change from baseline in the number of sub-epithelial CD68+ macrophages per unit area of tissue are provided in Table 14A.1B.

Table 18 Mean change from baseline in sub-epithelial CD68+ macrophages per area of tissue (cells/mm^2): intent-to-treat population

Week of Double-Blind Trt.	Treatment Group	n[1]	Assessment Mean[2]	Assessment SEM	Change from Baseline Mean[2]	Change from Baseline SEM	Change from Baseline Lower 95% CI	Change from Baseline Upper 95% CI	Comparison with Placebo Mean Difference	Comparison with Placebo Lower 95% CI	Comparison with Placebo Upper 95% CI	Comparison with Placebo P-value
Baseline	Placebo	52	137.2	11.7								
	Cilomilast	54	119.1	10.9								
Week 12	Placebo	52	92.6	8.3	-44.6	13.5	-71.5	-17.6				
	Cilomilast	54	99.4	7.7	-19.7	12.6	-44.8	5.4	24.8	-9.3	59.0	0.152
Endpoint	Placebo	52	92.6	8.3	-44.6	13.5	-71.5	-17.6				
	Cilomilast	54	99.4	7.7	-19.7	12.6	-44.8	5.4	24.8	-9.3	59.0	0.152

Data source: Table 14A.1A

1. Number of subjects with evaluation at baseline and the specified week.
2. Mean values are adjusted for centre.

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An analysis in which a Poisson model was fitted to the data supported the main results for change in CD68+ macrophages, and showed no significant differences between treatments in either the per-protocol population (p=0.6499) (Table 14.1D) or the intent-to-treat population (p=0.6726) (Table 14A.1D). This Poisson model adjusted for baseline CD68+ macrophage value, centre and baseline smoking status.

7.1.2. Sub-epithelial CD8+ T-Lymphocytes per Unit Area of Tissue

7.1.2.1. Primary analysis

The adjusted mean changes from baseline in the number of sub-epithelial CD8+ T-lymphocytes per unit area of biopsy tissue at Week 12/Endpoint are shown in Table 19 for the per-protocol population.

At endpoint, reductions from baseline were similar in both groups: 75.3 cells/mm^2 in the cilomilast group and 69.8 cells/mm^2 in the placebo group. The difference between the groups was not statistically significant. These values represent reductions in the level of CD8+ T lymphocytes of 37.3% and 32.7% from baseline in the cilomilast and placebo treatment options, respectively.

Descriptive statistics for the change from baseline in the number of sub-epithelial CD8+ T-lymphocytes per unit area of tissue are provided in Table 14.2B.

Table 19 **Mean change from baseline in sub-epithelial CD8+ T-lymphocytes per area of tissue (cells/mm^2): per-protocol population**

Week of Double-Blind Trt.	Treatment Group	n[1]	Assessment		Change from Baseline				Comparison with Placebo			
			Mean[2]	SEM	Mean[2]	SEM	Lower 95% CI	Upper 95% CI	Mean Difference	Lower 95% CI	Upper 95% CI	P-value
Baseline	Placebo	49	213.5	10.9								
	Cilomilast	54	201.9	9.6								
Week 12	Placebo	49	143.7	11.2	-69.8	13.6	-96.8	-42.7				
	Cilomilast	54	126.6	9.9	-75.3	12.0	-99.2	-51.4	-5.5	-39.3	28.2	0.744
Endpoint	Placebo	49	143.7	11.2	-69.8	13.6	-96.8	-42.7				
	Cilomilast	54	126.6	9.9	-75.3	12.0	-99.2	-51.4	-5.5	-39.3	28.2	0.744

Data source: Table 14.2A

1. Number of subjects with evaluation at baseline and the specified week.
2. Mean values are adjusted for centre.

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The adjusted mean changes from baseline in the number of sub-epithelial CD8+ T-lymphocytes per unit area of tissue at Week 12/Endpoint for smokers and non-smokers are shown in Table 20 for the per-protocol population.

Reductions from baseline in the number of sub-epithelial CD8+ T-lymphocytes per unit area of tissue were slightly larger among non-smokers than among smokers for both treatment groups. When considered as percentage reductions the placebo group showed a 32.9% and 31.2% reduction in smokers and current non-smokers and 32.7% and 40.1% reduction in the cilomilast group for smokers and current non-smokers, respectively.

Baseline levels were marginally higher in the placebo group current non-smokers and broadly comparable in the cilomilast group. Although the reductions were larger in the cilomilast groups, there were no statistically significant treatment differences.

Descriptive statistics for the change from baseline in the number of sub-epithelial CD8+ T-lymphocytes per unit area of tissue for smokers and non-smokers are provided in Table 14.2G and Table 14.2H.

Table 20 **Mean change from baseline in sub-epithelial CD8+ T-lymphocytes per area of tissue (cells/mm^2) for smoker and non-smokers: per-protocol population**

Week of Double-Blind Trt.	Treatment Group	n[1]	Assessment		Change from Baseline				Comparison with Placebo			
			Mean[2]	SEM	Mean[2]	SEM	Lower 95% CI	Upper 95% CI	Mean Difference	Lower 95% CI	Upper 95% CI	P-value
Smokers												
Baseline	Placebo	21	188.6	20.6								
	Cilomilast	26	202.1	16.8								
Week 12	Placebo	21	126.5	16.2	-62.1	26.7	-117.2	-7.0				
	Cilomilast	26	136.0	13.2	-66.1	21.7	-110.9	-21.4	-4.1	-76.4	68.3	0.909
Endpoint	Placebo	21	126.5	16.2	-62.1	26.7	-117.2	-7.0				
	Cilomilast	26	136.0	13.2	-66.1	21.7	-110.9	-21.4	-4.1	-76.4	68.3	0.909
Non-Smokers												
Baseline	Placebo	28	226.9	11.7								
	Cilomilast	28	195.3	12.1								
Week 12	Placebo	28	156.0	16.5	-70.9	16.9	-105.3	-36.5				
	Cilomilast	28	117.0	17.1	-78.4	17.6	-114.1	-42.7	-7.5	-55.0	40.1	0.752
Endpoint	Placebo	28	156.0	16.5	-70.9	16.9	-105.3	-36.5				
	Cilomilast	28	117.0	17.1	-78.4	17.6	-114.1	-42.7	-7.5	-55.0	40.1	0.752

Data source: Table 14.2E, Table 14.2F

1. Number of subjects with evaluation at baseline and the specified week.
2. Mean values are adjusted for centre.

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7.1.2.2. Supportive analysis

The adjusted mean changes from baseline in the number of sub-epithelial CD8+ T-lymphocytes per unit area of biopsy tissue at Week 12/Endpoint are shown in Table 18 for the intent-to-treat population.

At endpoint there were similar reductions from baseline in both treatment groups: 76.4 cells/mm^2 in the cilomilast group and 69.7 cells/mm^2 in the placebo group. The difference between the groups was not statistically significant. The difference from baseline expressed as a percentage change were 38.4% and 32.9% change for cilomilast and placebo respectively.

Descriptive statistics for the change from baseline in the number of sub-epithelial CD8+ T-lymphocytes per unit area of tissue are provided in Table 14A.2B.

Table 21 **Mean change from baseline in sub-epithelial CD8+ T-lymphocytes per area of tissue (cells/mm^2): intent-to-treat population**

Week of Double-Blind Trt.	Treatment Group	n[1]	Assessment Mean[2]	Assessment SEM	Change from Baseline Mean[2]	Change from Baseline SEM	Change from Baseline Lower 95% CI	Change from Baseline Upper 95% CI	Comparison with Placebo Mean Difference	Comparison with Placebo Lower 95% CI	Comparison with Placebo Upper 95% CI	Comparison with Placebo P-value
Baseline	Placebo	52	211.4	10.5								
	Cilomilast	54	199.1	9.8								
Week 12	Placebo	52	141.7	10.8	-69.7	13.2	-95.9	-43.4				
	Cilomilast	54	122.8	10.1	-76.4	12.3	-100.8	-51.9	-6.7	-40.0	26.6	0.690
Endpoint	Placebo	52	141.7	10.8	-69.7	13.2	-95.9	-43.4				
	Cilomilast	54	122.8	10.1	-76.4	12.3	-100.8	-51.9	-6.7	-40.0	26.6	0.690

Data source: Table 14A.2A

1. Number of subjects with evaluation at baseline and the specified week.
2. Mean values are adjusted for centre.

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An analysis in which a Poisson model was fitted to the data supported the main results for change in CD8+ T-lymphocytes, and showed no significant differences between treatments in either the per-protocol population (p=0.2967) (Table 14.2D) or the intent-to-treat population (p=0.1775) (Table 14A.2D). This Poisson model adjusted for baseline CD68+ macrophage value, centre and baseline smoking status.

7.1.3. Results of Covariate Analyses

The tests of significance for covariates terms showed almost universally non-significant results. Age, sex and % predicted FEV_1 were not significant at the 0.1 level for CD68+ macrophages for either the per-protocol or intent-to-treat models (Table 14.1C and Table 14A.1C). In the CD8+ T-lymphocytes models, only sex was significant with p-values of 0.907 for the per-protocol analysis (Table 14.2C) and 0.0648 for the intent-to-treat analysis (Table 14A.2C). Smoking status was significant for the CD68+ macrophages models with p-values of 0.0275 for the per-protocol analysis (Table 14.2C) and 0.0200 for the intent-to-treat analysis (Table 14A.2C) and not significant for the CD8+ T-lymphocytes models.

7.2. Secondary Efficacy Results

The secondary efficacy endpoints concerned the cell numbers in biopsy tissue and sputum as detailed below.

Biopsy tissue: number of sub-epithelial cells per unit area

- Neutrophil elastase positive cells (neutrophils)
- CD4+ lymphocytes
- IL-8 mRNA positive cells
- TNFα mRNA positive cells
- CD45 positive cells
- Mucin expression

Sputum: number of cells per unit volume

- Sputum total cell count
- Macrophages as a percentage of total cells
- Eosinophils as a percentage of total cells
- Lymphocytes as a percentage of total cells
- Neutrophil elastase
- IL-8

7.2.1. Sub-epithelial Neutrophils (ne+) per Unit Area of Tissue

The adjusted mean changes from baseline in the number of sub-epithelial neutrophils (ne+) per unit area of biopsy tissue at Week 12 and at endpoint are shown in Table 22 for the per-protocol population. At endpoint there was a smaller reduction from baseline in the cilomilast group than in the placebo group: 2.2 cells/mm^2 vs. 21.6 cells/mm^2, and the difference between the groups was statistically significant (p=0.019). These reductions represented 5.8% and 46.1% of the baseline levels of sub-epithelial neutrophils in the cilomilast and placebo groups, respectively.

Table 22 **Mean change from baseline in sub-epithelial neutrophils (ne+) per area of tissue (cells/mm^2): per-protocol population**

Week of Double-Blind Trt.	Treatment Group	n[1]	Assessment		Change from Baseline				Comparison with Placebo			
			Mean[2]	SEM	Mean[2]	SEM	Lower 95% CI	Upper 95% CI	Mean Difference	Lower 95% CI	Upper 95% CI	P-value
Baseline	Placebo	49	46.9	5.0								
	Cilomilast	54	38.0	4.4								
Week 12	Placebo	49	25.2	4.1	-21.6	6.5	-34.6	-8.7				
	Cilomilast	54	35.8	3.6	-2.2	5.8	-13.7	9.3	19.4	3.3	35.6	0.019
Endpoint	Placebo	49	25.2	4.1	-21.6	6.5	-34.6	-8.7				
	Cilomilast	54	35.8	3.6	-2.2	5.8	-13.7	9.3	19.4	3.3	35.6	0.019

Data source: Table 14.3A

1. Number of subjects with evaluation at baseline and the specified week.
2. Mean values are adjusted for centre.

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Descriptive statistics for the change from baseline in the number of sub-epithelial neutrophils (ne+) per unit area of tissue are provided in Table 14.3B.

Results in the intent-to-treat population were similar to those in the per-protocol population (Table 14A.3A and Table 14A.3B). At endpoint there was a smaller reduction from baseline in the cilomilast group than in the placebo group: 1.8 cells/mm^2 vs. 20.1 cells/mm^2, and the difference between the groups was statistically significant (p=0.025).

7.2.2. Sub-epithelial CD4+ Lymphocytes per Unit Area of Tissue

The adjusted mean changes from baseline in the number of sub-epithelial CD4+ lymphocytes per unit area of biopsy tissue at Week 12 and at endpoint are shown in Table 23 for the per-protocol population. At endpoint there was a smaller reduction from baseline in the cilomilast group than in the placebo group: 8.1 cells/mm^2 vs. 21.6 cells/mm^2, but the difference between the groups was not statistically significant. These reductions represented 7.9% and 17.6% of the baseline levels of sub-epithelial CD4+ lymphocytes in the cilomilast and placebo groups, respectively.

Descriptive statistics for the change from baseline in the number of sub-epithelial CD4+ lymphocytes per unit area of tissue are provided in Table 14.4B.

Results in the intent-to-treat population were similar to those in the per-protocol population (Table 14A.4A and Table 14A.4B).

7.2.3. Sub-epithelial IL-8 mRNA+ Cells per Unit Area of Tissue

The adjusted mean changes from baseline in the number of sub-epithelial IL-8 mRNA+ cells per unit area of biopsy tissue at Week 12 and at endpoint are shown in Table 24 for the per-protocol population. At endpoint there was a smaller reduction from baseline in the cilomilast group than in the placebo group: 13.2 cells/mm^2 vs. 24.8 cells/mm^2, but the difference between the groups was not statistically significant. These reductions represented 36.6% and 55.9% of the baseline levels of sub-epithelial CD4+ IL-8 mRNA+ cells in the cilomilast and placebo groups, respectively.

Descriptive statistics for the change from baseline in the number of sub-epithelial IL-8 mRNA+ cells per unit area of tissue are provided in Table 14.5B.

Results in the intent-to-treat population were similar to those in the per-protocol population (Table 14A.5A and Table 14A.5B).

Table 23 **Mean change from baseline in sub-epithelial CD4+ lymphocytes per area of tissue (cells/mm^2): per-protocol population**

Week of Double-Blind Trt.	Treatment Group	n[1]	Assessment		Change from Baseline				Comparison with Placebo			
			Mean[2]	SEM	Mean[2]	SEM	Lower 95% CI	Upper 95% CI	Mean Difference	Lower 95% CI	Upper 95% CI	P-value
Baseline	Placebo	49	122.9	8.6								
	Cilomilast	54	102.3	7.6								
Week 12	Placebo	49	101.3	8.3	-21.6	12.0	-45.5	2.3				
	Cilomilast	54	94.2	7.3	-8.1	10.6	-29.2	13.0	13.6	-16.2	43.3	0.367
Endpoint	Placebo	49	101.3	8.3	-21.6	12.0	-45.5	2.3				
	Cilomilast	54	94.2	7.3	-8.1	10.6	-29.2	13.0	13.6	-16.2	43.3	0.367

Data source: Table 14.4A

1. Number of subjects with evaluation at baseline and the specified week.
2. Mean values are adjusted for centre.

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Table 24 Mean change from baseline in sub-epithelial IL-8 mRNA+ cells per area of tissue (cells/mm^2): per-protocol population

Week of Double-Blind Trt.	Treatment Group	n[1]	Assessment		Change from Baseline				Comparison with Placebo			
			Mean[2]	SEM	Mean[2]	SEM	Lower 95% CI	Upper 95% CI	Mean Difference	Lower 95% CI	Upper 95% CI	P-value
Baseline	Placebo	49	44.4	4.7								
	Cilomilast	54	36.1	4.2								
Week 12	Placebo	49	19.6	2.3	-24.8	4.7	-34.2	-15.4				
	Cilomilast	54	22.9	2.1	-13.2	4.2	-21.5	-4.9	11.6	-0.12	23.3	0.052
Endpoint	Placebo	49	19.6	2.3	-24.8	4.7	-34.2	-15.4				
	Cilomilast	54	22.9	2.1	-13.2	4.2	-21.5	-4.9	11.6	-0.12	23.3	0.052

Data source: Table 14.5A

1. Number of subjects with evaluation at baseline and the specified week.
2. Mean values are adjusted for centre.

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7.2.4. Sub-epithelial TNFα mRNA+ Cells per Unit Area of Tissue

The adjusted mean changes from baseline in the number of sub-epithelial TNFα mRNA+ cells per unit area of biopsy tissue at Week 12 and at endpoint are shown in Table 25 for the per-protocol population. At endpoint there was a slightly smaller reduction from baseline in the cilomilast group than in the placebo group: 34.9 cells/mm^2 vs. 42.5 cells/mm^2, but the difference between the groups was not statistically significant. These reductions represented 55.0% and 60.5% of the baseline levels of sub-epithelial TNFα mRNA+ cells in the cilomilast and placebo groups, respectively.

Descriptive statistics for the change from baseline in the number of sub-epithelial TNFα mRNA+ cells per unit area of tissue are provided in Table 14.6B.

Results in the intent-to-treat population were similar to those in the per-protocol population (Table 14A.6A and Table 14A.6B).

7.2.5. Sub-epithelial CD45+ Cells per Unit Area of Tissue

The adjusted mean changes from baseline in the number of sub-epithelial CD45+ cells per unit area of biopsy tissue at Week 12 and at endpoint are shown in Table 26 for the per-protocol population. At endpoint there was a slightly larger reduction from baseline in the cilomilast group than in the placebo group: 99.4 cells/mm^2 vs. 90.7 cells/mm^2, but the difference between the groups was not statistically significant. These reductions represented 25.1% and 23.1% of the baseline levels of sub-epithelial CD45+ cells in the cilomilast and placebo groups, respectively.

Descriptive statistics for the change from baseline in the number of sub-epithelial CD45+ cells per unit area of tissue are provided in Table 14.7B.

Results in the intent-to-treat population were similar to those in the per-protocol population (Table 14A.7A and Table 14A.7B).

Table 25 Mean change from baseline in sub-epithelial TNFα mRNA+ cells per area of tissue (cells/mm^2): per-protocol population

Week of Double-Blind Trt.	Treatment Group	n[1]	Assessment Mean[2]	Assessment SEM	Change from Baseline Mean[2]	Change from Baseline SEM	Change from Baseline Lower 95% CI	Change from Baseline Upper 95% CI	Comparison with Placebo Mean Difference	Comparison with Placebo Lower 95% CI	Comparison with Placebo Upper 95% CI	Comparison with Placebo P-value
Baseline	Placebo	49	70.3	5.2								
	Cilomilast	54	63.5	4.6								
Week 12	Placebo	49	27.8	2.9	-42.5	5.7	-54.0	-31.1				
	Cilomilast	54	28.6	2.6	-34.9	5.1	-45.0	-24.8	7.6	-6.6	21.8	0.289
Endpoint	Placebo	49	27.8	2.9	-42.5	5.7	-54.0	-31.1				
	Cilomilast	54	28.6	2.6	-34.9	5.1	-45.0	-24.8	7.6	-6.6	21.8	0.289

Data source: Table 14.6A

1. Number of subjects with evaluation at baseline and the specified week.
2. Mean values are adjusted for centre.

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Table 26 Mean change from baseline in sub-epithelial CD45+ cells per area of tissue (cells/mm^2): per-protocol population

Week of Double-Blind Trt.	Treatment Group	n[1]	Assessment		Change from Baseline				Comparison with Placebo			
			Mean[2]	SEM	Mean[2]	SEM	Lower 95% CI	Upper 95% CI	Mean Difference	Lower 95% CI	Upper 95% CI	P-value
Baseline	Placebo	49	393.1	17.1								
	Cilomilast	54	396.1	15.1								
Week 12	Placebo	49	302.4	17.7	-90.7	18.8	-128.1	-53.3				
	Cilomilast	54	296.8	15.6	-99.4	16.6	-132.4	-66.3	-8.6	-55.2	37.9	0.713
Endpoint	Placebo	49	302.4	17.7	-90.7	18.8	-128.1	-53.3				
	Cilomilast	54	296.8	15.6	-99.4	16.6	-132.4	-66.3	-8.6	-55.2	37.9	0.713

Data source: Table 14.7A

1. Number of subjects with evaluation at baseline and the specified week.
2. Mean values are adjusted for centre.

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7.2.6. Mucin Expression

Adjusted mean changes from baseline in the number of epithelial and sub-mucosal MUC5AC and MUC5B cells per unit area of biopsy tissue at Week 12 and at endpoint are shown in Table 27 and Table 28, respectively for the per-protocol population.

At endpoint there were small reductions from baseline for MUC5AC cells in the epithelium: 0.5 cells/mm^2 in the cilomilast group and 1.3 cells/mm^2 in the placebo group. For sub-mucosal MUC5AC cells, there were increases from baseline in both groups: 3.8 cells/mm^2 in the cilomilast group and 2.7 cells/mm^2 in the placebo group. In neither case was the difference between the groups statistically significant.

For epithelial MUC5B cells, there were reductions from baseline at endpoint in both groups: 9.3 cells/mm^2 in the cilomilast group and 1.2 cells/mm^2 in the placebo group. Sub-mucosal MUC5B cells, however, showed a small increase from baseline (1.0 cells/mm^2) in the cilomilast group compared with a reduction from baseline (9.5 cells/mm^2) in the placebo group. The differences between the groups were not statistically significant.

Descriptive statistics for the change from baseline in the number of epithelial and sub-mucosal MUC5AC and MUC5B cells per unit area of tissue are provided in Table 14.8B1, Table 14.8B2, Table 14.8B3 and Table 14.8B4.

Results in the intent-to-treat population were similar to those in the per-protocol population (Table 14A.8A1, Table 14A.8A2, Table 14A.8A3 Table 14A.8A4, Table 14A.8B1, Table 14A.8B2, Table 14A.8B3 and Table 14A.8B4).

Table 27 Mean change from baseline in mucin expression (MUC5AC) cells per area of tissue (cells/mm^2): per-protocol population

Week of Double-Blind Trt.	Treatment Group	n[1]	Assessment		Change from Baseline				Comparison with Placebo			
			Mean[2]	SEM	Mean[2]	SEM	Lower 95% CI	Upper 95% CI	Mean Difference	Lower 95% CI	Upper 95% CI	P-value
Epithelial Cells												
Baseline	Placebo	18	47.8	4.9								
	Cilomilast	21	41.2	4.7								
Week 12	Placebo	18	46.5	3.9	-1.3	5.2	-12.0	9.4				
	Cilomilast	21	40.7	3.7	-0.5	4.8	-10.6	9.6	0.8	-14.8	16.5	0.915
Endpoint	Placebo	18	46.5	3.9	-1.3	5.2	-12.0	9.4				
	Cilomilast	21	40.7	3.7	-0.5	4.8	-10.6	9.6	0.8	-14.8	16.5	0.915
Sub-mucosal Cells												
Baseline	Placebo	10	5.3	0.6								
	Cilomilast	14	4.3	0.4								
Week 12	Placebo	10	8.0	1.0	2.7	1.0	0.4	4.9				
	Cilomilast	14	8.2	0.7	3.8	0.7	2.3	5.3	1.2	-1.7	4.0	0.393
Endpoint	Placebo	10	8.0	1.0	2.7	1.0	0.4	4.9				
	Cilomilast	14	8.2	0.7	3.8	0.7	2.3	5.3	1.2	-1.7	4.0	0.393

Data source: Table 14.8A1, Table 14.8A2

1. Number of subjects with evaluation at baseline and the specified week.
2. Mean values are adjusted for centre.

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Table 28 Mean change from baseline in mucin expression (MUC5B) cells per area of tissue (cells/mm^2): per-protocol population

Week of Double-Blind Trt.	Treatment Group	n[1]	Assessment		Change from Baseline				Comparison with Placebo			
			Mean[2]	SEM	Mean[2]	SEM	Lower 95% CI	Upper 95% CI	Mean Difference	Lower 95% CI	Upper 95% CI	P-value
Epithelial Cells												
Baseline	Placebo	16	33.2	4.8								
	Cilomilast	21	32.9	4.7								
Week 12	Placebo	16	32.1	4.7	-1.2	6.3	-14.2	11.9				
	Cilomilast	20	23.6	4.7	-9.3	6.2	-22.2	3.7	-8.1	-27.0	10.8	0.383
Endpoint	Placebo	16	32.1	4.7	-1.2	6.3	-14.2	11.9				
	Cilomilast	20	23.6	4.7	-9.3	6.2	-22.2	3.7	-8.1	-27.0	10.8	0.383
Sub-mucosal Cells												
Baseline	Placebo	18	54.5	4.5								
	Cilomilast	19	56.8	4.3								
Week 12	Placebo	18	45.0	4.6	-9.5	6.5	-23.2	4.2				
	Cilomilast	19	57.8	4.5	1.0	6.4	-12.3	14.4	10.5	-9.1	30.1	0.275
Endpoint	Placebo	18	45.0	4.6	-9.5	6.5	-23.2	4.2				
	Cilomilast	19	57.8	4.5	1.0	6.4	-12.3	14.4	10.5	-9.1	30.1	0.275

Data source: Table 14.8A3, Table 14.8A4

1. Number of subjects with evaluation at baseline and the specified week.
2. Mean values are adjusted for centre.

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7.2.7. Sputum Total Cell Count per Unit Volume

The adjusted mean changes from baseline in the total cell count per unit volume of sputum at Week 13 and at endpoint are shown in Table 29 for the per-protocol population. At endpoint there was a slightly smaller reduction from baseline in the cilomilast group than in the placebo group: $5.3x10^6$/mL vs. $8.0x10^6$/mL, but the difference between the groups was not statistically significant. These reductions represented 56.4% and 55.2% of the baseline total sputum cell count in the cilomilast and placebo groups, respectively.

Descriptive statistics for the change from baseline in the total cell count per unit volume of sputum are provided in Table 14.10B.

Results in the intent-to-treat population were similar to those in the per-protocol population (Table 14A.10A and Table 14A.10B).

7.2.8. Sputum Macrophages as Percentage of Total Cells

The adjusted mean changes from baseline in sputum macrophages as a percentage of total cells at Week 13 and at endpoint are shown in Table 30 for the per-protocol population. At endpoint there was a small increase in the cilomilast group (4.8%) compared with a small decrease in the placebo group (3.9%), but the difference between the groups was not statistically significant.

Descriptive statistics for the change from baseline in sputum macrophages as a percentage of total cells are provided in Table 14.11B.

Results in the intent-to-treat population were similar to those in the per-protocol population (Table 14A.11A and Table 14A.11B).

Table 29 Mean change from baseline in sputum total cell count per unit volume (x10^6/mL): per-protocol population

Week of Double-Blind Trt.	Treatment Group	n[1]	Assessment		Change from Baseline				Comparison with Placebo			
			Mean[2]	SEM	Mean[2]	SEM	Lower 95% CI	Upper 95% CI	Mean Difference	Lower 95% CI	Upper 95% CI	P-value
Baseline	Placebo	42	14.5	2.9								
	Cilomilast	43	9.4	2.7								
Week 13	Placebo	42	6.5	0.8	-8.0	2.7	-13.4	-2.6				
	Cilomilast	43	4.1	0.7	-5.3	2.5	-10.3	-0.3	2.7	-4.2	9.6	0.439
Endpoint	Placebo	42	6.5	0.8	-8.0	2.7	-13.4	-2.6				
	Cilomilast	43	4.1	0.7	-5.3	2.5	-10.3	-0.3	2.7	-4.2	9.6	0.439

Data source: Table 14.10A

1. Number of subjects with evaluation at baseline and the specified week.
2. Mean values are adjusted for centre.

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Table 30 Mean change from baseline in sputum macrophages as a percentage of total cells: per-protocol population

Week of Double-Blind Trt.	Treatment Group		Assessment		Change from Baseline				Comparison with Placebo			
		n[1]	Mean[2]	SEM	Mean[2]	SEM	Lower 95% CI	Upper 95% CI	Mean Difference	Lower 95% CI	Upper 95% CI	P-value
Baseline	Placebo	33	44.3	4.2								
	Cilomilast	33	44.5	4.0								
Week 13	Placebo	33	40.4	3.4	-3.9	5.4	-14.8	7.1				
	Cilomilast	33	49.3	3.2	4.8	5.1	-5.5	15.1	8.6	-5.6	22.8	0.226
Endpoint	Placebo	33	40.4	3.4	-3.9	5.4	-14.8	7.1				
	Cilomilast	33	49.3	3.2	4.8	5.1	-5.5	15.1	8.6	-5.6	22.8	0.226

Data source: Table 14.11A

1. Number of subjects with evaluation at baseline and the specified week.
2. Mean values are adjusted for centre.

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7.2.9. Sputum Eosinophils as Percentage of Total Cells

The adjusted mean changes from baseline in sputum eosinophils as a percentage of total cells at Week 13 and at endpoint are shown in Table 31 for the per-protocol population. At endpoint there was a small decrease in the cilomilast group (0.5%) compared with a small increase in the placebo group (0.4%), but the difference between the groups was not statistically significant.

Descriptive statistics for the change from baseline in sputum eosinophils as a percentage of total cells are provided in Table 14.13B.

Results in the intent-to-treat population were similar to those in the per-protocol population (Table 14A.13A and Table 14A.13B).

7.2.10. Sputum Lymphocytes as Percentage of Total Cells

The adjusted mean changes from baseline in sputum lymphocytes as a percentage of total cells at Week 13 and at endpoint are shown in Table 32 for the per-protocol population. At endpoint there were virtually no changes from baseline and no statistically significant differences between the groups.

Descriptive statistics for the change from baseline in sputum lymphocytes as a percentage of total cells are provided in Table 14.14B.

Results in the intent-to-treat population were similar to those in the per-protocol population (Table 14A.14A and Table 14A.14B).

Table 31 Mean change from baseline in sputum eosinophils as a percentage of total cells: per-protocol population

Week of Double-Blind Trt.	Treatment Group		Assessment		Change from Baseline				Comparison with Placebo			
		n[1]	Mean[2]	SEM	Mean[2]	SEM	Lower 95% CI	Upper 95% CI	Mean Difference	Lower 95% CI	Upper 95% CI	P-value
Baseline	Placebo	33	3.5	2.4								
	Cilomilast	33	3.6	2.3								
Week 13	Placebo	33	3.8	1.7	0.4	2.5	-4.7	5.4				
	Cilomilast	33	3.0	1.6	-0.5	2.3	-5.3	4.2	-0.9	-7.4	5.6	0.782
Endpoint	Placebo	33	3.8	1.7	0.4	2.5	-4.7	5.4				
	Cilomilast	33	3.0	1.6	-0.5	2.3	-5.3	4.2	-0.9	-7.4	5.6	0.782

Data source: Table 14.13A

1. Number of subjects with evaluation at baseline and the specified week.
2. Mean values are adjusted for centre.

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Table 32 Mean change from baseline in sputum lymphocytes as a percentage of total cells: per-protocol population

Week of Double-Blind Trt.	Treatment Group		Assessment		Change from Baseline				Comparison with Placebo			
		n[1]	Mean[2]	SEM	Mean[2]	SEM	Lower 95% CI	Upper 95% CI	Mean Difference	Lower 95% CI	Upper 95% CI	P-value
Baseline	Placebo	33	0.89	0.33								
	Cilomilast	33	0.60	0.31								
Week 13	Placebo	33	0.90	0.21	0.01	0.32	-0.64	0.66				
	Cilomilast	33	0.60	0.20	-0.00	0.30	-0.62	0.61	-0.01	-0.85	0.83	0.980
Endpoint	Placebo	33	0.90	0.21	0.01	0.32	-0.64	0.66				
	Cilomilast	33	0.60	0.20	-0.00	0.30	-0.62	0.61	-0.01	-0.85	0.83	0.980

Data source: Table 14.14A

1. Number of subjects with evaluation at baseline and the specified week.
2. Mean values are adjusted for centre.

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7.2.11. Sputum Neutrophil Elastase per Unit Volume

The adjusted mean changes from baseline in neutrophil elastase per unit volume of sputum at Week 13/Endpoint are shown in Table 33 for the per-protocol population. At endpoint there was an increase in the cilomilast group (5054 ng/mL) compared with a decrease in the placebo group (9012 ng/mL), but the difference between the groups was not statistically significant (p=0.767). These changes represented 8.3% and 18.1% of the baseline levels of sputum neutrophil elastase in the cilomilast and placebo groups, respectively.

Descriptive statistics for the change from baseline in neutrophil elastase per unit volume of sputum are provided in Table 14.12B.

Results in the intent-to-treat population were similar to those in the per-protocol population (Table 14A.12A and Table 14A.12B).

7.2.12. Sputum IL-8 per Unit Volume

The adjusted mean changes from baseline in IL-8 per unit volume of sputum at Week 13/ Endpoint are shown in Table 34 for the per-protocol population. At endpoint there were similar reductions from baseline in both treatment groups: 18.6 ng/mL in the cilomilast group and 21.6 ng/mL in the placebo group. The (2.9 ng/mL) difference between the groups was not statistically significant (p=0.818). These reductions represented 40.6% and 30.0% of the baseline levels of sputum IL-8 in the cilomilast and placebo groups, respectively.

Descriptive statistics for the change from baseline in IL-8 per unit volume of sputum are provided in Table 14.15B.

Results in the intent-to-treat population were similar to those in the per-protocol population (Table 14A.15A and Table 14A.15B).

Table 33 Mean change from baseline in sputum neutrophil elastase per unit volume (ng/mL): per-protocol population

Week of Double-Blind Trt.	Treatment Group	Assessment			Change from Baseline				Comparison with Placebo			
		n[1]	Mean[2]	SEM	Mean[2]	SEM	Lower 95% CI	Upper 95% CI	Mean Difference	Lower 95% CI	Upper 95% CI	P-value
Baseline	Placebo	40	49781	32771								
	Cilomilast	41	61218	30970								
Week 13	Placebo	40	40769	40070	-9012	36206	-81572	63547				
	Cilomilast	41	66272	37868	5054	34216	-63517	73625	14066	-80707	108839	0.767
Endpoint	Placebo	40	40769	40070	-9012	36206	-81572	63547				
	Cilomilast	41	66272	37868	5054	34216	-63517	73625	14066	-80707	108839	0.767

Data source: Table 14.12A

1. Number of subjects with evaluation at baseline and the specified week.
2. Mean values are adjusted for centre.

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Table 34 Mean change from baseline in sputum IL-8 per unit volume (ng/mL): per-protocol population

Week of Double-Blind Trt.	Treatment Group		Assessment		Change from Baseline				Comparison with Placebo			
		n[1]	Mean[2]	SEM	Mean[2]	SEM	Lower 95% CI	Upper 95% CI	Mean Difference	Lower 95% CI	Upper 95% CI	P-value
Baseline	Placebo	40	71.9	8.6								
	Cilomilast	41	45.8	8.1								
Week 13	Placebo	40	50.4	8.0	-21.6	9.7	-41.0	-2.1				
	Cilomilast	41	27.2	7.5	-18.6	9.2	-37.0	-0.2	2.9	-22.5	28.4	0.818
Endpoint	Placebo	40	50.4	8.0	-21.6	9.7	-41.0	-2.1				
	Cilomilast	41	27.2	7.5	-18.6	9.2	-37.0	-0.2	2.9	-22.5	28.4	0.818

Data source: Table 14.15A

1. Number of subjects with evaluation at baseline and the specified week.
2. Mean values are adjusted for centre.

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7.3. Other Efficacy Results

The change from baseline in SVC for at each assessment during double-blind treatment, and at endpoint is summarised in Table 35.

At Week 4 there was a small increase in SVC in the cilomilast group compared with a small decrease in the placebo group (0.13 L vs. -0.02 L). Changes in the cilomilast group at other assessments were smaller, and at endpoint there were increases of 0.03 L and 0.04 L in the respective groups. At none of the assessments was the difference between the treatment groups statistically significant.

Descriptive statistics for the change from baseline in SVC are provided in Table 14.16B.

Results in the intent-to-treat population were similar to those in the per-protocol population, although, at Week 4, the difference between treatments was 0.16L in favour of cilomilast (p=0.050) (Table 14A.16A and Table 14A.16B).

Table 35 Mean change from baseline in SVC (L) by week: per-protocol population

Week of Double-Blind Trt.	Treatment Group		Assessment		Change from Baseline				Comparison with Placebo			
		n[1]	Mean[2]	SEM	Mean[2]	SEM	Lower 95% CI	Upper 95% CI	Mean Difference	Lower 95% CI	Upper 95% CI	P-value
Baseline	Placebo	59	3.12	0.13								
	Cilomilast	58	3.30	0.12								
Week 4	Placebo	57	3.10	0.12	-0.02	0.06	-0.14	0.10				
	Cilomilast	58	3.43	0.11	0.13	0.06	0.02	0.24	0.15	-0.00	0.31	0.054
Week 8	Placebo	57	3.08	0.12	-0.02	0.07	-0.15	0.12				
	Cilomilast	55	3.42	0.11	0.08	0.06	-0.05	0.20	0.09	-0.08	0.27	0.283
Week 12	Placebo	52	3.07	0.12	-0.01	0.07	-0.14	0.13				
	Cilomilast	54	3.25	0.11	-0.06	0.06	-0.18	0.07	-0.05	-0.22	0.12	0.586
Week 13	Placebo	49	3.18	0.12	0.04	0.06	-0.09	0.17				
	Cilomilast	51	3.30	0.11	0.03	0.06	-0.08	0.15	-0.00	-0.16	0.16	0.952
Endpoint	Placebo	59	3.16	0.11	0.04	0.07	-0.09	0.17				
	Cilomilast	58	3.33	0.11	0.03	0.06	-0.09	0.15	-0.01	-0.18	0.15	0.900

Data source: Table 14.16B

1. Number of subjects with evaluation at baseline and the specified week.
2. Mean values are adjusted for centre.

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7.4. Efficacy Conclusions

- There were reductions in CD68+ macrophages and CD6+ T-lymphocytes in both treatment groups, but the differences between the groups were not statistically significant.
- The overall reduction in CD68+ macrophages and CD8+ T Lymphocytes represented reductions in baseline values of 34.8-32.6% for the placebo group and 17.1-37.3% for the cilomilast group respectively.
- Reductions from baseline were highest in the current non-smokers in both treatment groups.
- All efficacy measures showed a consistent picture with none of the secondary variables distinguishing between cilomilast and placebo in reductions in cell numbers in bronchial tissue or sputum.
- There were no statistically significant differences in SVC between treatment groups at any timepoint.

8. SAFETY RESULTS

8.1. Extent of Exposure

The mean duration of exposure to study medication was 84 days (median 91 days) for subjects who received cilomilast and 87 days (median 90 days) for subjects who received placebo. More than 80% of subjects in each treatment group received double-blind medication for at least 84 days. The duration of exposure is summarised in Table 36.

Table 36 Duration of exposure (number (%) of subjects): all randomised subjects

Exposure[1] (days)	Treatment Group	
	Placebo (N = 62)	Cilomilast 15 mg bd (N = 65)
≤13	1 (1.6%)	1 (1.5%)
14 – 27	1 (1.6%)	3 (4.6%)
28 – 55	1 (1.6%)	3 (4.6%)
56 – 83	5 (8.1%)	3 (4.6%)
84 – 90	28 (45.2%)	17 (26.2%)
≥91	26 (41.9%)	38 (58.5%)
Mean (SD)	86.7 (15.9)	84.3 (22.2)
Median	90	91
Range	8 – 109	8 – 120

Data source: Table 15.1A and Table 15.1B
NB No adjustments have been made for dose interruptions.
1. Calculation of exposure: (Date of last dose of double-blind medication – Date of first dose of double-blind medication) + 1.

8.2. Adverse Events

All adverse events tabulations are sorted by descending order of frequency for the cilomilast treatment group.

Adverse events were reported by study phase for the placebo run-in, double-blind, and post-therapy periods. Events (Baseline Signs and Symptoms) reported during placebo run-in are presented in Table 13.12 and adverse events reported post-therapy are presented in Table 15.10. Adverse events by body system are summarised in Table 15.2B.

8.2.1. Incidence of On-therapy Adverse Events

During the double-blind phase, 41 subjects (63.1%) in the cilomilast group had adverse events, compared with 36 subjects (58.1%) in the placebo group. There was a higher

incidence of adverse events relating to the gastrointestinal body system in the cilomilast group compared with placebo (31% and 16% of subjects in the respective groups; Table 15.2B). The most commonly occurring adverse events (reported by at least 5% of subjects in either treatment group) are presented in Table 37.

Table 37 Most frequently reported (by least 5% of subjects in either group) adverse events (number (%) of subjects): all randomised subjects

Adverse Event (Preferred Term)	Treatment Group	
	Placebo (N = 62)	Cilomilast 15 mg bd (N = 65)
Subjects with at least one adverse event	36 (58.1%)	41 (63.1%)
Headache	12 (19.4%)	9 (13.8%)
Nasopharyngitis	8 (12.9%)	8 (12.3%)
Nausea	4 (6.5%)	6 (9.2%)
Diarrhoea	2 (3.2%)	5 (7.7%)
Pharyngolaryngeal pain	2 (3.2%)	5 (7.7%)
Vomiting	1 (1.6%)	5 (7.7%)

Data source: Table 15.2A

The overall incidence of adverse events was similar in the cilomilast and placebo treatment groups. The most frequently reported events in both groups were headache and nasopharyngitis. Gastrointestinal events, such as nausea, diarrhoea and vomiting, occurred more frequently in the cilomilast group.

8.2.2. Adverse Events by Relationship to Study Medication

During the double-blind phase of the study, 13 subjects (20.0%) in the cilomilast group and 11 subjects (17.7%) in the placebo group had adverse events reported as possibly related to study treatment. The most commonly occurring adverse events reported by the investigator as possibly related to study medication (i.e. those reported for at least 2% of subjects in either treatment group) are presented in Table 38.

Table 38 Most frequently reported (by least 2% of subjects in either group) adverse events considered possibly related to study medication (number (%) of subjects): all randomised subjects

Related[1] Adverse Event (Preferred Term)	Treatment Group	
	Placebo (N = 62)	Cilomilast 15 mg bd (N = 65)
Subjects with at least one related AE	11 (17.7%)	13 (20.0%)
Vomiting	1 (1.6%)	3 (4.6%)
Diarrhoea	0	3 (4.6%)
Dyspepsia	0	3 (4.6%)
Faecal occult blood	2 (3.2%)	2 (3.1%)
Nausea	2 (3.2%)	2 (3.1%)
Gastritis	0	2 (3.1%)
Loose stools	0	2 (3.1%)
Abdominal pain	2 (3.2%)	0
Headache	2 (3.2%)	0

Data source: Table 15.3

1. Relationships considered related are those where the investigator has determined a reasonable possibility that the event is related to study medication.

The overall incidence of adverse events considered possibly related to study treatment was similar in both groups. The most frequently occurring events possibly related to study treatment in the cilomilast group were gastrointestinal: vomiting, diarrhoea and dyspepsia.

Adverse events considered by the investigator not to have a reasonable possibility of relationship to study medication are also summarised in Table 15.3.

8.2.3. Adverse Events by Intensity

The total number of subjects with adverse events during double-blind treatment is summarised by investigator-determined intensity in Table 39.

Table 39 Number (%) of subjects with on-therapy adverse events by intensity: all randomised subjects

Intensity[1]	Treatment Group	
	Placebo (N = 62)	Cilomilast 15 mg bd (N = 65)
Subjects with at least one adverse event	36 (58.1%)	41 (63.1%)
Mild	17 (27.4%)	18 (27.7%)
Moderate	15 (24.2%)	18 (27.7%)
Severe	3 (4.8%)	5 (7.7%)
Not applicable	1 (1.6%)	0

Data source: Table 15.3

1. Maximum intensity has been used for each adverse event for each subject.

There were no clinically relevant differences between the treatment groups in the distribution of mild, moderate and severe adverse events during double-blind treatment. Of all subjects reporting adverse events during double-blind treatment, 36 of 41 subjects (88%) in the cilomilast group experienced mild to moderate events, compared with 32 of 36 subjects (89%) in the placebo group.

During the double-blind phase, 5 subjects (7.7%) in the cilomilast group and three subjects (4.8%) in the placebo group had severe adverse events. These are summarised in Table 40. Only severe nausea occurred in more than one subject.

Table 40 Number (%) of subjects with severe adverse events: all randomised subjects

Severe Adverse Event (Preferred Term)	Treatment Group	
	Placebo (N = 62)	Cilomilast 15 mg bd (N = 65)
Subjects with at least one severe AE	3 (4.8%)	5 (7.7%)
Nausea	0	2 (3.1%)
Enteritis	0	1 (1.5%)
Influenza	0	1 (1.5%)
Headache	0	1 (1.5%)
Bronchila polyp	1 (1.6%)	0
Diarrhoea	1 (1.6%)	0
Urinary retention	1 (1.6%)	0

Data source: Table 15.4a and Table 15.4b

8.2.4. Adverse Events by Time of First Occurrence

The time of first occurrence of the most commonly occurring adverse events in the cilomilast group (those occurring in at least 5% of subjects) is presented in Table 41.

Because of the relatively small numbers of subjects with these adverse events it was difficult to detect any trends over time. There were no marked differences between the treatment groups in the initial times of onset of these events. In the cilomilast group, most of the events of vomiting occurred during the first week.

Table 41 Most frequently reported on-therapy adverse events by initial time of onset (number (%) of subjects): all randomised subjects

Adverse Event (Preferred Term)	N[1]	Time of Initial Onset (days)							
		1	2 – 7	8 – 14	15 – 28	29 – 42	43 – 56	57 – 70	>70
Placebo									
Headache	12	0	1 (8.3%)	2 (16.7%)	2 (16.7%)	3 (25.0%)	0	2 (16.7%)	2 (16.7%)
Nasopharyngitis	8	0	0	1 (12.5%)	2 (25.0%)	1 (12.5%)	0	1 (12.5%)	3 (37.5%)
Nausea	4	0	1 (25.0%)	1 (25.0%)	0	1 (25.0%)	0	0	1 (25.0%)
Diarrhoea	2	0	0	0	0	1 (50.0%)	1 (50.0%)	0	0
Pharyngolaryngeal pain	2	0	0	1 (50.0%)	0	0	0	0	1 (50.0%)
Vomiting	1	0	0	0	0	0	0	0	1 (100%)
Cilomilast 15 mg bd									
Headache	9	1 (11.1%)	2 (22.2%)	1 (11.1%)	0	4 (44.4%)	1 (11.1%)	0	0
Nasopharyngitis	8	1 (12.5%)	0	0	3 (37.5%)	0	1 (12.5%)	3 (37.5%)	0
Nausea	6	1 (16.7%)	0	0	2 (33.3%)	2 (33.3%)	1 (16.7%)	0	0
Diarrhoea	5	0	1 (20.0%)	0	1 (20.0%)	1 (20.0%)	1 (20.0%)	0	1 (20.0%)
Pharyngolaryngeal pain	5	0	0	1 (20.0%)	0	1 (20.0%)	0	1 (20.0%)	2 (40.0%)
Vomiting	5	0	3 (60.0%)	0	0	1 (20.0%)	1 (20.0%)	0	0

Data source: Table 15.5

1. Percentage at each time interval is based on total number of subjects exposed to study medication with the particular AE at any time during the study.

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8.2.5. Adverse Events Requiring Corrective Treatment

There were no adverse events reported as requiring corrective treatment (Table 15.7).

8.3. Serious Adverse Events

8.3.1. Fatal Events

There were no fatalities during the double-blind treatment period or within 30 days of completing double-blind study treatment.

8.3.2. Non-Fatal Events

Serious, non-fatal adverse events during treatment with double-blind medication were reported for two subjects (3.1%) who received cilomilast and one subject (1.6%) who received placebo. Brief details are given below.

[redacted] The subject received treatment for the airflow obstruction, and study medication was interrupted for two days. The acute anxiety resolved after three days. The investigator considered there was no reasonable possibility that the acute anxiety might have been caused by the investigational product and also considered the event to be possibly associated with the disease under study.

[redacted] The rate decreased with carotid sinus massage. The subject was withdrawn from the study. [redacted] On follow-up the subject was still receiving treatment with anticoagulant and still had irregular heart rhythm. The investigator stated that as the event was still ongoing it did not appear to be related to study medication and reported that the cause of the atrial flutter was unknown.

[redacted] The investigator considered there was no reasonable possibility that the exacerbation of COPD might have been caused by investigational product and also considered that the exacerbation of COPD might possibly be associated with the disease under study.

In addition, serious, non-fatal adverse events were reported for four subjects during placebo run-in: two who were not subsequently randomised to treatment and two who

were subsequently randomised to placebo. There was also one subject (in the placebo group) who had a serious, non-fatal adverse event after completion of treatment. All subjects who had serious, non-fatal adverse events reported are listed in Table 42.

None of the serious adverse events was considered by the investigator to be possibly related to treatment with double-blind study medication.

Table 42 Non-fatal Serious Adverse Events

Data source: Table 15.8A, Table 15.8B, and Table 15.8C

1. Number of days relative to start of study medication (number of days relative to stop of study medication).
2. Subject withdrawn due to this SAE.
3. Small cell lung cancer stage unspecified.

Narratives for all subjects with non-fatal serious adverse events are provided in Section 11.

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

Five subjects were withdrawn from double-blind treatment due to adverse events, four in the cilomilast group and one in the placebo group. Adverse events leading to withdrawal are summarised in Table 43 and all subjects who were withdrawn due to on-therapy adverse events are listed in Table 44.

Table 43 Adverse events leading to withdrawal (number (%) of subjects): all randomised subjects

Adverse Event Leading to Withdrawal (Preferred Term)	Treatment Group	
	Placebo (N = 62)	Cilomilast 15 mg bd (N = 65)
Subjects withdrawn due to AEs	1 (1.6%)	4 (6.2%)
Atrial flutter	0	1 (1.5%)
Gastritis	0	1 (1.5%)
Gastro-oesophageal reflux disease	0	1 (1.5%)
Enteritis	0	1 (1.5%)
COAD exacerbated	1 (1.6%)	0

Data source: Table 15.9A

Table 44 Withdrawals due to on-therapy adverse events

[redacted]

1. Number of days relative to start of study medication (number of days relative to stop of study medication).
2. Last dose of study medication.
3. Serious adverse event.

Three of the five subjects (all in the cilomilast group) were withdrawn due to adverse events with a suspected or probable relationship to study treatment. All these were gastrointestinal events: gastro-oesophageal reflux disease, gastritis, nausea and enteritis.

Four subjects (two in each group) were withdrawn from placebo run-in due to adverse events.

Narratives for subjects withdrawn due to adverse events are provided in Section 11.

8.5. COPD Exacerbations

Ten subjects in the cilomilast group and 11 subjects in the placebo group had COPD exacerbations during the double-blind treatment period (Table 15.20). Most of these were of mild or moderate intensity, and there was only one subject (in the cilomilast group) with a severe exacerbation.

8.6. Gastrointestinal Adverse Events of Concern

Adverse events possibly related to the gastrointestinal (GI) tract were closely monitored during this study. Subjects were instructed to call the investigator to report any gastrointestinal symptoms (i.e. bloody or black stools, abdominal discomfort such as pain or cramps, diarrhoea or vomiting) which caused them concern or interfered with their daily activities. Any such reported event was referred to as a GI adverse event (GIAE) of concern and is described in detail in this section.

Three subjects, two in the cilomilast group and one in the placebo group, had GIAEs of concern. These are summarised in Table 45.

Table 45 Number (%) of subjects with GIAEs of concern: all randomised subjects

GIAEs of Concern (Preferred Term)	Treatment Group	
	Placebo (N = 62)	Cilomilast 15 mg bd (N = 65)
Subjects with at least one GIAE	1 (1.6%)	2 (3.1%)
Nausea	1 (1.6%)	1 (1.5%)
Enteritis	0	1 (1.5%)
Abdominal pain	1 (1.6%)	0

Data source: Table 15.11A

The subject in the placebo group had abdominal pain and nausea of, respectively, mild and moderate intensity. Both subjects in the cilomilast group had severe GIAEs of concern and details are summarised briefly below.

[redacted] Examination on Day 43 reported the subject to have abdominal tenderness and

haemorrhoids but no peritoneal signs or abdominal masses. She had dull epigastric pain with a gradual onset. A faecal occult blood test was negative and there were no orthostatic vital signs of potential clinical concern. Study medication was temporarily interrupted. The nausea lasted 17 days and was considered by the investigator to be possibly related to study treatment. The subject was recorded as completing the study after 43 days of treatment.

[redacted] The enteritis lasted 7 days and was considered by the investigator to be possibly related to study treatment.

There were no subjects with serious GIAEs of concern. [redacted]

Two of the three subjects who had on-therapy GIAEs of concern also had on-therapy faecal occult blood tests (one in each treatment group); neither of these was positive (Table 15.12A). Of the 81 subjects who had on-therapy faecal occult blood tests, 7.3% of subjects receiving cilomilast (3 of 41, one of whom had a positive test at baseline) and 12.5% of subjects receiving placebo (5 of 40, two of whom had a positive test at baseline) had positive results (Table 15.12B).

All subjects who had GIAEs of potential concern are listed in Table 46.

Table 46 Subjects with GIAEs of concern

[redacted]

1. Number of days relative to start of study medication.
2. Result specifically recorded by the investigator as a result of a GIAE.
3. SBP = systolic blood pressure (units are mmHg); DBP = diastolic blood pressure (units are mmHg); HR = heart rate (units are bpm); [+] indicates change of clinical concern recorded specifically by the investigator as a result of a GIAE. See Table 3 for clinical concern criteria.

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8.7. Pregnancies

No subject became pregnant during the study period.

8.8. Clinical Laboratory Evaluations

Laboratory evaluations (haematology, clinical chemistry, and urinalysis) were performed at Screening, Visit 7 and at Early Withdrawal. Mean values and mean changes from baseline by week for all clinical laboratory tests are presented in Table 15.14.

8.8.1. Laboratory Values Over Time

Mean changes from baseline at Week 13 for selected haematology and clinical chemistry variables are presented in Table 47.

Table 47 Summary of mean changes in selected clinical laboratory variables

Variable and Time Point	Treatment Group			
	Placebo		Cilomilast 15 mg bd	
	n	mean (SD)	n	mean (SD)
Haematology				
Haemoglobin (g/L)				
Baseline[1]	61	144.2 (12.3)	62	144.0 (12.1)
Week 13	50	144.2 (11.7)	50	143.1 (12.7)
Change[2]	50	-0.7 (7.3)	48	-0.8 (7.3)
Haematocrit (%)				
Baseline[1]	61	43.2 (3.6)	62	43.1 (3.7)
Week 13	50	42.8 (3.6)	50	42.7 (3.9)
Change[2]	50	-0.5 (2.6)	48	-0.3 (2.2)
White Blood Cell Count (10^9/L)				
Baseline[1]	61	7.8 (2.1)	62	7.4 (1.8)
Week 13	50	7.4 (1.8)	48	7.7 (2.3)
Change[2]	50	-0.2 (1.4)	46	0.2 (1.4)
Neutrophils (10^9/L)				
Baseline[1]	61	4.9 (1.8)	62	4.5 (1.5)
Week 13	50	4.5 (1.6)	48	4.7 (1.9)
Change[2]	50	-0.2 (1.4)	46	0.1 (1.3)
Eosinophils (10^9/L)				
Baseline[1]	61	0.2 (0.2)	62	0.2 (0.1)
Week 13	50	0.2 (0.2)	48	0.2 (0.1)
Change[2]	50	0.01 (0.2)	46	0.00 (0.1)
Platelets (10^9/L)				
Baseline[1]	60	263.2 (61.8)	62	262.2 (55.1)
Week 13	50	271.0 (77.2)	49	257.5 (52.1)
Change[2]	50	5.1 (48.0)	47	-1.2 (42.2)

Continued

Table 47 Summary of mean change in selected clinical laboratory variables (Continued)

Variable and Time Point	Treatment Group			
	Placebo		Cilomilast 15 mg bd	
	n	mean (SD)	n	mean (SD)
Clinical Chemistry				
AST (IU/L)				
Baseline[1]	61	22.9 (9.8)	64	23.8 (13.2)
Week 13	52	21.5 (8.5)	53	22.3 (8.6)
Change[2]	52	-1.8 (5.8)	52	-1.9 (11.8)
ALT (IU/L)				
Baseline[1]	61	21.5 (12.6)	63	21.2 (10.7)
Week 13	53	19.3 (9.3)	53	20.6 (10.8)
Change[2]	53	-2.4 (8.3)	52	-0.5 (4.5)
GGT (IU/L)				
Baseline[1]	61	41.7 (56.0)	63	31.8 (18.5)
Week 13	53	49.7 (123.2)	53	29.4 (18.9)
Change[2]	53	6.8 (67.8)	52	-1.1 (12.8)
Total Bilirubin (μmol/L)				
Baseline[1]	61	9.1 (2.9)	63	9.9 (3.9)
Week 13	53	9.0 (2.6)	53	9.4 (3.3)
Change[2]	53	-0.1 (3.1)	52	-0.5 (3.5)
Alkaline Phosphatase (IU/L)				
Baseline[1]	61	71.8 (19.4)	63	75.2 (17.6)
Week 13	53	71.6 (21.7)	53	72.5 (17.7)
Change[2]	53	1.6 (15.8)	52	-0.5 (8.9)
Creatinine (μmol/L)				
Baseline[1]	61	85.1 (14.9)	63	85.1 (20.1)
Week 13	53	121.6 (280.3)	53	88.6 (22.4)
Change[2]	53	35.9 (278.2)	52	2.2 (9.6)
Blood Urea Nitrogen (mmol/L)				
Baseline[1]	61	5.6 (1.7)	63	5.7 (1.5)
Week 13	53	6.1 (6.8)	53	5.4 (1.6)
Change[2]	53	0.6 (6.9)	52	-0.2 (1.2)
Sodium (mmol/L)				
Baseline[1]	61	141.0 (2.7)	63	141.2 (2.2)
Week 13	53	139.8 (3.4)	53	140.8 (2.9)
Change[2]	53	-1.4 (3.0)	52	-0.4 (2.6)
Potassium (mmol/L)				
Baseline[1]	61	4.5 (0.3)	64	4.4 (0.4)
Week 13	51	4.5 (0.4)	53	4.4 (0.4)
Change[2]	51	-0.00 (0.4)	52	0.02 (0.5)

Continued

Table 47 Summary of mean change in selected clinical laboratory variables (Continued)

Variable and Time Point	Treatment Group			
		Placebo		Cilomilast 15 mg bd
	n	mean (SD)	n	mean (SD)
Clinical Chemistry				
Glucose – Random (mmol/L)				
Baseline[1]	61	6.1 (1.6)	63	5.7 (1.0)
Week 13	53	6.3 (2.7)	53	5.9 (1.9)
Change[2]	53	0.2 (2.0)	52	0.2 (1.8)
Uric Acid (µmol/L)				
Baseline[1]	61	326.9 (84.1)	63	327.9 (90.8)
Week 13	53	334.7 (124.2)	53	322.4 (91.2)
Change[2]	53	2.9 (104.9)	52	3.5 (50.4)

Data source: Table 15.14

1. Includes all subjects evaluated at Baseline.
2. Change is reported for subjects (n) with both baseline and Week 13 assessments.

Mean changes from baseline in clinical laboratory parameters were small and generally similar in both treatment groups.

8.8.2. Adverse Events Related to Laboratory Results

Three subjects (4.8%), all of whom received placebo, reported on-therapy adverse events possibly related to laboratory results. These are summarised in Table 48. All of these adverse events were mild or moderate in intensity, and most were considered possibly related to study medication. There were no adverse events considered possibly related to laboratory results which led to withdrawal or were serious.

Table 48 Subjects with on-therapy laboratory values reported as adverse events

[redacted]

Data source: Table 15.2B

1. Number of days relative to start of study medication (number of days relative to stop of study medication).
2. Value of clinical concern.
3. Abnormal baseline value.
4. Verbatim term: increase in AST, ALT, GGT.

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8.9. Vital Signs

Sitting diastolic and systolic blood pressure and heart rate were recorded at Screening, Visits 2/2A, 3 6/6A, 7, 8 and at Early Withdrawal. Mean vital sign values and changes from baseline at Week 13 are presented in Table 49.

Table 49 Summary of mean changes in vital signs variables

Variable and Time Point	Treatment Group			
	Placebo		Cilomilast 15 mg bd	
	n	mean (SD)	n	mean (SD)
Systolic Blood Pressure (mmHg)				
Baseline[1]	62	131.9 (17.2)	65	133.5 (19.6)
Week 13	53	129.5 (14.2)	56	132.3 (18.8)
Change[2]	53	-1.9 (13.4)	56	-1.8 (16.5)
Diastolic Blood Pressure (mmHg)				
Baseline[1]	62	77.1 (9.8)	65	78.2 (11.5)
Week 13	53	76.9 (7.9)	56	76.7 (11.7)
Change[2]	53	-0.6 (10.4)	56	-1.3 (11.7)
Heart Rate (bpm)				
Baseline[1]	62	75.7 (9.2)	65	74.3 (12.2)
Week 13	53	78.9 (12.4)	56	75.1 (10.1)
Change[2]	53	3.0 (11.7)	56	0.2 (9.1)

Data source: Table 15.16

1. Includes all subjects evaluated at Baseline.
2. Change is reported for subjects (n) with both baseline and Week 13 assessments.

Mean changes in vital signs values were small with no clinically relevant changes from baseline in either group.

In addition to sitting vital signs, orthostatic vital signs were measured at visits associated with GIAEs of concern. Vital sign values or changes of potential clinical concern are defined in Table 3.

Transitions from normal range at baseline to outside normal range or to levels of potential clinical concern for sitting vital signs during the double-blind treatment phase are presented in Table 50.

Table 50 Number (%) of subjects with transitions from normal range at baseline for sitting vital signs – timepoint: on-therapy

Variable and Treatment Group	N[1]	On-therapy Category[2]				
		Low Concern	Low	Normal	High	High Concern
Systolic Blood Pressure (mmHg)						
Placebo	37	0	0	27 (73.0%)	10 (27.0%)	0
Cilomilast	32	0	0	26 (81.3%)	6 (18.8%)	0
Diastolic Blood Pressure (mmHg)						
Placebo	37	0	0	33 (89.2%)	4 (10.8%)	0
Cilomilast	32	0	0	28 (87.5%)	4 (12.5%)	0
Heart Rate (bpm)						
Placebo	48	0	1 (2.1%)	39 (81.3%)	8 (16.7%)	0
Cilomilast	43	0	1 (2.3%)	37 (86.0%)	5 (11.6%)	0

Data source: Table 15.17

NB Subjects with on-therapy values who met the criteria for both high and low values of interest and concern are reported in both categories, if applicable.
Percentages are based on the number of subjects with values within the normal range at baseline.
Subjects were assigned to categories based on their highest and/or lowest on-therapy value.

1. Number of subjects with values within the normal range at Baseline.
2. Low or high indicates value outside normal range and low concern or high concern indicates value of potential clinical concern.

During the double-blind treatment period, the percentages of subjects with transitions in sitting vital signs from normal at baseline to outside normal range on-therapy were similar in both the cilomilast and placebo groups. There were no subjects who had transitions from normal at baseline to potential clinical concern during treatment.

Transitions for sitting vital signs from normal range at baseline to outside normal range or to levels of potential clinical concern at endpoint are also summarised in Table 15.17.

8.10. Medical Device Incidents, Near-Incidents, Malfunctions and Remedial Action

No incidents, near incidents or malfunctions were reported with the use of the medical device(s) manufactured or marketed, by GSK or by a third party for GSK, for this study.

8.11. Safety Conclusions

- Cilomilast was generally well tolerated. The overall incidence of adverse events was similar in the cilomilast and placebo treatment groups (63.1% vs. 58.1%) and most events were of mild or moderate intensity. Serious adverse events occurred in two subjects in the cilomilast group and one subject in the placebo group.
- Gastrointestinal events occurred more frequently in the cilomilast group (31% vs. 16%).

- The number of subjects with GIAEs of concern was low (three subjects) and there was no evidence for a treatment effect of cilomilast on changes in orthostatic vital signs or on faecal occult blood results in subjects experiencing GIAEs of concern. There were no serious GIAEs of concern.
- There were no clinically significant effects on clinical laboratory parameters or vital signs values.

9. DISCUSSION AND CONCLUSIONS

9.1. Discussion

This study was designed to investigate the potential anti-inflammatory mechanisms of action of cilomilast 207499 (15 mg twice daily), a selective phosphodiesterase type 4 (PDE4) inhibitor. Cellular and pro-inflammatory mediator indices in bronchial tissue and sputum tissue were examined in subjects with COPD over a 13 week treatment period.

The rationale for use of cilomilast as an anti-inflammatory agent is based on the role of Cyclic AMP as a second messenger that modulates a variety of immune and inflammatory events of potential importance in the pathogenesis of COPD. As PDE4 is the major cyclic AMP-hydrolysing isozyme, cilomilast would be expected to have some effect on the localisation and activation of CD8+ lymphocytes, macrophages and neutrophils.

Although reductions were seen in tissue CD68+ macrophages and CD8+ T-lymphocytes in both treatment groups, no significant changes were found in the primary endpoints of reductions in CD8+ and CD68+ cells relative to placebo at endpoint. These findings were confirmed in an analysis using a Poisson regression model.

This discussion will look at factors which may have influenced these results.

The two treatment groups in the randomised subject population appeared well matched for mean demographic characteristics and for baseline characteristics of COPD. The subjects represented a moderate COPD population with a mean percentage predicted FEV_1 of approximately 60% of normal in both groups. At screening, subjects had a mean FEV_1/FVC ratio of approximately 0.55, low reversibility to salbutamol (approximately 5%) and percent predicted SVC of approximately 80%. The proportions of subjects with chronic bronchitis as opposed to emphysema were similar in both groups (approximately 55% vs. 45%). At entry, the groups had a smoking history of 41 or 46 mean pack years and approximately 47% of subjects were current smokers, with relatively few subjects in either group changing smoking status during the study. The characteristics of the per-protocol population were similar to those of the randomised population.

Subjects were provided with salbutamol metered dose inhalers for use on an ‘as-needed’ basis and were permitted to continue inhaled anticholinergic medication at a stable dose throughout the study; no other COPD medications were allowed except for the short term treatment of exacerbations. Apart from salbutamol, the most frequently received concomitant medications in both groups were paracetamol (36.9% and 38.7%), acetylsalicylate (18.5% and 17.7%) and codeine (16.9% and 8.1%); all percentages represent cilomilast and placebo, respectively. There were variations between treatment groups in specific medications such as fluticasone and budesonide although the overall numbers for each class of medication were broadly comparable. Compliance with study medication was good with more than 92% of subjects in both groups between 80 and 120% compliant during the double-blind treatment period.

After 12 weeks of treatment there was a mean decrease from baseline in sub-epithelial CD68+ macrophages per unit area of tissue of 20.8 cells/mm^2 with cilomilast, and 50.0 cells/mm^2 with placebo, although the difference between the groups was not statistically significant. These figures represent reductions from the baseline values of 17.1% and 34.8% in the cilomilast and placebo treatment groups, respectively.

Sub-epithelial CD8+ T-lymphocytes per unit area of tissue showed a reduction from baseline of 75.3 cells/mm^2 in the cilomilast group and 69.8 cells/mm^2 in the placebo group with no statistically significant difference between the treatments. The reduction in CD8+ cells represented mean reductions from baseline of 37.3% and 32.7% for the cilomilast and placebo treatment options, respectively.

The decrease in CD8+ and CD68+ cells is matched by similar percentage magnitudes of decrease in many biopsy- and sputum-based secondary endpoints (see Table 51).

Table 51 Comparison of change from baseline in biopsy and sputum data between current study (SB207499 181) and previous placebo group responses in biopsy studies SB207499 076 and SCO30005

Endpoint	Study Number					
	SB207499 181				SB207499 076[1]	SCO3005[2]
	Cilomilast		Placebo		Placebo	Placebo
Biopsy	**Δ cells per m²**	**% mean Δ baseline**	**Δ cells per m²**	**% mean Δ baseline**	**% mean Δ baseline**	**% median Δ baseline**
CD68+ macrophages	-20.8	-17.1	-50.0	-34.8	+55.9	+38.0
CD8+ lymphocytes	-75.3	-37.3	-69.8	-32.7	+8.0	-7.4
Subepithelial neutrophils (ne+)	-2.2	-5.8	-21.6	-46.1	+8.2	NA
CD4+ lymphocytes	-8.1	-7.9	-21.6	-17.6	-21.4	+6.3
IL-8 mRNA + cells	-13.2	36.6	-24.8	-55.9	NA	NA
TNFα mRNA + cells	-34.9	-55.0	-42.5	-60.5	NA	-8.6
CD45 + cells	-99.4	-25.1	-90.7	-23.1	NA	+3.4
Sputum	**Unit Δ**	**% Δ**	**Unit Δ**	**% Δ**	**% Δ**	**% Δ**
Total cell count (x10^6/mL)	-5.3	-56.4	-8.0	-55.2	+162.5	+25.5
Neutrophil elastase (ng/mL)	+5054	+8.3	-9012	-18.1	+244.2	NA
IL-8 (ng/mL)	-18.6	-40.6	-21.6	-30.0	-36.8	-1.7

NB Δ = change; NA = not available

1. [GlaxoSmithKline document number SB-207499/RSD-100J6D/1]
2. [GlaxoSmithKline document number GM2004/00500/00]

Epithelial and sub-mucosal mucin expression showed reductions in MUC5AC and MUC5B cells in the epithelium and, mainly, increases in MUC5AC and MUC5B cells in the sub-mucosa, although submucosal MUC5B cells were reduced in the placebo group. None of the differences between treatment groups was statistically significant.

Other secondary efficacy endpoints measured relative proportions of macrophages, eosinophils and lymphocytes in sputum. Results were generally similar in both groups and there were no statistically significant differences between treatments.

The consistent and significant reductions across a broad range of inflammatory markers in both the cilomilast and placebo treatment groups from baseline are unexpected. Prior biopsy studies of similar design within similar patient populations have generally shown an increase in the level of inflammatory markers within the placebo group during the treatment period from baseline [Gamble, 2003; GlaxoSmithKline document number GM2004/00500/00]. These data are summarised in Table 51. This increase of inflammation would be anticipated as these subjects have had the majority of treatment withdrawn prior to baseline, including corticosteroids. The cilomilast study 076 [Gamble, 2003; GlaxoSmithKline document number SB-207499/RSD-100J6D/1] showed an 8%, 56% and 8% increase in CD8+, CD68+ and Neutrophil (ne+) cells, respectively, within the placebo group whilst the SERETIDE™ study [GlaxoSmithKline document number GM2004/00500/00] showed a 7% decrease and a 38% increase in the median levels of placebo group CD8+ and CD68+ cells, respectively. Within the SERETIDE study these values were reported as medians due to the large skew in distribution of values.

The significant decline in the placebo group may relate to a number of potential factors. These include an artificially high baseline, factors during treatment which result in a reduction in the inflammatory provocation, sampling, counting or staining inconsistencies, or inadequate sampling of tissue expressing a heterogeneous distribution of inflammation at a biopsy scale.

Exacerbations of COPD are associated with increased levels of inflammatory markers such as CD8+ cells, neutrophils and IL-6 [Bhowmik, 2000; Fujimoto, 2005] as seen in induced sputum and percentage neutrophils, IL-8 and mononuclear cells in BAL [Drost, 2005]. An artificially high baseline may result from inadequate recovery from a marked inflammatory stimulus such as a viral infection or exacerbation. The stability of these markers over time is poorly known and the length of time post exacerbation for return to a more stable inflammatory profile is also unknown. The placebo group patients show a slightly higher level of exacerbations requiring oral steroids and hospitalisations in the last year (17.2% and 10.3% compared with 13.1% and 6.6% for placebo and cilomilast, respectively). These will all have occurred at least 6 weeks prior to study entry, although data are not available to see if there is a bias between groups relating to the proximity of exacerbations to baseline. The placebo group shows a higher baseline level of sputum IL-8 (61.5 ng/mL (range: 0.4-532) vs. 22.9 ng/mL (range: 0.1-142.4)). In a study of moderate COPD patients Bhowmik et al demonstrated that elevated IL-8 levels (above 3 ng/mL) were seen in subjects with increased levels of exacerbation frequency (>3 vs. <2) [Bhowmik, 2000].

Smoking status at baseline in terms of mean pack years, cigarettes per day and number of active smokers is broadly 10% higher within the cilomilast group for each of these categories. The number of smokers reporting a change in status is relatively small although not evenly matched with 14.3% of placebo subjects vs. 3.1% of cilomilast subjects stopping and no subjects restarting smoking in the placebo treatment arm vs. 3.0% in the cilomilast treatment arm. The short-term effects of smoking cessation or resumption on the inflammatory profile of the lung within an individual are not known. Cross sectional studies suggest that the abnormal inflammatory profile of COPD remains after smoking cessation, although the absolute change in inflammation within a subject

has not been measured. The rate of decline in FEV_1 clearly slows post-cessation and it has been postulated that this might be the result of a decline in inflammatory provocation [Willemse, 2005].

Processing and counting errors are less likely to be a significant factor as mean reductions, of a similar magnitude, have occurred in a broad number of endpoints which are evaluated by both different techniques and laboratories.

Work by Gamble and Sullivan [Gamble, 2003; Sullivan, 1998] has shown the variability of the inflammatory profile on a microscopic scale in chronic bronchitic and COPD patients. Inadequate sampling of tissue can provide an unrepresentative mean which will increase the likelihood of a type 2 error occurring. Within this study a total of 4 mm of basement membrane tissue was defined as the minimum length permitted. This was taken from two biopsies and included an area of subepithelial membrane of at least 0.3 mm^2. Gamble suggested a reticular basement membrane length of 5 mm was required to achieve a representative count [Gamble, 2003]. However, the 5 mm section to which Gamble referred was a total of 5 (1 mm) samples. Sullivan et al measured variation on repeat sections from a single biopsy sample in COPD patients. This suggested that up to six sections were need to be counted to ensure that 75% of samples fell within 20% of the mean count. This required tissue from 7.8 mm of reticular basement membrane length [Sullivan, 1998].

The amount of tissue required adequately to power COPD studies is still poorly understood. Whilst it has been possible to show statistically significant treatment effect on inflammatory agents, the level of potential variation is still not understood and the possibility of a type 1 or type 2 error is very difficult to predict accurately or to exclude.

Lung function results of SVC did not show a significant difference between treatment groups, although the study was not powered on this endpoint.

The safety of cilomilast was closely evaluated in this study with particular emphasis on gastrointestinal monitoring in addition to the routine reporting of adverse events.

The study showed that cilomilast was generally well tolerated. There were a similar proportion of subjects in each group with adverse events during the double blind treatment period (63% in the cilomilast group and 58% in the placebo group). The most frequently reported events in both groups were headache and nasopharyngitis (14% and 12% of subjects, respectively, in the cilomilast group and 19% and 13%, respectively in the placebo group). There was a higher incidence of gastrointestinal adverse events in the cilomilast group (31% vs. 16%) which would be expected from the known pharmacology of cilomilast. Most adverse events were of mild or moderate intensity in both treatment groups and 8% of subjects in the cilomilast group and 5% of subjects in the placebo group experienced severe events.

There were no deaths reported during the study or within 30 days of completing study treatment. Three subjects had serious adverse events during double-blind treatment; two receiving cilomilast (anxiety and atrial flutter) and one receiving placebo (COAD exacerbated), and one serious adverse event occurred after the end of treatment (lung cancer in the placebo group). None of these was reported as possibly related to study

medication. Five subjects had adverse events leading to withdrawal; four (6.2%) in the cilomilast group and one (1.6%) in the placebo group. The events of gastritis, gastro-oesophageal reflux disease, nausea and enteritis in cilomilast subjects were reported as possibly related to study medication.

GIAEs of concern were reported by three subjects: two in the cilomilast group (nausea and enteritis) and one in the placebo group (nausea/abdominal pain). None of the subjects had positive faecal occult blood tests (when performed). The subject in the placebo group had orthostatic vital signs of potential clinical concern, but the magnitude of the change was small (an increase in heart rate of 16 bpm) and not considered to be of clinical significance. Both subjects in the cilomilast group had severe GIAEs of concern and one was withdrawn following the event (severe enteritis). There were no serious GIAEs of concern. There was no evidence for a treatment effect of cilomilast on changes in orthostatic vital signs or on faecal occult blood results in subjects experiencing GIAEs of concern. Of all the subjects who had on-therapy faecal occult blood tests, 7.3% of those receiving cilomilast (3 of 41, one of whom had a positive test at baseline) and 12.5% of those receiving placebo (5 of 40, two of whom had a positive test at baseline) had a positive test result during the double blind period.

Mean changes from baseline in laboratory parameters and vital signs values were small with no clinically relevant changes from baseline in either group. During the double-blind treatment period, the percentages of subjects with transitions in sitting vital signs from normal at baseline to outside normal range on-therapy were similar in both the cilomilast and placebo groups. There were no subjects who had transitions from normal at baseline to potential clinical concern during treatment.

9.2. Conclusions

- The present study demonstrated a mean reduction in inflammatory cell and mediator profiles in subjects with COPD for both treatment groups over the 13 week study interval. No significant changes compared with placebo were found in the primary endpoints and these findings were confirmed in an analysis using a Poisson regression model.
- Secondary endpoints showed reductions in both groups for an array of biopsy and sputum inflammatory markers. Reductions were variable relative to baseline values and more commonly larger in the placebo group. Differences failed to reach statistical significance in the majority of cases. Only sub-epithelial neutrophils showed a statistical difference in favour of placebo.
- The large placebo group reductions in a range of inflammatory cells and mediators remain unexplained. Such a placebo response may result from a combination of stability problems at baseline, inflammatory drivers which are not balanced between treatment arms, processing inconsistencies, or natural intra-patient variation in inflammatory profile.
- Lung function results of SVC did not show a significant difference between treatment groups, although the study was not powered on this endpoint.

- Cilomilast 15 mg bd was generally well tolerated. The incidence of on-therapy adverse events was similar to placebo and the majority of adverse events were of mild or moderate intensity.
- The incidence of gastrointestinal events was higher than placebo. GIAEs of concern occurred in subjects receiving both cilomilast and placebo, but all resolved during study treatment.
- There were no consistent clinically significant effects on vital signs or laboratory results. The safety profile of cilomilast observed in this study is in line with the currently established adverse event profile and no new safety concerns were identified.

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This section contained patient narratives which are textual descriptions of medical history, treatment and outcome for individual patients who experienced a clinically important adverse event including serious adverse events during the trial. They have been excluded to protect patient privacy. This data may be made available subject to an approved research proposal and a determination of the ability to provide information from the specific narratives whilst protecting the patient's privacy. For further information please see the Patient Level Data section of the ***GSK Clinical Study Register****.*

STUDY POPULATION DATA SOURCE TABLES

Page

TABLE 13.1B - SUMMARY OF PATIENT DISPOSITION BY COUNTRY AND TREATMENT GROUP 150
TABLE 13.2 - DISTRIBUTION OF RANDOMISED PATIENTS IN STUDY BY VISIT/WEEK AND TREATMENT GROUP 152
TABLE 13.3 - REASONS FOR CONCLUDING THE RUN-IN PERIOD 153
TABLE 13.4 - REASONS FOR CONCLUDING THE DOUBLE BLIND PERIOD BY TREATMENT GROUP 154
TABLE 13.6A - SUMMARY OF PROTOCOL VIOLATIONS RESULTING IN EXCLUSION FROM PER PROTOCOL ANALYSIS BY TREATMENT GROUP 155
TABLE 13.6B - SUMMARY OF PROTOCOL VIOLATIONS RESULTING IN EXCLUSION FROM PER PROTOCOL ANALYSIS BY TREATMENT GROUP AND VISIT/WEEK 156
TABLE 13.6C - SUMMARY OF CONDUCT OF STUDY DEVIATIONS BY TREATMENT GROUP 157
TABLE 13.7A - SUMMARY OF DEMOGRAPHIC CHARACTERISTICS AT SCREENING BY TREATMENT GROUP - ALL RANDOMIZED PATIENTS 158
TABLE 13.7B - SUMMARY OF DEMOGRAPHIC CHARACTERISTICS AT SCREENING BY TREATMENT GROUP - PP 159
TABLE 13.8A - DESCRIPTIVE STATISTICS FOR PULMONARY FUNCTION PARAMETERS* AT SCREENING BY TREATMENT GROUP - - ALL RANDOMISED PATIENTS 160
TABLE 13.8B - DESCRIPTIVE STATISTICS FOR PULMONARY FUNCTION PARAMETERS AT SCREENING BY TREATMENT GROUP - PP 162
TABLE 13.9A - DESCRIPTIVE STATISTICS FOR SMOKING HISTORY AT SCREENING BY TREATMENT GROUP - ALL RANDOMISED PATIENTS 164
TABLE 13.9B - DESCRIPTIVE STATISTICS FOR SMOKING HISTORY AT SCREENING BY TREATMENT GROUP - PP 165
TABLE 13.10A - SUMMARY OF PULMONARY HISTORY BY TREATMENT GROUP - ALL RANDOMISED PATIENTS 166
TABLE 13.10B - SUMMARY OF PULMONARY HISTORY BY TREATMENT GROUP - PP 167

TABLE 13.12 - SUMMARY OF BASELINE SIGNS AND SYMPTOMS BY MEDDRA SYSTEM ORGAN CLASS AND VERBATIM TERM - ALL RANDOMISED PATIENTS 168
TABLE 13.13A - SUMMARY OF PRIOR MEDICATIONS BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMISED PATIENTS . . 173
TABLE 13.13B - SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMISED PATIENTS. 184
TABLE 13.13C - SUMMARY OF POST-THERAPY MEDICATIONS BY GENERIC TERM AND TREATMENT GROUP. 196
TABLE 13.13D - SUMMARY OF MEDICATIONS GIVEN FOR COPD EXACERBATIONS BY GENERIC TERM AND TREATMENT GROUP . . 199
TABLE 13.14A - SUMMARY OF STUDY MEDICATION COMPLIANCE (%) BY TREATMENT GROUP AND VISIT/WEEK 201
TABLE 13.14B - DESCRIPTIVE STATISTICS FOR STUDY MEDICATION COMPLIANCE (%) BY TREATMENT GROUP AND VISIT/WEEK 202
TABLE 13.15 - SUMMARY OF PATIENT SMOKING STATUS BY BASELINE STATUS AND TREATMENT GROUP AT VISIT 7. 204

SB 207499

TABLE 13.1B

SUMMARY OF PATIENT DISPOSITION BY COUNTRY AND TREATMENT GROUP

PROTOCOL 181

COUNTRY	DISPOSITION	TREATMENT GROUP PLACEBO	SB 207499	NON. RAND	TOTAL
Australia	SINGLE-BLIND	6	9	8	23
	RANDOMIZED	6 (100.0%)	9 (100.0%)	0 .	15 (100.0%)
	ITT EFFICACY	5 (83.3%)	8 (88.9%)	0 .	13 (86.7%)
	PP EFFICACY	4 (66.7%)	8 (88.9%)	0 .	12 (80.0%)
	COMPLETED DB	4 (66.7%)	6 (66.7%)	0 .	10 (66.7%)
Canada	SINGLE-BLIND	9	10	7	26
	RANDOMIZED	9 (100.0%)	10 (100.0%)	0 .	19 (100.0%)
	ITT EFFICACY	9 (100.0%)	10 (100.0%)	0 .	19 (100.0%)
	PP EFFICACY	9 (100.0%)	10 (100.0%)	0 .	19 (100.0%)
	COMPLETED DB	9 (100.0%)	10 (100.0%)	0 .	19 (100.0%)
Finland	SINGLE-BLIND	5	5	3	13
	RANDOMIZED	5 (100.0%)	5 (100.0%)	0 .	10 (100.0%)
	ITT EFFICACY	5 (100.0%)	4 (80.0%)	0 .	9 (90.0%)
	PP EFFICACY	5 (100.0%)	4 (80.0%)	0 .	9 (90.0%)
	COMPLETED DB	5 (100.0%)	4 (80.0%)	0 .	9 (90.0%)
Ireland	SINGLE-BLIND	4	5	1	10
	RANDOMIZED	4 (100.0%)	5 (100.0%)	0 .	9 (100.0%)
	ITT EFFICACY	4 (100.0%)	4 (80.0%)	0 .	8 (88.9%)
	PP EFFICACY	4 (100.0%)	4 (80.0%)	0 .	8 (88.9%)
	COMPLETED DB	4 (100.0%)	4 (80.0%)	0 .	8 (88.9%)
Lithuania	SINGLE-BLIND	5	4	5	14
	RANDOMIZED	5 (100.0%)	4 (100.0%)	0 .	9 (100.0%)
	ITT EFFICACY	5 (100.0%)	3 (75.0%)	0 .	8 (88.9%)
	PP EFFICACY	5 (100.0%)	3 (75.0%)	0 .	8 (88.9%)
	COMPLETED DB	4 (80.0%)	3 (75.0%)	0 .	7 (77.8%)
Norway	SINGLE-BLIND	3	3	0	6
	RANDOMIZED	3 (100.0%)	3 (100.0%)	0 .	6 (100.0%)
	ITT EFFICACY	3 (100.0%)	3 (100.0%)	0 .	6 (100.0%)
	PP EFFICACY	3 (100.0%)	3 (100.0%)	0 .	6 (100.0%)
	COMPLETED DB	3 (100.0%)	2 (66.7%)	0 .	5 (83.3%)
Romania	SINGLE-BLIND	8	5	2	15
	RANDOMIZED	8 (100.0%)	5 (100.0%)	0 .	13 (100.0%)
	ITT EFFICACY	8 (100.0%)	5 (100.0%)	0 .	13 (100.0%)
	PP EFFICACY	8 (100.0%)	5 (100.0%)	0 .	13 (100.0%)
	COMPLETED DB	7 (87.5%)	5 (100.0%)	0 .	12 (92.3%)
Slovakia	SINGLE-BLIND	0	2	1	3
	RANDOMIZED	0 .	2 (100.0%)	0 .	2 (100.0%)

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED WITHIN EACH COUNTRY.
2. TOTAL ROWS REPRESENT THE TOTAL ACROSS ALL COUNTRIES.

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SB 207499

TABLE 13.1B

SUMMARY OF PATIENT DISPOSITION BY COUNTRY AND TREATMENT GROUP

PROTOCOL 181

COUNTRY	DISPOSITION	TREATMENT GROUP PLACEBO	SB 207499	NON. RAND	TOTAL
Slovakia	ITT EFFICACY	0 .	2 (100.0%)	0 .	2 (100.0%)
	PP EFFICACY	0 .	2 (100.0%)	0 .	2 (100.0%)
	COMPLETED DB	0 .	2 (100.0%)	0 .	2 (100.0%)
Slovenia	SINGLE-BLIND	4	3	1	8
	RANDOMIZED	4 (100.0%)	3 (100.0%)	0 .	7 (100.0%)
	ITT EFFICACY	4 (100.0%)	3 (100.0%)	0 .	7 (100.0%)
	PP EFFICACY	3 (75.0%)	3 (100.0%)	0 .	6 (85.7%)
	COMPLETED DB	4 (100.0%)	3 (100.0%)	0 .	7 (100.0%)
South Africa	SINGLE-BLIND	3	5	1	9
	RANDOMIZED	3 (100.0%)	5 (100.0%)	0 .	8 (100.0%)
	ITT EFFICACY	3 (100.0%)	5 (100.0%)	0 .	8 (100.0%)
	PP EFFICACY	3 (100.0%)	5 (100.0%)	0 .	8 (100.0%)
	COMPLETED DB	3 (100.0%)	5 (100.0%)	0 .	8 (100.0%)
Sweden	SINGLE-BLIND	9	8	0	17
	RANDOMIZED	9 (100.0%)	8 (100.0%)	0 .	17 (100.0%)
	ITT EFFICACY	9 (100.0%)	8 (100.0%)	0 .	17 (100.0%)
	PP EFFICACY	8 (88.9%)	8 (100.0%)	0 .	16 (94.1%)
	COMPLETED DB	7 (77.8%)	7 (87.5%)	0 .	14 (82.4%)
United Kingdom	SINGLE-BLIND	6	6	4	16
	RANDOMIZED	6 (100.0%)	6 (100.0%)	0 .	12 (100.0%)
	ITT EFFICACY	6 (100.0%)	6 (100.0%)	0 .	12 (100.0%)
	PP EFFICACY	6 (100.0%)	6 (100.0%)	0 .	12 (100.0%)
	COMPLETED DB	6 (100.0%)	6 (100.0%)	0 .	12 (100.0%)
TOTAL	SINGLE-BLIND	62	65	33	160
	RANDOMIZED	62 (100.0%)	65 (100.0%)	0 .	127 (100.0%)
	ITT EFFICACY	61 (98.4%)	61 (93.8%)	0 .	122 (96.1%)
	PP EFFICACY	58 (93.5%)	61 (93.8%)	0 .	119 (93.7%)
	COMPLETED DB	56 (90.3%)	57 (87.7%)	0 .	113 (89.0%)

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED WITHIN EACH COUNTRY.
2. TOTAL ROWS REPRESENT THE TOTAL ACROSS ALL COUNTRIES.

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SB 207499

TABLE 13.2

DISTRIBUTION OF RANDOMISED PATIENTS IN STUDY BY VISIT/WEEK AND TREATMENT GROUP

PROTOCOL 181

VISIT/WEEK	TREATMENT GROUP PLACEBO (N=62)		SB 207499 (N=65)		TOTAL (N=127)	
VISIT 2/BASELINE	62	(100.0%)	65	(100.0%)	127	(100.0%)
VISIT 2A/BASELINE	7	(11.3%)	2	(3.1%)	9	(7.1%)
VISIT 3/WEEK 0	62	(100.0%)	65	(100.0%)	127	(100.0%)
VISIT 4/WEEK 4	60	(96.8%)	61	(93.8%)	121	(95.3%)
VISIT 5/WEEK 8	59	(95.2%)	59	(90.8%)	118	(92.9%)
VISIT 6/WEEK 12	56	(90.3%)	57	(87.7%)	113	(89.0%)
VISIT 6A/WEEK 12	2	(3.2%)	4	(6.2%)	6	(4.7%)
VISIT 7/WEEK 13	56	(90.3%)	57	(87.7%)	113	(89.0%)
FOLLOW-UP	60	(96.8%)	64	(98.5%)	124	(97.6%)
EARLY WITHDRAWAL	6	(9.7%)	8	(12.3%)	14	(11.0%)

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED AT VISIT 3.

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GM2004/00090/00
SB-207499/181

SB 207499

TABLE 13.3

REASONS FOR CONCLUDING THE RUN-IN PERIOD

PROTOCOL 181

CONCLUSION REASON	TOTAL (N=160)
ADVERSE EVENT	3 (1.9%)
PROTOCOL VIOLATION	3 (1.9%)
LOST TO FOLLOW-UP	1 (0.6%)
CONSENT WITHDRAWN	8 (5.0%)
OTHER	4 (2.5%)
DID NOT FULFIL ENTRY CRITERIA	4 (2.5%)
COPD EXACERBATION	10 (6.3%)
TOTAL WITHDRAWN	33 (20.6%)
COMPLETED SINGLE BLIND RUN-IN	127 (79.4%)

1. PERCENTAGES ARE BASED ON TOTAL NUMBER OF PATIENTS ENTERING SINGLE-BLIND RUN-IN.

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GM2004/00090/00
SB-207499/181

SB 207499

TABLE 13.4

REASONS FOR CONCLUDING THE DOUBLE BLIND PERIOD BY TREATMENT GROUP

PROTOCOL 181

REASON	TREATMENT GROUP PLACEBO (N=62)	SB 207499 (N=65)
ADVERSE EVENT	3 (4.8%)	6 (9.2%)
INSUFFICIENT THERAPEUTIC EFFECT		1 (1.5%)
CONSENT WITHDRAWN	1 (1.6%)	1 (1.5%)
COPD EXACERBATION	2 (3.2%)	
TOTAL WITHDRAWN	6 (9.7%)	8 (12.3%)
COMPLETED STUDY	56 (90.3%)	57 (87.7%)

1. PERCENTAGES ARE BASED ON NUMBER OF RANDOMISED PATIENTS.
2. [redacted]
3. [redacted]

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SB 207499

TABLE 13.6A

SUMMARY OF PROTOCOL VIOLATIONS RESULTING IN EXCLUSION FROM PER PROTOCOL ANALYSIS BY TREATMENT GROUP

PROTOCOL 181

TYPE OF VIOLATION	VIOLATION	TREATMENT GROUP PLACEBO (N=61)	SB 207499 (N=61)
EXCLUSIONARY MEDICATIONS	Inhaled, oral and systemic corticosteriod use within 4 weeks prior to Visit 1	3 (4.9%)	2 (3.3%)
	Concomitant NACs (N- Acetyl Cysteine	1 (1.6%)	
	TOTAL	4 (6.6%)	2 (3.3%)
VISIT SPECIFIC VIOLATIONS	Study medication compliance < 80 percent or > 120 percent during active, on-therapy dosing	2 (3.3%)	1 (1.6%)
	Salbutamol and/or anti-cholinergic medication within 6 hours of pulmonary function testing	2 (3.3%)	2 (3.3%)
	TOTAL	4 (6.6%)	3 (4.9%)
ALL VIOLATIONS	Complete Exclusions	2 (3.3%)	
	At Least One Protocol Violation	7 (11.5%)	4 (6.6%)

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS WITH EFFICACY DATA WITHIN EACH TREATMENT GROUP.

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SB 207499

TABLE 13.6B

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

PROTOCOL 181

VISIT/WEEK	VIOLATION	TREATMENT GROUP PLACEBO (N=61)	SB 207499 (N=61)
VISIT 2/BASELINE	Inhaled, oral and systemic corticosteriod use within 4 weeks prior to Visit 1	2/ 57 (3.5%)	0/ 61 (0.0%)
	TOTAL	2/ 57 (3.5%)	0/ 61 (0.0%)
VISIT 3/WEEK 0	Inhaled, oral and systemic corticosteriod use within 4 weeks prior to Visit 1	2/ 61 (3.3%)	0/ 61 (0.0%)
	TOTAL	2/ 61 (3.3%)	0/ 61 (0.0%)
VISIT 4/WEEK 4	Inhaled, oral and systemic corticosteriod use within 4 weeks prior to Visit 1	2/ 60 (3.3%)	0/ 61 (0.0%)
	Salbutamol and/or anti-cholinergic medication within 6 hours of pulmonary function testing	1/ 60 (1.7%)	1/ 61 (1.6%)
	TOTAL	3/ 60 (5.0%)	1/ 61 (1.6%)
VISIT 5/WEEK 8	Inhaled, oral and systemic corticosteriod use within 4 weeks prior to Visit 1	2/ 59 (3.4%)	0/ 59 (0.0%)
	Salbutamol and/or anti-cholinergic medication within 6 hours of pulmonary function testing	1/ 59 (1.7%)	1/ 59 (1.7%)
	TOTAL	2/ 59 (3.4%)	1/ 59 (1.7%)
VISIT 6/WEEK 12	Inhaled, oral and systemic corticosteriod use within 4 weeks prior to Visit 1	2/ 56 (3.6%)	0/ 56 (0.0%)
	Concomitant NACs (N- Acetyl Cysteine	1/ 56 (1.8%)	0/ 56 (0.0%)
	Salbutamol and/or anti-cholinergic medication within 6 hours of pulmonary function testing	1/ 56 (1.8%)	1/ 56 (1.8%)
	TOTAL	3/ 56 (5.4%)	1/ 56 (1.8%)
VISIT 7/WEEK 13	Inhaled, oral and systemic corticosteriod use within 4 weeks prior to Visit 1	2/ 56 (3.6%)	1/ 56 (1.8%)
	Concomitant NACs (N- Acetyl Cysteine	1/ 56 (1.8%)	0/ 56 (0.0%)
	Study medication compliance < 80 percent or > 120 percent during active, on-therapy dosing	2/ 56 (3.6%)	1/ 56 (1.8%)
	Salbutamol and/or anti-cholinergic medication within 6 hours of pulmonary function testing	0/ 56 (0.0%)	2/ 56 (3.6%)
	TOTAL	5/ 56 (8.9%)	3/ 56 (5.4%)

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS WITH EFFICACY DATA WITHIN EACH GROUP AT EACH VISIT.
2. TOTAL ROW REPRESENTS THE TOTAL NUMBER OF PATIENTS EXCLUDED FOR A PROTOCOL VIOLATION AT A GIVEN VISIT.

CONFIDENTIAL

SB 207499

TABLE 13.6C

SUMMARY OF CONDUCT OF STUDY DEVIATIONS BY TREATMENT GROUP

PROTOCOL 181

CONDUCT OF STUDY DEVIATION	TREATMENT GROUP PLACEBO (N=61)	SB 207499 (N=61)
Study medication compliance <80 percent or >120 percent during placebo run-in period	2 (3.3%)	1 (1.6%)
TOTAL	2 (3.3%)	1 (1.6%)

1. PERCENTAGES ARE BASED ON TOTAL NUMBER OF PATIENTS WITH EFFICACY DATA WITHIN EACH TREATMENT GROUP.

CONFIDENTIAL

GM2004/00090/00
SB-207499/181

SB 207499

TABLE 13.7A

SUMMARY OF DEMOGRAPHIC CHARACTERISTICS AT SCREENING BY TREATMENT GROUP - ALL RANDOMIZED PATIENTS

PROTOCOL 181

CHARACTERISTIC		TREATMENT GROUP PLACEBO (N=62)	SB 207499 (N=65)	TOTAL (N=127)
SEX	Female	15 (24.2%)	18 (27.7%)	33 (26.0%)
	Male	47 (75.8%)	47 (72.3%)	94 (74.0%)
RACE	OTHER	2 (3.2%)	3 (4.6%)	5 (3.9%)
	WHITE	60 (96.8%)	62 (95.4%)	122 (96.1%)
AGE (YRS)	< 50	5 (8.1%)	4 (6.2%)	9 (7.1%)
	50-65	30 (48.4%)	40 (61.5%)	70 (55.1%)
	> 65	27 (43.5%)	21 (32.3%)	48 (37.8%)
	N	62	65	127
	MEAN	63.4	61.4	62.4
	MEDIAN	65.0	61.0	62.0
	STD	9.1	8.4	8.7
	MIN	45	47	45
	MAX	79	78	79
WEIGHT (KG)	N	62	64	126
	MEAN	75.6	77.7	76.7
	MEDIAN	75.6	74.4	75.1
	STD	14.5	17.8	16.2
	MIN	40	36	36
	MAX	120	123	123
HEIGHT (CM)	N	62	65	127
	MEAN	169.8	170.2	170.0
	MEDIAN	170.0	170.0	170.0
	STD	7.9	7.9	7.8
	MIN	153	156	153
	MAX	187	189	189

1. PERCENTAGES ARE BASED ON THE TOTAL NUMBER OF PATIENTS RANDOMIZED WITHIN EACH TREATMENT GROUP.

CONFIDENTIAL
GM2004/00090/00
SB-207499/181

SB 207499

TABLE 13.7B

SUMMARY OF DEMOGRAPHIC CHARACTERISTICS AT SCREENING BY TREATMENT GROUP - PP

PROTOCOL 181

CHARACTERISTIC		TREATMENT GROUP PLACEBO (N=58)	SB 207499 (N=61)	TOTAL (N=119)
SEX	Female	12 (20.7%)	15 (24.6%)	27 (22.7%)
	Male	46 (79.3%)	46 (75.4%)	92 (77.3%)
RACE	OTHER	2 (3.4%)	3 (4.9%)	5 (4.2%)
	WHITE	56 (96.6%)	58 (95.1%)	114 (95.8%)
AGE (YRS)	< 50	4 (6.9%)	3 (4.9%)	7 (5.9%)
	50-65	29 (50.0%)	38 (62.3%)	67 (56.3%)
	> 65	25 (43.1%)	20 (32.8%)	45 (37.8%)
	N	58	61	119
	MEAN	63.6	61.6	62.6
	MEDIAN	65.0	61.0	63.0
	STD	8.9	8.4	8.7
	MIN	45	49	45
	MAX	79	78	79
WEIGHT (KG)	N	58	60	118
	MEAN	76.4	76.3	76.3
	MEDIAN	77.2	74.1	75.1
	STD	13.6	16.9	15.3
	MIN	50	36	36
	MAX	120	118	120
HEIGHT (CM)	N	58	61	119
	MEAN	170.1	170.3	170.2
	MEDIAN	170.5	170.0	170.0
	STD	7.8	8.0	7.8
	MIN	153	156	153
	MAX	187	189	189

1. PERCENTAGES ARE BASED ON THE TOTAL NUMBER OF PATIENTS IN THE PP POPULATION WITHIN EACH TREATMENT GROUP.

CONFIDENTIAL
GM2004/00090/00
SB-207499/181

SB 207499

TABLE 13.8A

DESCRIPTIVE STATISTICS FOR PULMONARY FUNCTION PARAMETERS* AT SCREENING BY TREATMENT GROUP - ALL RANDOMISED PATIENTS
PROTOCOL 181

PARAMETER		TREATMENT GROUP PLACEBO (N=62)	SB 207499 (N=65)	TOTAL (N=127)
FEV1 (L)	N	62	65	127
	MEAN	1.61	1.70	1.65
	STD	0.50	0.40	0.45
	MEDIAN	1.50	1.63	1.59
	MIN	0.80	0.97	0.80
	MAX	3.19	2.59	3.19
FVC (L)	N	62	65	127
	MEAN	3.03	3.18	3.10
	STD	0.78	0.93	0.86
	MEDIAN	2.98	3.01	3.01
	MIN	1.63	1.61	1.61
	MAX	4.71	5.87	5.87
SVC (L)	N	60	64	124
	MEAN	3.17	3.32	3.25
	STD	0.86	0.95	0.91
	MEDIAN	3.09	3.22	3.14
	MIN	1.63	1.10	1.10
	MAX	4.99	6.25	6.25
%PREDICTED FEV1	N	62	65	127
	MEAN	59.79	61.95	60.90
	STD	11.68	10.11	10.92
	MEDIAN	59.94	64.65	61.99
	MIN	33.73	41.26	33.73
	MAX	79.98	79.79	79.98
%PREDICTED FVC	N	61	65	126
	MEAN	75.62	78.18	76.94
	STD	28.29	33.77	31.14
	MEDIAN	81.30	82.20	81.95
	MIN	2.62	3.45	2.62
	MAX	126.90	132.40	132.40
%PREDICTED SVC	N	53	58	111
	MEAN	80.12	80.13	80.12

* PULMONARY FUNCTION PARAMETERS INCLUDE FEV1, FVC, SVC, PERCENT PREDICTED FEV1, PERCENT PREDICTED FVC, PERCENT PREDICTED SVC, SALBUTAMOL REVERSIBILITY, AND FEV1/FVC RATIO.
1. FEV1, FVC, SVC, AND FEV1/FVC ARE REPORTED PRE-ALBUTEROL INHALATION.
2. PERCENT PREDICTED FEV1, PERCENT PREDICTED FVC, AND PERCENT PREDICTED SVC ARE REPORTED POST-ALBUTEROL INHALATION.
3. SUMMARY IS FOR RANDOMIZED PATIENTS.
4. PREDICTED SALBUTAMOL REVERSIBILITY (%) IS CALCULATED USING THE FOLLOWING FORMULA:
100x(HIGHEST POST BRONCHODILATOR FEV1 - HIGHEST PRE BRONCHODILATOR FEV1) / PREDICTED NORMAL FEV1

CONFIDENTIAL
GM2004/00090/00
SB-207499/181

SB 207499

TABLE 13.8A

DESCRIPTIVE STATISTICS FOR PULMONARY FUNCTION PARAMETERS* AT SCREENING BY TREATMENT GROUP - ALL RANDOMISED PATIENTS
PROTOCOL 181

PARAMETER		TREATMENT GROUP PLACEBO (N=62)	SB 207499 (N=65)	TOTAL (N=127)
%PREDICTED SVC	STD	26.74	36.10	31.83
	MEDIAN	84.20	85.50	84.90
	MIN	2.91	3.45	2.91
	MAX	122.90	153.00	153.00
REVERSIBILITY (%)	N	62	65	127
	MEAN	4.57	4.19	4.38
	STD	3.84	3.29	3.56
	MEDIAN	5.25	4.64	5.00
	MIN	-7.30	-5.10	-7.30
	MAX	14.00	9.40	14.00
FEV1/FVC (%)	N	62	65	127
	MEAN	0.54	0.55	0.54
	STD	0.10	0.10	0.10
	MEDIAN	0.53	0.57	0.55
	MIN	0.30	0.33	0.30
	MAX	0.70	0.72	0.72

* PULMONARY FUNCTION PARAMETERS INCLUDE FEV1, FVC, SVC, PERCENT PREDICTED FEV1, PERCENT PREDICTED FVC, PERCENT PREDICTED SVC, SALBUTAMOL REVERSIBILITY, AND FEV1/FVC RATIO.
1. FEV1, FVC, SVC, AND FEV1/FVC ARE REPORTED PRE-ALBUTEROL INHALATION.
2. PERCENT PREDICTED FEV1, PERCENT PREDICTED FVC, AND PERCENT PREDICTED SVC ARE REPORTED POST-ALBUTEROL INHALATION.
3. SUMMARY IS FOR RANDOMIZED PATIENTS.
4. PREDICTED SALBUTAMOL REVERSIBILITY (%) IS CALCULATED USING THE FOLLOWING FORMULA: 100x(HIGHEST POST BRONCHODILATOR FEV1 - HIGHEST PRE BRONCHODILATOR FEV1) / PREDICTED NORMAL FEV1

CONFIDENTIAL
GM2004/00090/00
SB-207499/181

SB 207499

TABLE 13.8B

DESCRIPTIVE STATISTICS FOR PULMONARY FUNCTION PARAMETERS AT SCREENING BY TREATMENT GROUP - PP

PROTOCOL 181

PARAMETER		TREATMENT GROUP PLACEBO (N=58)	SB 207499 (N=61)	TOTAL (N=119)
FEV1 (L)	N	58	61	119
	MEAN	1.61	1.69	1.65
	STD	0.50	0.40	0.45
	MEDIAN	1.52	1.60	1.59
	MIN	0.80	0.97	0.80
	MAX	3.19	2.59	3.19
FVC (L)	N	58	61	119
	MEAN	3.01	3.19	3.10
	STD	0.80	0.96	0.89
	MEDIAN	2.90	3.01	3.00
	MIN	1.63	1.61	1.61
	MAX	4.71	5.87	5.87
SVC (L)	N	56	61	117
	MEAN	3.17	3.34	3.26
	STD	0.88	0.96	0.92
	MEDIAN	3.09	3.26	3.16
	MIN	1.63	1.10	1.10
	MAX	4.99	6.25	6.25
%PREDICTED FEV1	N	58	61	119
	MEAN	59.71	61.45	60.60
	STD	11.76	10.24	11.00
	MEDIAN	59.94	62.90	61.19
	MIN	33.73	41.26	33.73
	MAX	79.98	79.79	79.98
%PREDICTED FVC	N	57	61	118
	MEAN	75.32	77.15	76.27
	STD	26.46	34.55	30.79
	MEDIAN	81.00	82.10	81.15
	MIN	2.62	3.45	2.62
	MAX	110.90	132.40	132.40
%PREDICTED SVC	N	50	55	105
	MEAN	81.02	79.56	80.26

* PULMONARY FUNCTION PARAMETERS* INCLUDE FEV1, FVC, SVC, PERCENT PREDICTED FEV1, PERCENT PREDICTED FVC, PERCENT PREDICTED SVC, SALBUTAMOL REVERSIBILITY, AND FEV1/FVC RATIO.
1. FEV1, FVC, SVC, AND FEV1/FVC ARE REPORTED PRE-ALBUTEROL INHALATION.
2. PERCENT PREDICTED FEV1, PERCENT PREDICTED FVC, AND PERCENT PREDICTED SVC ARE REPORTED POST-ALBUTEROL INHALATION.
3. SUMMARY IS FOR PER PROTOCOL PATIENTS.
4. PREDICTED SALBUTAMOL REVERSIBILITY (%) IS CALCULATED USING THE FOLLOWING FORMULA: 100x(HIGHEST POST BRONCHODILATOR FEV1 - HIGHEST PRE BRONCHODILATOR FEV1) / PREDICTED NORMAL FEV1

CONFIDENTIAL

SB 207499

TABLE 13.8B

DESCRIPTIVE STATISTICS FOR PULMONARY FUNCTION PARAMETERS AT SCREENING BY TREATMENT GROUP - PP

PROTOCOL 181

PARAMETER		TREATMENT GROUP PLACEBO (N=58)	SB 207499 (N=61)	TOTAL (N=119)
%PREDICTED SVC	STD	24.98	36.92	31.66
	MEDIAN	83.60	84.90	84.60
	MIN	3.39	3.45	3.39
	MAX	122.90	153.00	153.00
REVERSIBILITY (%)	N	58	61	119
	MEAN	4.69	4.25	4.46
	STD	3.88	3.37	3.62
	MEDIAN	5.60	4.70	5.20
	MIN	-7.30	-5.10	-7.30
	MAX	14.00	9.40	14.00
FEV1/FVC (%)	N	58	61	119
	MEAN	0.54	0.55	0.55
	STD	0.10	0.10	0.10
	MEDIAN	0.54	0.56	0.55
	MIN	0.32	0.33	0.32
	MAX	0.70	0.72	0.72

* PULMONARY FUNCTION PARAMETERS* INCLUDE FEV1, FVC, SVC, PERCENT PREDICTED FEV1, PERCENT PREDICTED FVC, PERCENT PREDICTED SVC, SALBUTAMOL REVERSIBILITY, AND FEV1/FVC RATIO.
1. FEV1, FVC, SVC, AND FEV1/FVC ARE REPORTED PRE-ALBUTEROL INHALATION.
2. PERCENT PREDICTED FEV1, PERCENT PREDICTED FVC, AND PERCENT PREDICTED SVC ARE REPORTED POST-ALBUTEROL INHALATION.
3. SUMMARY IS FOR PER PROTOCOL PATIENTS.
4. PREDICTED SALBUTAMOL REVERSIBILITY (%) IS CALCULATED USING THE FOLLOWING FORMULA: 100x(HIGHEST POST BRONCHODILATOR FEV1 - HIGHEST PRE BRONCHODILATOR FEV1) / PREDICTED NORMAL FEV1

CONFIDENTIAL

SB 207499

TABLE 13.9A

DESCRIPTIVE STATISTICS FOR SMOKING HISTORY AT SCREENING BY TREATMENT GROUP - ALL RANDOMISED PATIENTS

PROTOCOL 181

Parameter		TREATMENT GROUP PLACEBO (N=62)	SB 207499 (N=65)	Total (N=127)
SMOKING STATUS AT BASELINE	FORMER SMOKER	34 (54.8%)	33 (50.8%)	67 (52.8%)
	CURRENT SMOKER	28 (45.2%)	32 (49.2%)	60 (47.2%)
PACK YEARS	N	62	65	127
	MEAN	41.3	46.3	43.9
	STD	22.1	28.2	25.4
	MEDIAN	40.0	40.0	40.0
	MIN	12.0	10.0	10.0
	MAX	108.0	128.0	128.0
CIGARETTES/DAY	N	62	65	127
	MEAN	20.8	23.3	22.1
	STD	11.5	12.3	12.0
	MEDIAN	20.0	20.0	20.0
	MIN	4.0	1.0	1.0
	MAX	60.0	60.0	60.0

PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED

CONFIDENTIAL
GM2004/00090/00
SB-207499/181

SB 207499

TABLE 13.9B

DESCRIPTIVE STATISTICS FOR SMOKING HISTORY AT SCREENING BY TREATMENT GROUP - PP

PROTOCOL 181

Parameter		TREATMENT GROUP PLACEBO (N=58)	SB 207499 (N=61)	Total (N=119)
SMOKING STATUS AT BASELINE	FORMER SMOKER	32 (55.2%)	30 (49.2%)	62 (52.1%)
	CURRENT SMOKER	26 (44.8%)	31 (50.8%)	57 (47.9%)
PACK YEARS	N	58	61	119
	MEAN	42.1	47.3	44.7
	STD	22.5	28.8	25.9
	MEDIAN	41.0	40.0	40.0
	MIN	12.0	10.0	10.0
	MAX	108.0	128.0	128.0
CIGARETTES/DAY	N	58	61	119
	MEAN	21.1	23.7	22.4
	STD	11.5	12.6	12.1
	MEDIAN	20.0	20.0	20.0
	MIN	5.0	1.0	1.0
	MAX	60.0	60.0	60.0

PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED

CONFIDENTIAL

SB 207499

TABLE 13.10A

SUMMARY OF PULMONARY HISTORY BY TREATMENT GROUP - ALL RANDOMISED PATIENTS

PROTOCOL 181

Characteristic		TREATMENT GROUP PLACEBO (N=62)	SB 207499 (N=65)	Total (N=127)
Duration COPD (years)	No response	1 (1.6%)	1 (1.5%)	2 (1.6%)
	<5 years	32 (51.6%)	24 (36.9%)	56 (44.1%)
	>=5 to <10 years	14 (22.6%)	25 (38.5%)	39 (30.7%)
	>=10 to <15 years	9 (14.5%)	9 (13.8%)	18 (14.2%)
	>=15 to <20 years	4 (6.5%)	5 (7.7%)	9 (7.1%)
	>=20 to <25 years	2 (3.2%)	0 .	2 (1.6%)
	>=25 years	0 .	1 (1.5%)	1 (0.8%)
Exacerbations In The Last 12 Months That Were Self-managed	N	8	6	14
	MEAN	1.0	1.0	1.0
	STD	0.0	0.0	0.0
	MEDIAN	1.0	1.0	1.0
	MIN	1.0	1.0	1.0
	MAX	1.0	1.0	1.0
Exacerbations In The Last 12 Months That Required Oral Corticosteroids And/Or Antibiotics	N	13	10	23
	MEAN	1.0	1.0	1.0
	STD	0.0	0.0	0.0
	MEDIAN	1.0	1.0	1.0
	MIN	1.0	1.0	1.0
	MAX	1.0	1.0	1.0
Exacerbations In The Last 12 Months That Required Hospitalisaton	N	7	5	12
	MEAN	1.0	1.0	1.0
	STD	0.0	0.0	0.0
	MEDIAN	1.0	1.0	1.0
	MIN	1.0	1.0	1.0
	MAX	1.0	1.0	1.0
Type of COPD	Chronic bronchitis	34 (54.8%)	35 (53.8%)	69 (54.3%)
	Emphysema	27 (43.5%)	29 (44.6%)	56 (44.1%)
	No response	1 (1.6%)	1 (1.5%)	2 (1.6%)

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED

CONFIDENTIAL

SB 207499

TABLE 13.10B

SUMMARY OF PULMONARY HISTORY BY TREATMENT GROUP - PP

PROTOCOL 181

Characteristic		TREATMENT GROUP PLACEBO (N=58)	SB 207499 (N=61)	Total (N=119)
Duration COPD (years)	No response	1 (1.7%)	1 (1.6%)	2 (1.7%)
	<5 years	30 (51.7%)	22 (36.1%)	52 (43.7%)
	>=5 to <10 years	13 (22.4%)	24 (39.3%)	37 (31.1%)
	>=10 to <15 years	9 (15.5%)	9 (14.8%)	18 (15.1%)
	>=15 to <20 years	3 (5.2%)	4 (6.6%)	7 (5.9%)
	>=20 to <25 years	2 (3.4%)	0 .	2 (1.7%)
	>=25 years	0 .	1 (1.6%)	1 (0.8%)
Exacerbations In The Last 12 Months That Were Self-managed	N	6	6	12
	MEAN	1.0	1.0	1.0
	STD	0.0	0.0	0.0
	MEDIAN	1.0	1.0	1.0
	MIN	1.0	1.0	1.0
	MAX	1.0	1.0	1.0
Exacerbations In The Last 12 Months That Required Oral Corticosteroids And/Or Antibiotics	N	10	8	18
	MEAN	1.0	1.0	1.0
	STD	0.0	0.0	0.0
	MEDIAN	1.0	1.0	1.0
	MIN	1.0	1.0	1.0
	MAX	1.0	1.0	1.0
Exacerbations In The Last 12 Months That Required Hospitalisaton	N	6	4	10
	MEAN	1.0	1.0	1.0
	STD	0.0	0.0	0.0
	MEDIAN	1.0	1.0	1.0
	MIN	1.0	1.0	1.0
	MAX	1.0	1.0	1.0
Type of COPD	Chronic bronchitis	33 (56.9%)	32 (52.5%)	65 (54.6%)
	Emphysema	24 (41.4%)	28 (45.9%)	52 (43.7%)
	No response	1 (1.7%)	1 (1.6%)	2 (1.7%)

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED

CONFIDENTIAL

SB 207499

TABLE 13.12

SUMMARY OF BASELINE SIGNS AND SYMPTOMS BY MEDDRA SYSTEM ORGAN CLASS AND VERBATIM TERM
ALL RANDOMISED PATIENTS
PROTOCOL 181

MEDDRA SYSTEM ORGAN CLASS	VERBATIM TERM	PLACEBO (N=62)	SB 207499 (N=65)	NON-RAND. (N=33)	Total (N=160)
TOTAL	TOTAL	31 (50.0%)	34 (52.3%)	14 (42.4%)	79 (49.4%)
GASTROINTESTINAL DISORDERS	TOTAL	7 (11.3%)	20 (30.8%)	6 (18.2%)	33 (20.6%)
	NAUSEA	1 (1.6%)	8 (12.3%)	0 .	9 (5.6%)
	DIARRHEA	1 (1.6%)	1 (1.5%)	2 (6.1%)	4 (2.5%)
	LOOSE STOOLS	1 (1.6%)	1 (1.5%)	0 .	2 (1.3%)
	STOMACHE PAIN	1 (1.6%)	1 (1.5%)	0 .	2 (1.3%)
	VOMITING	1 (1.6%)	1 (1.5%)	0 .	2 (1.3%)
	ABDOMINAL CRAMPS	0 .	1 (1.5%)	0 .	1 (0.6%)
	ABNORMOLY SOFT STOOLS	0 .	1 (1.5%)	0 .	1 (0.6%)
	CONSTIPATION	0 .	0 .	1 (3.0%)	1 (0.6%)
	CONSTIPATION, WORSE	0 .	1 (1.5%)	0 .	1 (0.6%)
	DIARRHEA (INTERMITTENT)	0 .	1 (1.5%)	0 .	1 (0.6%)
	DIARRHOEA	0 .	0 .	1 (3.0%)	1 (0.6%)
	DRY MOUTH DURING THE NIGHT	0 .	1 (1.5%)	0 .	1 (0.6%)
	EXACERBATION OF OESOPHAGEAL REFLUX	0 .	1 (1.5%)	0 .	1 (0.6%)
	GASTRIC REFLUX	0 .	0 .	1 (3.0%)	1 (0.6%)
	GASTRITIS	0 .	1 (1.5%)	0 .	1 (0.6%)
	HEART BURN	0 .	1 (1.5%)	0 .	1 (0.6%)
	HEARTBURN	0 .	0 .	1 (3.0%)	1 (0.6%)
	INDIGESTION	0 .	1 (1.5%)	0 .	1 (0.6%)
	LOOSE STOOLS OCCASIONALLY	1 (1.6%)	0 .	0 .	1 (0.6%)
	MILD DIARRHEA	0 .	0 .	1 (3.0%)	1 (0.6%)
	MOUTH ULCERS	0 .	1 (1.5%)	0 .	1 (0.6%)
	PAIN AFTER DENTAL TREATMENT	0 .	1 (1.5%)	0 .	1 (0.6%)
	RECTAL BLEEDING	0 .	0 .	1 (3.0%)	1 (0.6%)
	RIGHT FEMORAL HERNIORRHAPHY	1 (1.6%)	0 .	0 .	1 (0.6%)
	SORE ON LEFT LIP	1 (1.6%)	0 .	0 .	1 (0.6%)
	STOMACH DISEASE	1 (1.6%)	0 .	0 .	1 (0.6%)
	STOMACH-ACHE	0 .	1 (1.5%)	0 .	1 (0.6%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER SYSTEM ORGAN CLASS/VERBATIM TERM
2. TOTAL ROWS REPRESENT TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE WITHIN SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED FOR PLACEBO AND SB 207499 COLUMNS AND TOTAL NUMBER OF PATIENTS ENTERING RUN-IN FOR TOTAL COLUMN

CONFIDENTIAL
GM2004/00090/00
SB-207499/181

SB 207499

TABLE 13.12

SUMMARY OF BASELINE SIGNS AND SYMPTOMS BY MEDDRA SYSTEM ORGAN CLASS AND VERBATIM TERM
ALL RANDOMISED PATIENTS
PROTOCOL 181

MEDDRA SYSTEM ORGAN CLASS	VERBATIM TERM	PLACEBO (N=62)	SB 207499 (N=65)	NON-RAND. (N=33)	Total (N=160)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	TOTAL	10 (16.1%)	9 (13.8%)	4 (12.1%)	23 (14.4%)
	SORE THROAT	2 (3.2%)	4 (6.2%)	1 (3.0%)	7 (4.4%)
	COUGH	3 (4.8%)	3 (4.6%)	0 .	6 (3.8%)
	HEMOPTYSIS	2 (3.2%)	1 (1.5%)	0 .	3 (1.9%)
	(R) NOSTRIL PAIN	0 .	1 (1.5%)	0 .	1 (0.6%)
	BLOOD IN SPUTUM	1 (1.6%)	0 .	0 .	1 (0.6%)
	BREATHLESSNESS	1 (1.6%)	0 .	0 .	1 (0.6%)
	COPD EXACERBATION	0 .	0 .	1 (3.0%)	1 (0.6%)
	ENGORGED RIGHT VOCAL CORD CYST	0 .	1 (1.5%)	0 .	1 (0.6%)
	HOARSENESS	0 .	1 (1.5%)	0 .	1 (0.6%)
	INCREASED CLEARING OF THROAT	0 .	0 .	1 (3.0%)	1 (0.6%)
	INCREASED COUGH	0 .	0 .	1 (3.0%)	1 (0.6%)
	INCREASED PRODUCTION OF SPUTUM	1 (1.6%)	0 .	0 .	1 (0.6%)
	INCREASED SHORTNESS OF BREATH	0 .	0 .	1 (3.0%)	1 (0.6%)
	NASAL CONGESTION	1 (1.6%)	0 .	0 .	1 (0.6%)
	SCANT BLOOD IN SPUTUM	0 .	0 .	1 (3.0%)	1 (0.6%)
	SHORTNESS OF BREATH	0 .	1 (1.5%)	0 .	1 (0.6%)
	SORE NOSE	1 (1.6%)	0 .	0 .	1 (0.6%)
NERVOUS SYSTEM DISORDERS	TOTAL	7 (11.3%)	9 (13.8%)	3 (9.1%)	19 (11.9%)
	HEADACHE	7 (11.3%)	4 (6.2%)	1 (3.0%)	12 (7.5%)
	DIZZINESS	0 .	1 (1.5%)	0 .	1 (0.6%)
	DROWSINESS	0 .	0 .	1 (3.0%)	1 (0.6%)
	HEADACH	0 .	1 (1.5%)	0 .	1 (0.6%)
	HEADACHE (INTERMITTENT)	0 .	1 (1.5%)	0 .	1 (0.6%)
	LETHARGY	0 .	1 (1.5%)	0 .	1 (0.6%)
	MILD HEADACHES	0 .	1 (1.5%)	0 .	1 (0.6%)
	NAUSEA	0 .	1 (1.5%)	0 .	1 (0.6%)
	POUR SENSE OF TASTE	0 .	0 .	1 (3.0%)	1 (0.6%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER SYSTEM ORGAN CLASS/VERBATIM TERM
2. TOTAL ROWS REPRESENT TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE WITHIN SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED FOR PLACEBO AND SB 207499 COLUMNS AND TOTAL NUMBER OF PATIENTS ENTERING RUN-IN FOR TOTAL COLUMN

CONFIDENTIAL

SB 207499

TABLE 13.12

SUMMARY OF BASELINE SIGNS AND SYMPTOMS BY MEDDRA SYSTEM ORGAN CLASS AND VERBATIM TERM
ALL RANDOMISED PATIENTS
PROTOCOL 181

MEDDRA SYSTEM ORGAN CLASS	VERBATIM TERM	PLACEBO (N=62)	SB 207499 (N=65)	NON-RAND. (N=33)	Total (N=160)
INFECTIONS AND INFESTATIONS	TOTAL	5 (8.1%)	5 (7.7%)	5 (15.2%)	15 (9.4%)
	COMMON COLD	0 .	4 (6.2%)	0 .	4 (2.5%)
	RHINITIS	1 (1.6%)	1 (1.5%)	0 .	2 (1.3%)
	CORYZAL SYMPTOMS	1 (1.6%)	0 .	0 .	1 (0.6%)
	FLUE	1 (1.6%)	0 .	0 .	1 (0.6%)
	HEAD COLD	0 .	0 .	1 (3.0%)	1 (0.6%)
	INFLUENZA	0 .	0 .	1 (3.0%)	1 (0.6%)
	PNEUMONIA	0 .	0 .	1 (3.0%)	1 (0.6%)
	PROLONGED UPPER AIRWAY VIRAL INFECTION	0 .	0 .	1 (3.0%)	1 (0.6%)
	SKIN INFECTION (UNDER THE CAST)	1 (1.6%)	0 .	0 .	1 (0.6%)
	UPPER RESP. TRACT INFECTION	1 (1.6%)	0 .	0 .	1 (0.6%)
	UPPER RESPIRATORY TRACT INFECTION	0 .	0 .	1 (3.0%)	1 (0.6%)
	VIRAL DISEASE	1 (1.6%)	0 .	0 .	1 (0.6%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	TOTAL	5 (8.1%)	6 (9.2%)	3 (9.1%)	14 (8.8%)
	BACK PAIN	2 (3.2%)	0 .	1 (3.0%)	3 (1.9%)
	BACKACHE	0 .	1 (1.5%)	0 .	1 (0.6%)
	INTERMITTENT BILATERAL THIGH PAIN INCREASE	0 .	1 (1.5%)	0 .	1 (0.6%)
	MUSCLE ACHES	0 .	1 (1.5%)	0 .	1 (0.6%)
	MUSCLE SORENESS	0 .	0 .	1 (3.0%)	1 (0.6%)
	NECK PAIN	0 .	1 (1.5%)	0 .	1 (0.6%)
	PAIN IN FOOT	0 .	1 (1.5%)	0 .	1 (0.6%)
	PAINFUL (R) ACHILES TENDON	1 (1.6%)	0 .	0 .	1 (0.6%)
	PAINFUL RIGHT THUMB	1 (1.6%)	0 .	0 .	1 (0.6%)
	SPINAL PAIN	1 (1.6%)	0 .	0 .	1 (0.6%)
	SPONDYLOSIS PAIN	0 .	1 (1.5%)	0 .	1 (0.6%)
	SWOLLEN LEFT THUMB JOINT	0 .	0 .	1 (3.0%)	1 (0.6%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER SYSTEM ORGAN CLASS/VERBATIM TERM
2. TOTAL ROWS REPRESENT TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE WITHIN SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED FOR PLACEBO AND SB 207499 COLUMNS AND TOTAL NUMBER OF PATIENTS ENTERING RUN-IN FOR TOTAL COLUMN

CONFIDENTIAL

SB 207499

TABLE 13.12

SUMMARY OF BASELINE SIGNS AND SYMPTOMS BY MEDDRA SYSTEM ORGAN CLASS AND VERBATIM TERM
ALL RANDOMISED PATIENTS
PROTOCOL 181

MEDDRA SYSTEM ORGAN CLASS	VERBATIM TERM	PLACEBO (N=62)	SB 207499 (N=65)	NON-RAND. (N=33)	Total (N=160)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	TOTAL	3 (4.8%)	1 (1.5%)	4 (12.1%)	8 (5.0%)
	FEVER	1 (1.6%)	1 (1.5%)	2 (6.1%)	4 (2.5%)
	BODY PAIN	1 (1.6%)	0 .	0 .	1 (0.6%)
	CHEST SORENESS	0 .	0 .	1 (3.0%)	1 (0.6%)
	FATIGUE	0 .	0 .	1 (3.0%)	1 (0.6%)
	LEFT SIDE CHEST PAIN	0 .	0 .	1 (3.0%)	1 (0.6%)
	TIREDNESS	1 (1.6%)	0 .	0 .	1 (0.6%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	TOTAL	2 (3.2%)	3 (4.6%)	2 (6.1%)	7 (4.4%)
	SWEATING	0 .	1 (1.5%)	1 (3.0%)	2 (1.3%)
	ANGIODEMA	0 .	0 .	1 (3.0%)	1 (0.6%)
	ANGIOEDEMA	0 .	0 .	1 (3.0%)	1 (0.6%)
	RASH ON BACK	1 (1.6%)	0 .	0 .	1 (0.6%)
	SWEATING IN THE MORNINGS	0 .	1 (1.5%)	0 .	1 (0.6%)
	SWELLING ON FACIAL AREA RIGHT SIDE	1 (1.6%)	0 .	0 .	1 (0.6%)
	SWOLLEN RIGHT CHEEK	0 .	1 (1.5%)	0 .	1 (0.6%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	TOTAL	6 (9.7%)	0 .	0 .	6 (3.8%)
	CHEST PAIN (POST BRONCHOSCOPY)	1 (1.6%)	0 .	0 .	1 (0.6%)
	FRACTURE OF RADIUS	1 (1.6%)	0 .	0 .	1 (0.6%)
	FRACTURED RIGHT WRIST	1 (1.6%)	0 .	0 .	1 (0.6%)
	INJURY TO RIGHT KNEE	1 (1.6%)	0 .	0 .	1 (0.6%)
	PULLED MUSCLE IN BACK	1 (1.6%)	0 .	0 .	1 (0.6%)
	RIGHT THUMB SPRAIN	1 (1.6%)	0 .	0 .	1 (0.6%)
INVESTIGATIONS	TOTAL	2 (3.2%)	2 (3.1%)	0 .	4 (2.5%)
	ABNORMAL APTR ACTIVATED PARTIAL THROMBOPLASTIN TIME	0 .	1 (1.5%)	0 .	1 (0.6%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER SYSTEM ORGAN CLASS/VERBATIM TERM
2. TOTAL ROWS REPRESENT TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE WITHIN SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED FOR PLACEBO AND SB 207499 COLUMNS AND TOTAL NUMBER OF PATIENTS ENTERING RUN-IN FOR TOTAL COLUMN

CONFIDENTIAL
GM2004/00090/00
SB-207499/181

SB 207499

TABLE 13.12

SUMMARY OF BASELINE SIGNS AND SYMPTOMS BY MEDDRA SYSTEM ORGAN CLASS AND VERBATIM TERM
ALL RANDOMISED PATIENTS
PROTOCOL 181

MEDDRA SYSTEM ORGAN CLASS	VERBATIM TERM	PLACEBO (N=62)	SB 207499 (N=65)	NON-RAND. (N=33)	Total (N=160)
INVESTIGATIONS	FECOL OCCULT BLOOD TEST POSITIVE	1 (1.6%)	0 .	0 .	1 (0.6%)
	INCREASED BLOOD GLUCOSE	1 (1.6%)	0 .	0 .	1 (0.6%)
	POSITIVE FOB RESULT (NO ABDOMINAL PAIN)	0 .	1 (1.5%)	0 .	1 (0.6%)
PSYCHIATRIC DISORDERS	TOTAL	0 .	2 (3.1%)	1 (3.0%)	3 (1.9%)
	DIFFICULTY SLEEPING	0 .	1 (1.5%)	0 .	1 (0.6%)
	SLEEP DISTURBANCE	0 .	1 (1.5%)	0 .	1 (0.6%)
	WORSENING OF INSOMNIA	0 .	0 .	1 (3.0%)	1 (0.6%)
RENAL AND URINARY DISORDERS	TOTAL	3 (4.8%)	0 .	0 .	3 (1.9%)
	FREQUENT NEED TO URINATE	1 (1.6%)	0 .	0 .	1 (0.6%)
	HEMATURI	1 (1.6%)	0 .	0 .	1 (0.6%)
	TRACE OF KETONE IN URINE	1 (1.6%)	0 .	0 .	1 (0.6%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	TOTAL	1 (1.6%)	1 (1.5%)	0 .	2 (1.3%)
	LYMPHADENOPATHY	0 .	1 (1.5%)	0 .	1 (0.6%)
	THROMBOCYTOSIS	1 (1.6%)	0 .	0 .	1 (0.6%)
METABOLISM AND NUTRITION DISORDERS	TOTAL	0 .	1 (1.5%)	0 .	1 (0.6%)
	INCREASED APPETITE	0 .	1 (1.5%)	0 .	1 (0.6%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	TOTAL	1 (1.6%)	0 .	0 .	1 (0.6%)
	LUNG CANCER (SCLC) SCLC = SMALL CELL LUNG CANCER	1 (1.6%)	0 .	0 .	1 (0.6%)
VASCULAR DISORDERS	TOTAL	0 .	1 (1.5%)	0 .	1 (0.6%)
	HIGH BLOOD PRESSURE	0 .	1 (1.5%)	0 .	1 (0.6%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER SYSTEM ORGAN CLASS/VERBATIM TERM
2. TOTAL ROWS REPRESENT TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE WITHIN SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED FOR PLACEBO AND SB 207499 COLUMNS AND TOTAL NUMBER OF PATIENTS ENTERING RUN-IN FOR TOTAL COLUMN

CONFIDENTIAL
GM2004/00090/00
SB-207499/181

SB 207499

TABLE 13.13A

SUMMARY OF PRIOR MEDICATIONS BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMISED PATIENTS

PROTOCOL 181

GENERIC TERM	TREATMENT GROUP PLACEBO (N=62)	SB 207499 (N=65)	Total (N=127)
TOTAL	61 (98.4%)	65 (100.0%)	126 (99.2%)
SALBUTAMOL	45 (72.6%)	45 (69.2%)	90 (70.9%)
IPRATROPIUM BROMIDE	38 (61.3%)	44 (67.7%)	82 (64.6%)
PARACETAMOL	22 (35.5%)	22 (33.8%)	44 (34.6%)
ACETYLSALICYLIC ACID	12 (19.4%)	13 (20.0%)	25 (19.7%)
SALBUTAMOL SULFATE	11 (17.7%)	12 (18.5%)	23 (18.1%)
CODEINE PHOSPHATE	7 (11.3%)	9 (13.8%)	16 (12.6%)
FLUTICASONE PROPIONATE	5 (8.1%)	9 (13.8%)	14 (11.0%)
SALMETEROL XINAFOATE	8 (12.9%)	7 (10.8%)	15 (11.8%)
CAFFEINE	1 (1.6%)	5 (7.7%)	6 (4.7%)
FENOTEROL HYDROBROMIDE	9 (14.5%)	5 (7.7%)	14 (11.0%)
HYDROCHLOROTHIAZIDE	1 (1.6%)	5 (7.7%)	6 (4.7%)
AMBIGUOUS MEDICATION	1 (1.6%)	4 (6.2%)	5 (3.9%)
BECLOMETASONE DIPROPIONATE	5 (8.1%)	4 (6.2%)	9 (7.1%)
EFORMOTEROL FUMARATE	2 (3.2%)	4 (6.2%)	6 (4.7%)
FENTANYL	2 (3.2%)	4 (6.2%)	6 (4.7%)
LEVOTHYROXINE SODIUM	2 (3.2%)	4 (6.2%)	6 (4.7%)
SIMVASTATIN	2 (3.2%)	4 (6.2%)	6 (4.7%)
THEOPHYLLINE	5 (8.1%)	4 (6.2%)	9 (7.1%)
TIOTROPIUM BROMIDE	3 (4.8%)	4 (6.2%)	7 (5.5%)
ATORVASTATIN CALCIUM	2 (3.2%)	3 (4.6%)	5 (3.9%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED AND ASSESSED FOR PRIOR MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED POST-RANDOMISATION AND MEDICATIONS DISCONTINUED PRIOR TO RANDOMISATION
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.13A

SUMMARY OF PRIOR MEDICATIONS BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMISED PATIENTS

PROTOCOL 181

GENERIC TERM	TREATMENT GROUP PLACEBO (N=62)	SB 207499 (N=65)	Total (N=127)
BISOPROLOL FUMARATE	0 .	3 (4.6%)	3 (2.4%)
BUDESONIDE	6 (9.7%)	3 (4.6%)	9 (7.1%)
CALCIUM	0 .	3 (4.6%)	3 (2.4%)
ENALAPRIL	3 (4.8%)	3 (4.6%)	6 (4.7%)
OMEPRAZOLE	1 (1.6%)	3 (4.6%)	4 (3.1%)
ALFENTANIL	2 (3.2%)	2 (3.1%)	4 (3.1%)
ALLOPURINOL	0 .	2 (3.1%)	2 (1.6%)
ALUMINIUM HYDROXIDE GEL, DRIED	0 .	2 (3.1%)	2 (1.6%)
AMILORIDE HYDROCHLORIDE	0 .	2 (3.1%)	2 (1.6%)
AMOXICILLIN TRIHYDRATE	1 (1.6%)	2 (3.1%)	3 (2.4%)
CITALOPRAM HYDROBROMIDE	0 .	2 (3.1%)	2 (1.6%)
CLAVULANATE POTASSIUM	1 (1.6%)	2 (3.1%)	3 (2.4%)
DIPHENHYDRAMINE HYDROCHLORIDE	0 .	2 (3.1%)	2 (1.6%)
ENALAPRIL MALEATE	2 (3.2%)	2 (3.1%)	4 (3.1%)
FELODIPINE	0 .	2 (3.1%)	2 (1.6%)
FUROSEMIDE	0 .	2 (3.1%)	2 (1.6%)
INDAPAMIDE	0 .	2 (3.1%)	2 (1.6%)
MAGNESIUM	1 (1.6%)	2 (3.1%)	3 (2.4%)
MAGNESIUM HYDROXIDE	0 .	2 (3.1%)	2 (1.6%)
MINERALS NOS	0 .	2 (3.1%)	2 (1.6%)
MORPHINE	1 (1.6%)	2 (3.1%)	3 (2.4%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
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CONFIDENTIAL

SB 207499

TABLE 13.13A

SUMMARY OF PRIOR MEDICATIONS BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMISED PATIENTS

PROTOCOL 181

GENERIC TERM	TREATMENT GROUP PLACEBO (N=62)	SB 207499 (N=65)	Total (N=127)
NAPROXEN	2 (3.2%)	2 (3.1%)	4 (3.1%)
PRAVASTATIN SODIUM	0 .	2 (3.1%)	2 (1.6%)
RAMIPRIL	6 (9.7%)	2 (3.1%)	8 (6.3%)
SIMETICONE	0 .	2 (3.1%)	2 (1.6%)
TELMISARTAN	0 .	2 (3.1%)	2 (1.6%)
TERBUTALINE SULFATE	3 (4.8%)	2 (3.1%)	5 (3.9%)
VENLAFAXINE HYDROCHLORIDE	0 .	2 (3.1%)	2 (1.6%)
VITAMIN D NOS	1 (1.6%)	2 (3.1%)	3 (2.4%)
ZOPICLONE	1 (1.6%)	2 (3.1%)	3 (2.4%)
ACETYLCYSTEINE	1 (1.6%)	1 (1.5%)	2 (1.6%)
ACYCLOVIR	1 (1.6%)	1 (1.5%)	2 (1.6%)
ALENDRONATE SODIUM	1 (1.6%)	1 (1.5%)	2 (1.6%)
ALLIUM SATIVUM	0 .	1 (1.5%)	1 (0.8%)
AMITRIPTYLINE HYDROCHLORIDE	1 (1.6%)	1 (1.5%)	2 (1.6%)
AMLODIPINE BESILATE	1 (1.6%)	1 (1.5%)	2 (1.6%)
ASCORBIC ACID	3 (4.8%)	1 (1.5%)	4 (3.1%)
ATENOLOL	1 (1.6%)	1 (1.5%)	2 (1.6%)
BENDROFLUMETHIAZIDE	2 (3.2%)	1 (1.5%)	3 (2.4%)
BROMAZEPAM	0 .	1 (1.5%)	1 (0.8%)
CALCITRIOL	0 .	1 (1.5%)	1 (0.8%)
CALCIUM CARBONATE	1 (1.6%)	1 (1.5%)	2 (1.6%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
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CONFIDENTIAL

SB 207499

TABLE 13.13A

SUMMARY OF PRIOR MEDICATIONS BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMISED PATIENTS

PROTOCOL 181

GENERIC TERM	TREATMENT GROUP PLACEBO (N=62)	SB 207499 (N=65)	Total (N=127)
CANDESARTAN CILEXETIL	0 .	1 (1.5%)	1 (0.8%)
CEFALEXIN	1 (1.6%)	1 (1.5%)	2 (1.6%)
CILOMILAST	3 (4.8%)	1 (1.5%)	4 (3.1%)
CITALOPRAM	2 (3.2%)	1 (1.5%)	3 (2.4%)
CLONAZEPAM	1 (1.6%)	1 (1.5%)	2 (1.6%)
COCILLANA	1 (1.6%)	1 (1.5%)	2 (1.6%)
COLECALCIFEROL	1 (1.6%)	1 (1.5%)	2 (1.6%)
CYCLOBENZAPRINE HYDROCHLORIDE	0 .	1 (1.5%)	1 (0.8%)
DIHYDROCODEINE BITARTRATE	0 .	1 (1.5%)	1 (0.8%)
DORZOLAMIDE HYDROCHLORIDE	0 .	1 (1.5%)	1 (0.8%)
DOXAZOSIN MESILATE	0 .	1 (1.5%)	1 (0.8%)
DOXYLAMINE SUCCINATE	0 .	1 (1.5%)	1 (0.8%)
EPINEPHRINE HYDROCHLORIDE	0 .	1 (1.5%)	1 (0.8%)
EQUISETUM ARVENSE	0 .	1 (1.5%)	1 (0.8%)
ESOMEPRAZOLE MAGNESIUM	2 (3.2%)	1 (1.5%)	3 (2.4%)
ESTRADIOL	1 (1.6%)	1 (1.5%)	2 (1.6%)
ESTROGENS CONJUGATED	1 (1.6%)	1 (1.5%)	2 (1.6%)
ETHYLMORPHINE HYDROCHLORIDE	1 (1.6%)	1 (1.5%)	2 (1.6%)
FINASTERIDE	0 .	1 (1.5%)	1 (0.8%)
FIORINAL NOS	0 .	1 (1.5%)	1 (0.8%)
FISH OIL	0 .	1 (1.5%)	1 (0.8%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
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CONFIDENTIAL
GM2004/00090/00
SB-207499/181

SB 207499

TABLE 13.13A

SUMMARY OF PRIOR MEDICATIONS BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMISED PATIENTS

PROTOCOL 181

GENERIC TERM	TREATMENT GROUP PLACEBO (N=62)	SB 207499 (N=65)	Total (N=127)
FLECAINIDE	0 .	1 (1.5%)	1 (0.8%)
FLUOXETINE	0 .	1 (1.5%)	1 (0.8%)
FLUOXETINE HYDROCHLORIDE	0 .	1 (1.5%)	1 (0.8%)
FORMOTEROL	0 .	1 (1.5%)	1 (0.8%)
GLUCOSAMINE	0 .	1 (1.5%)	1 (0.8%)
IBUPROFEN	3 (4.8%)	1 (1.5%)	4 (3.1%)
INFLUENZA VACCINE	0 .	1 (1.5%)	1 (0.8%)
INFLUENZA VIRUS VACCINE INACTIVATED	2 (3.2%)	1 (1.5%)	3 (2.4%)
ISOSORBIDE DINITRATE	0 .	1 (1.5%)	1 (0.8%)
LACTULOSE	0 .	1 (1.5%)	1 (0.8%)
LANSOPRAZOLE	0 .	1 (1.5%)	1 (0.8%)
LATANOPROST	1 (1.6%)	1 (1.5%)	2 (1.6%)
LEVOTHYROXINE	0 .	1 (1.5%)	1 (0.8%)
LISINOPRIL	3 (4.8%)	1 (1.5%)	4 (3.1%)
LYSINE HYDROCHLORIDE	0 .	1 (1.5%)	1 (0.8%)
MAGNESIUM CARBONATE	0 .	1 (1.5%)	1 (0.8%)
MELOXICAM	0 .	1 (1.5%)	1 (0.8%)
METAMIZOLE SODIUM	0 .	1 (1.5%)	1 (0.8%)
METFORMIN	3 (4.8%)	1 (1.5%)	4 (3.1%)
METHADONE HYDROCHLORIDE	0 .	1 (1.5%)	1 (0.8%)
METOPROLOL	1 (1.6%)	1 (1.5%)	2 (1.6%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
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CONFIDENTIAL

SB 207499

TABLE 13.13A

SUMMARY OF PRIOR MEDICATIONS BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMISED PATIENTS

PROTOCOL 181

GENERIC TERM	TREATMENT GROUP PLACEBO (N=62)	SB 207499 (N=65)	Total (N=127)
MICONAZOLE NITRATE	0 .	1 (1.5%)	1 (0.8%)
MOMETASONE FUROATE	1 (1.6%)	1 (1.5%)	2 (1.6%)
NALOXONE	0 .	1 (1.5%)	1 (0.8%)
NIFEDIPINE	4 (6.5%)	1 (1.5%)	5 (3.9%)
NITRENDIPINE	0 .	1 (1.5%)	1 (0.8%)
NONOXINOL	0 .	1 (1.5%)	1 (0.8%)
NORETHISTERONE	0 .	1 (1.5%)	1 (0.8%)
NYSTATIN	0 .	1 (1.5%)	1 (0.8%)
OXAZEPAM	1 (1.6%)	1 (1.5%)	2 (1.6%)
PAMIDRONIC ACID	0 .	1 (1.5%)	1 (0.8%)
PAROXETINE HYDROCHLORIDE	0 .	1 (1.5%)	1 (0.8%)
PHENOXYMETHYLPENICILLIN	0 .	1 (1.5%)	1 (0.8%)
PHENYLPROPANOLAMINE HYDROCHLORIDE	0 .	1 (1.5%)	1 (0.8%)
PHENYLTOLOXAMINE CITRATE	0 .	1 (1.5%)	1 (0.8%)
PHOLCODINE	0 .	1 (1.5%)	1 (0.8%)
PILOCARPINE	0 .	1 (1.5%)	1 (0.8%)
PRAVASTATIN	0 .	1 (1.5%)	1 (0.8%)
PREDNISOLONE	0 .	1 (1.5%)	1 (0.8%)
QUINAPRIL	0 .	1 (1.5%)	1 (0.8%)
RABEPRAZOLE	0 .	1 (1.5%)	1 (0.8%)
RANITIDINE HYDROCHLORIDE	1 (1.6%)	1 (1.5%)	2 (1.6%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
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CONFIDENTIAL

SB 207499

TABLE 13.13A

SUMMARY OF PRIOR MEDICATIONS BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMISED PATIENTS

PROTOCOL 181

GENERIC TERM	TREATMENT GROUP PLACEBO (N=62)	SB 207499 (N=65)	Total (N=127)
RESERPINE	0 .	1 (1.5%)	1 (0.8%)
ROFECOXIB	1 (1.6%)	1 (1.5%)	2 (1.6%)
SENEGA	1 (1.6%)	1 (1.5%)	2 (1.6%)
SERTRALINE HYDROCHLORIDE	0 .	1 (1.5%)	1 (0.8%)
SOTALOL	0 .	1 (1.5%)	1 (0.8%)
SOTALOL HYDROCHLORIDE	0 .	1 (1.5%)	1 (0.8%)
TAMOXIFEN CITRATE	0 .	1 (1.5%)	1 (0.8%)
TERBUTALINE	7 (11.3%)	1 (1.5%)	8 (6.3%)
TESTOSTERONE UNDECANOATE	0 .	1 (1.5%)	1 (0.8%)
TIMOLOL MALEATE	0 .	1 (1.5%)	1 (0.8%)
VALSARTAN	0 .	1 (1.5%)	1 (0.8%)
VERAPAMIL HYDROCHLORIDE	1 (1.6%)	1 (1.5%)	2 (1.6%)
VITAMINS NOS	0 .	1 (1.5%)	1 (0.8%)
ZINC	0 .	1 (1.5%)	1 (0.8%)
ZINGIBER OFFICINALE	0 .	1 (1.5%)	1 (0.8%)
ALPRAZOLAM	1 (1.6%)	0 .	1 (0.8%)
AMINOPHYLLINE	1 (1.6%)	0 .	1 (0.8%)
ATORVASTATIN	1 (1.6%)	0 .	1 (0.8%)
BECLOMETASONE	1 (1.6%)	0 .	1 (0.8%)
BENSERAZIDE HYDROCHLORIDE	1 (1.6%)	0 .	1 (0.8%)
BUPROPION HYDROCHLORIDE	3 (4.8%)	0 .	3 (2.4%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
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CONFIDENTIAL

SB 207499

TABLE 13.13A

SUMMARY OF PRIOR MEDICATIONS BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMISED PATIENTS

PROTOCOL 181

GENERIC TERM	TREATMENT GROUP PLACEBO (N=62)	SB 207499 (N=65)	Total (N=127)
CALCIPOTRIOL	1 (1.6%)	0 .	1 (0.8%)
CAMPHOR	1 (1.6%)	0 .	1 (0.8%)
CARBAMAZEPINE	1 (1.6%)	0 .	1 (0.8%)
CEFACLOR	1 (1.6%)	0 .	1 (0.8%)
CELECOXIB	1 (1.6%)	0 .	1 (0.8%)
CIPROFLOXACIN	1 (1.6%)	0 .	1 (0.8%)
CLINDAMYCIN	1 (1.6%)	0 .	1 (0.8%)
CLOPIDOGREL SULFATE	1 (1.6%)	0 .	1 (0.8%)
CYANOCOBALAMIN	2 (3.2%)	0 .	2 (1.6%)
DALTEPARIN SODIUM	1 (1.6%)	0 .	1 (0.8%)
DIAZEPAM	2 (3.2%)	0 .	2 (1.6%)
DICLOFENAC SODIUM	1 (1.6%)	0 .	1 (0.8%)
DIFLUNISAL	1 (1.6%)	0 .	1 (0.8%)
DIHYDROCODEINE	1 (1.6%)	0 .	1 (0.8%)
DIHYDROXYALUMINUM SODIUM CARBONATE	1 (1.6%)	0 .	1 (0.8%)
DIPYRIDAMOLE	1 (1.6%)	0 .	1 (0.8%)
DOXYCYCLINE	1 (1.6%)	0 .	1 (0.8%)
ERDOSTEINE	1 (1.6%)	0 .	1 (0.8%)
ESTRADIOL VALERATE	1 (1.6%)	0 .	1 (0.8%)
ESTROPIPATE	1 (1.6%)	0 .	1 (0.8%)
FAMOTIDINE	1 (1.6%)	0 .	1 (0.8%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED AND ASSESSED FOR PRIOR MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED POST-RANDOMISATION AND MEDICATIONS DISCONTINUED PRIOR TO RANDOMISATION
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.13A

SUMMARY OF PRIOR MEDICATIONS BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMISED PATIENTS

PROTOCOL 181

GENERIC TERM	TREATMENT GROUP PLACEBO (N=62)	SB 207499 (N=65)	Total (N=127)
FLUOCINOLONE ACETONIDE	1 (1.6%)	0 .	1 (0.8%)
FOLIC ACID	1 (1.6%)	0 .	1 (0.8%)
GAVISCON NOS	1 (1.6%)	0 .	1 (0.8%)
GLIBENCLAMIDE	2 (3.2%)	0 .	2 (1.6%)
GLICLAZIDE	1 (1.6%)	0 .	1 (0.8%)
GLYCERYL TRINITRATE	1 (1.6%)	0 .	1 (0.8%)
GUAIFENESIN	1 (1.6%)	0 .	1 (0.8%)
HYDROXYZINE	1 (1.6%)	0 .	1 (0.8%)
HYDROXYZINE HYDROCHLORIDE	1 (1.6%)	0 .	1 (0.8%)
INSULIN HUMAN	1 (1.6%)	0 .	1 (0.8%)
INSULIN ISOPHANE, HUMAN BIOSYNTHETIC	1 (1.6%)	0 .	1 (0.8%)
KETOPROFEN	1 (1.6%)	0 .	1 (0.8%)
LEVODOPA	1 (1.6%)	0 .	1 (0.8%)
LEVOMENTHOL	1 (1.6%)	0 .	1 (0.8%)
LIDOCAINE	1 (1.6%)	0 .	1 (0.8%)
LOCAL ANESTHETIC NOS	1 (1.6%)	0 .	1 (0.8%)
LOPERAMIDE	1 (1.6%)	0 .	1 (0.8%)
MEDROXYPROGESTERONE ACETATE	1 (1.6%)	0 .	1 (0.8%)
MEFENAMIC ACID	1 (1.6%)	0 .	1 (0.8%)
METFORMIN HYDROCHLORIDE	2 (3.2%)	0 .	2 (1.6%)
METHYL SALICYLATE	1 (1.6%)	0 .	1 (0.8%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED AND ASSESSED FOR PRIOR MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED POST-RANDOMISATION AND MEDICATIONS DISCONTINUED PRIOR TO RANDOMISATION
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CONFIDENTIAL

SB 207499

TABLE 13.13A

SUMMARY OF PRIOR MEDICATIONS BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMISED PATIENTS

PROTOCOL 181

GENERIC TERM	TREATMENT GROUP PLACEBO (N=62)	SB 207499 (N=65)	Total (N=127)
MIDAZOLAM	1 (1.6%)	0 .	1 (0.8%)
NICERGOLINE	1 (1.6%)	0 .	1 (0.8%)
NICOTINE	1 (1.6%)	0 .	1 (0.8%)
NORETHISTERONE ACETATE	1 (1.6%)	0 .	1 (0.8%)
NORFLOXACIN	1 (1.6%)	0 .	1 (0.8%)
ORLISTAT	1 (1.6%)	0 .	1 (0.8%)
PERINDOPRIL	1 (1.6%)	0 .	1 (0.8%)
PERMETHRIN	1 (1.6%)	0 .	1 (0.8%)
PHENYLEPHRINE HYDROCHLORIDE	1 (1.6%)	0 .	1 (0.8%)
PIOGLITAZONE HYDROCHLORIDE	1 (1.6%)	0 .	1 (0.8%)
PREDNISONE	1 (1.6%)	0 .	1 (0.8%)
PSEUDOEPHEDRINE	1 (1.6%)	0 .	1 (0.8%)
PSEUDOEPHEDRINE HYDROCHLORIDE	2 (3.2%)	0 .	2 (1.6%)
PYRIDOXINE HYDROCHLORIDE	2 (3.2%)	0 .	2 (1.6%)
QUININE SULPHATE	1 (1.6%)	0 .	1 (0.8%)
RISEDRONATE SODIUM	1 (1.6%)	0 .	1 (0.8%)
ROSIGLITAZONE MALEATE	1 (1.6%)	0 .	1 (0.8%)
ROSUVASTATIN CALCIUM	1 (1.6%)	0 .	1 (0.8%)
ROXITHROMYCIN	1 (1.6%)	0 .	1 (0.8%)
SALICYLIC ACID	1 (1.6%)	0 .	1 (0.8%)
SILDENAFIL	1 (1.6%)	0 .	1 (0.8%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED AND ASSESSED FOR PRIOR MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED POST-RANDOMISATION AND MEDICATIONS DISCONTINUED PRIOR TO RANDOMISATION
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

SB 207499

TABLE 13.13A

SUMMARY OF PRIOR MEDICATIONS BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMISED PATIENTS

PROTOCOL 181

GENERIC TERM	TREATMENT GROUP PLACEBO (N=62)	SB 207499 (N=65)	Total (N=127)
SULFUR	1 (1.6%)	0 .	1 (0.8%)
SUMATRIPTAN	1 (1.6%)	0 .	1 (0.8%)
TERAZOSIN HYDROCHLORIDE	1 (1.6%)	0 .	1 (0.8%)
TETANUS TOXOID	1 (1.6%)	0 .	1 (0.8%)
TIOTROPIUM	1 (1.6%)	0 .	1 (0.8%)
TOCOPHEROL	2 (3.2%)	0 .	2 (1.6%)
TRAMADOL HYDROCHLORIDE	1 (1.6%)	0 .	1 (0.8%)
VALACICLOVIR HYDROCHLORIDE	1 (1.6%)	0 .	1 (0.8%)
VALPROATE SODIUM	1 (1.6%)	0 .	1 (0.8%)
VERAPAMIL	1 (1.6%)	0 .	1 (0.8%)
ZAFIRLUKAST	1 (1.6%)	0 .	1 (0.8%)
ZOLPIDEM TARTRATE	1 (1.6%)	0 .	1 (0.8%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED AND ASSESSED FOR PRIOR MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED POST-RANDOMISATION AND MEDICATIONS DISCONTINUED PRIOR TO RANDOMISATION
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL

GM2004/00090/00
SB-207499/181

SB 207499

TABLE 13.13B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMISED PATIENTS

PROTOCOL 181

GENERIC TERM	TREATMENT GROUP PLACEBO (N=62)	SB 207499 (N=65)	Total (N=127)
TOTAL	59 (95.2%)	63 (96.9%)	122 (96.1%)
IPRATROPIUM BROMIDE	29 (46.8%)	43 (66.2%)	72 (56.7%)
SALBUTAMOL	42 (67.7%)	40 (61.5%)	82 (64.6%)
PARACETAMOL	24 (38.7%)	24 (36.9%)	48 (37.8%)
ACETYLSALICYLIC ACID	11 (17.7%)	12 (18.5%)	23 (18.1%)
CODEINE PHOSPHATE	5 (8.1%)	11 (16.9%)	16 (12.6%)
SALBUTAMOL SULFATE	8 (12.9%)	9 (13.8%)	17 (13.4%)
CAFFEINE	2 (3.2%)	6 (9.2%)	8 (6.3%)
HYDROCHLOROTHIAZIDE	2 (3.2%)	5 (7.7%)	7 (5.5%)
AMBIGUOUS MEDICATION	1 (1.6%)	4 (6.2%)	5 (3.9%)
IBUPROFEN	4 (6.5%)	4 (6.2%)	8 (6.3%)
LEVOTHYROXINE SODIUM	2 (3.2%)	4 (6.2%)	6 (4.7%)
OMEPRAZOLE	1 (1.6%)	4 (6.2%)	5 (3.9%)
SIMVASTATIN	2 (3.2%)	4 (6.2%)	6 (4.7%)
AMOXICILLIN TRIHYDRATE	3 (4.8%)	3 (4.6%)	6 (4.7%)
ATORVASTATIN CALCIUM	3 (4.8%)	3 (4.6%)	6 (4.7%)
BISOPROLOL FUMARATE	0 .	3 (4.6%)	3 (2.4%)
CALCIUM	0 .	3 (4.6%)	3 (2.4%)
CLARITHROMYCIN	2 (3.2%)	3 (4.6%)	5 (3.9%)
CLAVULANATE POTASSIUM	3 (4.8%)	3 (4.6%)	6 (4.7%)
DIPHENHYDRAMINE HYDROCHLORIDE	0 .	3 (4.6%)	3 (2.4%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. SAMPLE SIZE IS BASEED ON NUMBER OF RANDOMISED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMISATION AND MEDICATIONS INITIATED POST-RANDOMISATION

CONFIDENTIAL

SB 207499

TABLE 13.13B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMISED PATIENTS

PROTOCOL 181

GENERIC TERM	TREATMENT GROUP PLACEBO (N=62)	SB 207499 (N=65)	Total (N=127)
ENALAPRIL	3 (4.8%)	3 (4.6%)	6 (4.7%)
ESOMEPRAZOLE MAGNESIUM	3 (4.8%)	3 (4.6%)	6 (4.7%)
FENTANYL	0 .	3 (4.6%)	3 (2.4%)
ALLOPURINOL	0 .	2 (3.1%)	2 (1.6%)
ALUMINIUM HYDROXIDE GEL, DRIED	0 .	2 (3.1%)	2 (1.6%)
AMILORIDE HYDROCHLORIDE	0 .	2 (3.1%)	2 (1.6%)
AMOXICILLIN	2 (3.2%)	2 (3.1%)	4 (3.1%)
ASCORBIC ACID	4 (6.5%)	2 (3.1%)	6 (4.7%)
CITALOPRAM HYDROBROMIDE	0 .	2 (3.1%)	2 (1.6%)
DOXYCYCLINE	0 .	2 (3.1%)	2 (1.6%)
FELODIPINE	0 .	2 (3.1%)	2 (1.6%)
FUROSEMIDE	0 .	2 (3.1%)	2 (1.6%)
GAVISCON NOS	2 (3.2%)	2 (3.1%)	4 (3.1%)
INDAPAMIDE	0 .	2 (3.1%)	2 (1.6%)
INFLUENZA VIRUS VACCINE INACTIVATED	0 .	2 (3.1%)	2 (1.6%)
MAGNESIUM	1 (1.6%)	2 (3.1%)	3 (2.4%)
MAGNESIUM HYDROXIDE	0 .	2 (3.1%)	2 (1.6%)
MINERALS NOS	1 (1.6%)	2 (3.1%)	3 (2.4%)
PRAVASTATIN SODIUM	0 .	2 (3.1%)	2 (1.6%)
PREDNISOLONE	1 (1.6%)	2 (3.1%)	3 (2.4%)
RAMIPRIL	6 (9.7%)	2 (3.1%)	8 (6.3%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. SAMPLE SIZE IS BASEED ON NUMBER OF RANDOMISED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
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CONFIDENTIAL

SB 207499

TABLE 13.13B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMISED PATIENTS

PROTOCOL 181

GENERIC TERM	TREATMENT GROUP PLACEBO (N=62)	SB 207499 (N=65)	Total (N=127)
SIMETICONE	0 .	2 (3.1%)	2 (1.6%)
TELMISARTAN	0 .	2 (3.1%)	2 (1.6%)
VENLAFAXINE HYDROCHLORIDE	0 .	2 (3.1%)	2 (1.6%)
VITAMIN D NOS	1 (1.6%)	2 (3.1%)	3 (2.4%)
VITAMINS NOS	1 (1.6%)	2 (3.1%)	3 (2.4%)
ZOPICLONE	1 (1.6%)	2 (3.1%)	3 (2.4%)
AGAROL NOS	0 .	1 (1.5%)	1 (0.8%)
ALENDRONATE SODIUM	1 (1.6%)	1 (1.5%)	2 (1.6%)
ALFENTANIL	0 .	1 (1.5%)	1 (0.8%)
ALLIUM SATIVUM	0 .	1 (1.5%)	1 (0.8%)
AMBAZONE	1 (1.6%)	1 (1.5%)	2 (1.6%)
AMITRIPTYLINE HYDROCHLORIDE	1 (1.6%)	1 (1.5%)	2 (1.6%)
AMLODIPINE BESILATE	1 (1.6%)	1 (1.5%)	2 (1.6%)
ATENOLOL	1 (1.6%)	1 (1.5%)	2 (1.6%)
BENDROFLUMETHIAZIDE	2 (3.2%)	1 (1.5%)	3 (2.4%)
BROMAZEPAM	0 .	1 (1.5%)	1 (0.8%)
CALCITRIOL	0 .	1 (1.5%)	1 (0.8%)
CALCIUM CARBONATE	1 (1.6%)	1 (1.5%)	2 (1.6%)
CALCIUM CITRATE	0 .	1 (1.5%)	1 (0.8%)
CANDESARTAN CILEXETIL	0 .	1 (1.5%)	1 (0.8%)
CELECOXIB	1 (1.6%)	1 (1.5%)	2 (1.6%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. SAMPLE SIZE IS BASEED ON NUMBER OF RANDOMISED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMISATION AND MEDICATIONS INITIATED POST-RANDOMISATION

CONFIDENTIAL

SB 207499

TABLE 13.13B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMISED PATIENTS

PROTOCOL 181

GENERIC TERM	TREATMENT GROUP PLACEBO (N=62)	SB 207499 (N=65)	Total (N=127)
CHLORPHENAMINE MALEATE	1 (1.6%)	1 (1.5%)	2 (1.6%)
CITALOPRAM	1 (1.6%)	1 (1.5%)	2 (1.6%)
CLONAZEPAM	1 (1.6%)	1 (1.5%)	2 (1.6%)
COCILLANA	2 (3.2%)	1 (1.5%)	3 (2.4%)
COLECALCIFEROL	1 (1.6%)	1 (1.5%)	2 (1.6%)
CYCLOBENZAPRINE HYDROCHLORIDE	0 .	1 (1.5%)	1 (0.8%)
DOCUSATE SODIUM	0 .	1 (1.5%)	1 (0.8%)
DORZOLAMIDE HYDROCHLORIDE	0 .	1 (1.5%)	1 (0.8%)
DOXAZOSIN MESILATE	0 .	1 (1.5%)	1 (0.8%)
DOXYLAMINE SUCCINATE	0 .	1 (1.5%)	1 (0.8%)
ENALAPRIL MALEATE	2 (3.2%)	1 (1.5%)	3 (2.4%)
EPHEDRINE HYDROCHLORIDE	1 (1.6%)	1 (1.5%)	2 (1.6%)
EPINEPHRINE HYDROCHLORIDE	0 .	1 (1.5%)	1 (0.8%)
EQUISETUM ARVENSE	0 .	1 (1.5%)	1 (0.8%)
ERGOCALCIFEROL	0 .	1 (1.5%)	1 (0.8%)
ESTRADIOL	1 (1.6%)	1 (1.5%)	2 (1.6%)
ESTROGENS CONJUGATED	1 (1.6%)	1 (1.5%)	2 (1.6%)
ETHYLMORPHINE HYDROCHLORIDE	2 (3.2%)	1 (1.5%)	3 (2.4%)
EUCALYPTUS GLOBULUS	0 .	1 (1.5%)	1 (0.8%)
FAMOTIDINE	1 (1.6%)	1 (1.5%)	2 (1.6%)
FINASTERIDE	0 .	1 (1.5%)	1 (0.8%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
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CONFIDENTIAL
GM2004/00090/00
SB-207499/181

SB 207499

TABLE 13.13B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMISED PATIENTS

PROTOCOL 181

GENERIC TERM	TREATMENT GROUP PLACEBO (N=62)	SB 207499 (N=65)	Total (N=127)
FIORINAL NOS	0 .	1 (1.5%)	1 (0.8%)
FISH OIL	0 .	1 (1.5%)	1 (0.8%)
FLECAINIDE	0 .	1 (1.5%)	1 (0.8%)
FLUCLOXACILLIN	0 .	1 (1.5%)	1 (0.8%)
FLUOXETINE	0 .	1 (1.5%)	1 (0.8%)
FLUOXETINE HYDROCHLORIDE	1 (1.6%)	1 (1.5%)	2 (1.6%)
FLUTICASONE PROPIONATE	0 .	1 (1.5%)	1 (0.8%)
GATIFLOXACIN	0 .	1 (1.5%)	1 (0.8%)
GLUCOSAMINE	0 .	1 (1.5%)	1 (0.8%)
GUAIFENESIN	0 .	1 (1.5%)	1 (0.8%)
HYDROCORTISONE	0 .	1 (1.5%)	1 (0.8%)
ISOSORBIDE DINITRATE	0 .	1 (1.5%)	1 (0.8%)
KETOROLAC TROMETAMOL	0 .	1 (1.5%)	1 (0.8%)
LACTULOSE	0 .	1 (1.5%)	1 (0.8%)
LANSOPRAZOLE	0 .	1 (1.5%)	1 (0.8%)
LATANOPROST	1 (1.6%)	1 (1.5%)	2 (1.6%)
LEVOMENTHOL	1 (1.6%)	1 (1.5%)	2 (1.6%)
LEVOTHYROXINE	0 .	1 (1.5%)	1 (0.8%)
LISINOPRIL	3 (4.8%)	1 (1.5%)	4 (3.1%)
LOPERAMIDE HYDROCHLORIDE	0 .	1 (1.5%)	1 (0.8%)
LYSINE HYDROCHLORIDE	0 .	1 (1.5%)	1 (0.8%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
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CONFIDENTIAL

SB 207499

TABLE 13.13B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMISED PATIENTS

PROTOCOL 181

GENERIC TERM	TREATMENT GROUP PLACEBO (N=62)	SB 207499 (N=65)	Total (N=127)
MAGNESIUM CARBONATE	0 .	1 (1.5%)	1 (0.8%)
MELOXICAM	0 .	1 (1.5%)	1 (0.8%)
METAMIZOLE SODIUM	0 .	1 (1.5%)	1 (0.8%)
METFORMIN	3 (4.8%)	1 (1.5%)	4 (3.1%)
METHADONE HYDROCHLORIDE	0 .	1 (1.5%)	1 (0.8%)
METOPROLOL	0 .	1 (1.5%)	1 (0.8%)
MIDAZOLAM	0 .	1 (1.5%)	1 (0.8%)
MOMETASONE FUROATE	1 (1.6%)	1 (1.5%)	2 (1.6%)
MOXIFLOXACIN	0 .	1 (1.5%)	1 (0.8%)
NAPROXEN	0 .	1 (1.5%)	1 (0.8%)
NICOTINE	0 .	1 (1.5%)	1 (0.8%)
NIFEDIPINE	4 (6.5%)	1 (1.5%)	5 (3.9%)
NITRENDIPINE	1 (1.6%)	1 (1.5%)	2 (1.6%)
NONOXINOL	0 .	1 (1.5%)	1 (0.8%)
NORETHISTERONE	0 .	1 (1.5%)	1 (0.8%)
NYSTATIN	0 .	1 (1.5%)	1 (0.8%)
OXAZEPAM	1 (1.6%)	1 (1.5%)	2 (1.6%)
PAMIDRONIC ACID	0 .	1 (1.5%)	1 (0.8%)
PANTOPRAZOLE SODIUM	0 .	1 (1.5%)	1 (0.8%)
PAROXETINE HYDROCHLORIDE	0 .	1 (1.5%)	1 (0.8%)
PHENYLEPHRINE HYDROCHLORIDE	1 (1.6%)	1 (1.5%)	2 (1.6%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. SAMPLE SIZE IS BASEED ON NUMBER OF RANDOMISED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
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CONFIDENTIAL
GM2004/00090/00
SB-207499/181

SB 207499

TABLE 13.13B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMISED PATIENTS

PROTOCOL 181

GENERIC TERM	TREATMENT GROUP PLACEBO (N=62)	SB 207499 (N=65)	Total (N=127)
PHENYLPROPANOLAMINE HYDROCHLORIDE	1 (1.6%)	1 (1.5%)	2 (1.6%)
PHENYLTOLOXAMINE CITRATE	0 .	1 (1.5%)	1 (0.8%)
PILOCARPINE	0 .	1 (1.5%)	1 (0.8%)
PIROXICAM	0 .	1 (1.5%)	1 (0.8%)
PRAVASTATIN	0 .	1 (1.5%)	1 (0.8%)
PROPOFOL	0 .	1 (1.5%)	1 (0.8%)
QUINAPRIL	0 .	1 (1.5%)	1 (0.8%)
RABEPRAZOLE	0 .	1 (1.5%)	1 (0.8%)
RABEPRAZOLE SODIUM	0 .	1 (1.5%)	1 (0.8%)
RANITIDINE HYDROCHLORIDE	1 (1.6%)	1 (1.5%)	2 (1.6%)
RESERPINE	0 .	1 (1.5%)	1 (0.8%)
ROBITUSSIN (NOS)	0 .	1 (1.5%)	1 (0.8%)
ROFECOXIB	2 (3.2%)	1 (1.5%)	3 (2.4%)
ROXITHROMYCIN	0 .	1 (1.5%)	1 (0.8%)
SENEGA	2 (3.2%)	1 (1.5%)	3 (2.4%)
SENNA	0 .	1 (1.5%)	1 (0.8%)
SERTRALINE HYDROCHLORIDE	0 .	1 (1.5%)	1 (0.8%)
SETLERS (NOS)	0 .	1 (1.5%)	1 (0.8%)
SODIUM CITRATE	0 .	1 (1.5%)	1 (0.8%)
SOTALOL	0 .	1 (1.5%)	1 (0.8%)
SOTALOL HYDROCHLORIDE	0 .	1 (1.5%)	1 (0.8%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. SAMPLE SIZE IS BASEED ON NUMBER OF RANDOMISED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMISATION AND MEDICATIONS INITIATED POST-RANDOMISATION

CONFIDENTIAL

SB 207499

TABLE 13.13B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMISED PATIENTS

PROTOCOL 181

GENERIC TERM	TREATMENT GROUP PLACEBO (N=62)	SB 207499 (N=65)	Total (N=127)
TAMOXIFEN CITRATE	0 .	1 (1.5%)	1 (0.8%)
TESTOSTERONE UNDECANOATE	0 .	1 (1.5%)	1 (0.8%)
TIMOLOL MALEATE	0 .	1 (1.5%)	1 (0.8%)
TIZANIDINE	0 .	1 (1.5%)	1 (0.8%)
TRAMADOL	0 .	1 (1.5%)	1 (0.8%)
VALSARTAN	0 .	1 (1.5%)	1 (0.8%)
VERAPAMIL	1 (1.6%)	1 (1.5%)	2 (1.6%)
ZINC	0 .	1 (1.5%)	1 (0.8%)
ZINGIBER OFFICINALE	0 .	1 (1.5%)	1 (0.8%)
ZOLMITRIPTAN	0 .	1 (1.5%)	1 (0.8%)
ACETYLCYSTEINE	1 (1.6%)	0 .	1 (0.8%)
ALPRAZOLAM	1 (1.6%)	0 .	1 (0.8%)
ARTICAINE HYDROCHLORIDE	1 (1.6%)	0 .	1 (0.8%)
ATORVASTATIN	1 (1.6%)	0 .	1 (0.8%)
ATROPINE SULFATE	1 (1.6%)	0 .	1 (0.8%)
AZITHROMYCIN	1 (1.6%)	0 .	1 (0.8%)
BECLOMETASONE DIPROPIONATE	1 (1.6%)	0 .	1 (0.8%)
BENSERAZIDE HYDROCHLORIDE	1 (1.6%)	0 .	1 (0.8%)
BENYLIN (NOS)	1 (1.6%)	0 .	1 (0.8%)
BROMHEXINE HYDROCHLORIDE	1 (1.6%)	0 .	1 (0.8%)
CALCIPOTRIOL	1 (1.6%)	0 .	1 (0.8%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. SAMPLE SIZE IS BASEED ON NUMBER OF RANDOMISED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMISATION AND MEDICATIONS INITIATED POST-RANDOMISATION

CONFIDENTIAL

SB 207499

TABLE 13.13B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMISED PATIENTS

PROTOCOL 181

GENERIC TERM	TREATMENT GROUP PLACEBO (N=62)	SB 207499 (N=65)	Total (N=127)
CAMPHOR	1 (1.6%)	0 .	1 (0.8%)
CAPTOPRIL	1 (1.6%)	0 .	1 (0.8%)
CARBAMAZEPINE	1 (1.6%)	0 .	1 (0.8%)
CEFALEXIN	1 (1.6%)	0 .	1 (0.8%)
CLOPIDOGREL SULFATE	1 (1.6%)	0 .	1 (0.8%)
CYANOCOBALAMIN	2 (3.2%)	0 .	2 (1.6%)
DEXTROMETHORPHAN HYDROBROMIDE	1 (1.6%)	0 .	1 (0.8%)
DIAZEPAM	2 (3.2%)	0 .	2 (1.6%)
DIFLUNISAL	1 (1.6%)	0 .	1 (0.8%)
DIHYDROCODEINE	1 (1.6%)	0 .	1 (0.8%)
DIHYDROXYALUMINUM SODIUM CARBONATE	1 (1.6%)	0 .	1 (0.8%)
DIMETAPP NOS	1 (1.6%)	0 .	1 (0.8%)
DIPHENOXYLATE HYDROCHLORIDE	1 (1.6%)	0 .	1 (0.8%)
DIPYRIDAMOLE	1 (1.6%)	0 .	1 (0.8%)
ERYTHROMYCIN	1 (1.6%)	0 .	1 (0.8%)
ESTRADIOL VALERATE	1 (1.6%)	0 .	1 (0.8%)
ESTROPIPATE	1 (1.6%)	0 .	1 (0.8%)
FLUOCINOLONE ACETONIDE	1 (1.6%)	0 .	1 (0.8%)
FOLIC ACID	1 (1.6%)	0 .	1 (0.8%)
GLIBENCLAMIDE	2 (3.2%)	0 .	2 (1.6%)
GLICLAZIDE	1 (1.6%)	0 .	1 (0.8%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. SAMPLE SIZE IS BASEED ON NUMBER OF RANDOMISED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMISATION AND MEDICATIONS INITIATED POST-RANDOMISATION

CONFIDENTIAL

SB 207499

TABLE 13.13B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMISED PATIENTS

PROTOCOL 181

GENERIC TERM	TREATMENT GROUP PLACEBO (N=62)	SB 207499 (N=65)	Total (N=127)
GLYCERYL TRINITRATE	2 (3.2%)	0 .	2 (1.6%)
HYDROXYZINE	1 (1.6%)	0 .	1 (0.8%)
HYDROXYZINE HYDROCHLORIDE	1 (1.6%)	0 .	1 (0.8%)
INFLUENZA VACCINE	2 (3.2%)	0 .	2 (1.6%)
INSULIN HUMAN	1 (1.6%)	0 .	1 (0.8%)
INSULIN ISOPHANE, HUMAN BIOSYNTHETIC	1 (1.6%)	0 .	1 (0.8%)
KETOPROFEN	1 (1.6%)	0 .	1 (0.8%)
LEVODOPA	1 (1.6%)	0 .	1 (0.8%)
LEVOFLOXACIN	1 (1.6%)	0 .	1 (0.8%)
LIDOCAINE	1 (1.6%)	0 .	1 (0.8%)
LIDOCAINE HYDROCHLORIDE	1 (1.6%)	0 .	1 (0.8%)
LOPERAMIDE	1 (1.6%)	0 .	1 (0.8%)
MEDROXYPROGESTERONE ACETATE	1 (1.6%)	0 .	1 (0.8%)
MEFENAMIC ACID	1 (1.6%)	0 .	1 (0.8%)
METFORMIN HYDROCHLORIDE	2 (3.2%)	0 .	2 (1.6%)
MIRTAZAPINE	1 (1.6%)	0 .	1 (0.8%)
MORPHINE	1 (1.6%)	0 .	1 (0.8%)
NICERGOLINE	1 (1.6%)	0 .	1 (0.8%)
NORETHISTERONE ACETATE	1 (1.6%)	0 .	1 (0.8%)
NORFLOXACIN	1 (1.6%)	0 .	1 (0.8%)
ORLISTAT	1 (1.6%)	0 .	1 (0.8%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. SAMPLE SIZE IS BASEED ON NUMBER OF RANDOMISED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMISATION AND MEDICATIONS INITIATED POST-RANDOMISATION

CONFIDENTIAL

SB 207499

TABLE 13.13B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMISED PATIENTS

PROTOCOL 181

GENERIC TERM	TREATMENT GROUP PLACEBO (N=62)	SB 207499 (N=65)	Total (N=127)
PAINAGON (NOS)	1 (1.6%)	0 .	1 (0.8%)
PERINDOPRIL	1 (1.6%)	0 .	1 (0.8%)
PERMETHRIN	1 (1.6%)	0 .	1 (0.8%)
PIOGLITAZONE HYDROCHLORIDE	1 (1.6%)	0 .	1 (0.8%)
PREDNISONE	1 (1.6%)	0 .	1 (0.8%)
PYRIDOXINE HYDROCHLORIDE	2 (3.2%)	0 .	2 (1.6%)
QUININE SULPHATE	1 (1.6%)	0 .	1 (0.8%)
RISEDRONATE SODIUM	1 (1.6%)	0 .	1 (0.8%)
ROSIGLITAZONE MALEATE	1 (1.6%)	0 .	1 (0.8%)
ROSUVASTATIN CALCIUM	1 (1.6%)	0 .	1 (0.8%)
SALICYLIC ACID	1 (1.6%)	0 .	1 (0.8%)
SILDENAFIL	1 (1.6%)	0 .	1 (0.8%)
SINUTAB (NOS)	1 (1.6%)	0 .	1 (0.8%)
SMECTITE	1 (1.6%)	0 .	1 (0.8%)
SULFUR	1 (1.6%)	0 .	1 (0.8%)
SUMATRIPTAN	1 (1.6%)	0 .	1 (0.8%)
TERAZOSIN HYDROCHLORIDE	1 (1.6%)	0 .	1 (0.8%)
TERBUTALINE	1 (1.6%)	0 .	1 (0.8%)
TOCOPHEROL	2 (3.2%)	0 .	2 (1.6%)
VALPROATE SODIUM	1 (1.6%)	0 .	1 (0.8%)
VERAPAMIL HYDROCHLORIDE	1 (1.6%)	0 .	1 (0.8%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. SAMPLE SIZE IS BASEED ON NUMBER OF RANDOMISED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMISATION AND MEDICATIONS INITIATED POST-RANDOMISATION

CONFIDENTIAL
GM2004/00090/00
SB-207499/181

SB 207499

TABLE 13.13B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND TREATMENT GROUP - ALL RANDOMISED PATIENTS

PROTOCOL 181

GENERIC TERM	TREATMENT GROUP PLACEBO (N=62)	SB 207499 (N=65)	Total (N=127)
ZOLPIDEM TARTRATE	1 (1.6%)	0 .	1 (0.8%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. SAMPLE SIZE IS BASEED ON NUMBER OF RANDOMISED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMISATION AND MEDICATIONS INITIATED POST-RANDOMISATION

CONFIDENTIAL

SB 207499

TABLE 13.13C

SUMMARY OF POST-THERAPY MEDICATIONS BY GENERIC TERM AND TREATMENT GROUP

PROTOCOL 181

GENERIC TERM	TREATMENT GROUP PLACEBO (N=62)	SB 207499 (N=65)	Total (N=127)
TOTAL	16 (25.8%)	22 (33.8%)	38 (29.9%)
SALBUTAMOL	4 (6.5%)	5 (7.7%)	9 (7.1%)
SALMETEROL XINAFOATE	1 (1.6%)	4 (6.2%)	5 (3.9%)
FLUTICASONE PROPIONATE	1 (1.6%)	3 (4.6%)	4 (3.1%)
BECLOMETASONE DIPROPIONATE	0 .	2 (3.1%)	2 (1.6%)
IPRATROPIUM BROMIDE	1 (1.6%)	2 (3.1%)	3 (2.4%)
PREDNISOLONE	1 (1.6%)	2 (3.1%)	3 (2.4%)
ACETYLSALICYLIC ACID	2 (3.2%)	1 (1.5%)	3 (2.4%)
AMOXICILLIN TRIHYDRATE	1 (1.6%)	1 (1.5%)	2 (1.6%)
ATROPINE SULFATE	0 .	1 (1.5%)	1 (0.8%)
BUDESONIDE	2 (3.2%)	1 (1.5%)	3 (2.4%)
CAFFEINE	0 .	1 (1.5%)	1 (0.8%)
CLAVULANATE POTASSIUM	1 (1.6%)	1 (1.5%)	2 (1.6%)
DICLOFENAC SODIUM	0 .	1 (1.5%)	1 (0.8%)
DIPHENOXYLATE HYDROCHLORIDE	0 .	1 (1.5%)	1 (0.8%)
DOXYCYCLINE	0 .	1 (1.5%)	1 (0.8%)
EFORMOTEROL FUMARATE	1 (1.6%)	1 (1.5%)	2 (1.6%)
FENOTEROL HYDROBROMIDE	0 .	1 (1.5%)	1 (0.8%)
FLUCONAZOLE	0 .	1 (1.5%)	1 (0.8%)
HYDROCODONE	0 .	1 (1.5%)	1 (0.8%)
IBUPROFEN	1 (1.6%)	1 (1.5%)	2 (1.6%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. SAMPLE SIZE IS BASEED ON NUMBER OF RANDOMISED PATIENTS ASSESSED FOR POST-THERAPY MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS INITIATED ON OR AFTER DATE OF LAST DOSE OF DOUBLE-BLIND TREATMENT

CONFIDENTIAL

SB 207499

TABLE 13.13C

SUMMARY OF POST-THERAPY MEDICATIONS BY GENERIC TERM AND TREATMENT GROUP

PROTOCOL 181

GENERIC TERM	TREATMENT GROUP PLACEBO (N=62)	SB 207499 (N=65)	Total (N=127)
INDOMETACIN	0 .	1 (1.5%)	1 (0.8%)
METFORMIN	0 .	1 (1.5%)	1 (0.8%)
NYSTATIN	0 .	1 (1.5%)	1 (0.8%)
OMEPRAZOLE	0 .	1 (1.5%)	1 (0.8%)
PARACETAMOL	1 (1.6%)	1 (1.5%)	2 (1.6%)
PHENYLEPHRINE HYDROCHLORIDE	0 .	1 (1.5%)	1 (0.8%)
PHENYLTOLOXAMINE	0 .	1 (1.5%)	1 (0.8%)
TIOTROPIUM	0 .	1 (1.5%)	1 (0.8%)
TIOTROPIUM BROMIDE	2 (3.2%)	1 (1.5%)	3 (2.4%)
ACETYLCYSTEINE	1 (1.6%)	0 .	1 (0.8%)
BETAMETHASONE SODIUM PHOSPHATE	1 (1.6%)	0 .	1 (0.8%)
CEFACLOR	1 (1.6%)	0 .	1 (0.8%)
DEXTROMETHORPHAN HYDROBROMIDE	1 (1.6%)	0 .	1 (0.8%)
FUROSEMIDE	1 (1.6%)	0 .	1 (0.8%)
HEPATITIS A VACCINE	1 (1.6%)	0 .	1 (0.8%)
MACROGOL	1 (1.6%)	0 .	1 (0.8%)
METOCLOPRAMIDE	1 (1.6%)	0 .	1 (0.8%)
NALTREXONE	1 (1.6%)	0 .	1 (0.8%)
POTASSIUM CHLORIDE	1 (1.6%)	0 .	1 (0.8%)
SACCHARIN SODIUM	1 (1.6%)	0 .	1 (0.8%)
SODIUM BICARBONATE	1 (1.6%)	0 .	1 (0.8%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. SAMPLE SIZE IS BASEED ON NUMBER OF RANDOMISED PATIENTS ASSESSED FOR POST-THERAPY MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS INITIATED ON OR AFTER DATE OF LAST DOSE OF DOUBLE-BLIND TREATMENT

CONFIDENTIAL

SB 207499

TABLE 13.13C

SUMMARY OF POST-THERAPY MEDICATIONS BY GENERIC TERM AND TREATMENT GROUP

PROTOCOL 181

GENERIC TERM	TREATMENT GROUP PLACEBO (N=62)	SB 207499 (N=65)	Total (N=127)
SODIUM CHLORIDE	1 (1.6%)	0 .	1 (0.8%)
SODIUM SULFATE ANHYDROUS	1 (1.6%)	0 .	1 (0.8%)
TERBUTALINE	1 (1.6%)	0 .	1 (0.8%)
TERBUTALINE SULFATE	1 (1.6%)	0 .	1 (0.8%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. SAMPLE SIZE IS BASEED ON NUMBER OF RANDOMISED PATIENTS ASSESSED FOR POST-THERAPY MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS INITIATED ON OR AFTER DATE OF LAST DOSE OF DOUBLE-BLIND TREATMENT

CONFIDENTIAL

SB 207499

TABLE 13.13D

SUMMARY OF MEDICATIONS GIVEN FOR COPD EXACERBATIONS BY GENERIC TERM AND TREATMENT GROUP

PROTOCOL 181

GENERIC TERM	TREATMENT GROUP PLACEBO (N=62)	SB 207499 (N=65)	Total (N=127)
TOTAL	9 (14.5%)	10 (15.4%)	19 (15.0%)
DOXYCYCLINE	0 .	3 (4.6%)	3 (2.4%)
PREDNISOLONE	2 (3.2%)	3 (4.6%)	5 (3.9%)
AMOXICILLIN TRIHYDRATE	3 (4.8%)	2 (3.1%)	5 (3.9%)
CLARITHROMYCIN	0 .	2 (3.1%)	2 (1.6%)
CLAVULANATE POTASSIUM	3 (4.8%)	2 (3.1%)	5 (3.9%)
IPRATROPIUM BROMIDE	2 (3.2%)	2 (3.1%)	4 (3.1%)
SALBUTAMOL SULFATE	1 (1.6%)	2 (3.1%)	3 (2.4%)
AMOXICILLIN	2 (3.2%)	1 (1.5%)	3 (2.4%)
HYDROCORTISONE	0 .	1 (1.5%)	1 (0.8%)
IBUPROFEN	0 .	1 (1.5%)	1 (0.8%)
MOXIFLOXACIN	0 .	1 (1.5%)	1 (0.8%)
PARACETAMOL	0 .	1 (1.5%)	1 (0.8%)
ROXITHROMYCIN	0 .	1 (1.5%)	1 (0.8%)
SALBUTAMOL	3 (4.8%)	1 (1.5%)	4 (3.1%)
ACETYLCYSTEINE	1 (1.6%)	0 .	1 (0.8%)
BECLOMETASONE DIPROPIONATE	1 (1.6%)	0 .	1 (0.8%)
BETAMETHASONE SODIUM PHOSPHATE	1 (1.6%)	0 .	1 (0.8%)
BUDESONIDE	1 (1.6%)	0 .	1 (0.8%)
CEFACLOR	1 (1.6%)	0 .	1 (0.8%)
ERYTHROMYCIN	1 (1.6%)	0 .	1 (0.8%)
PREDNISONE	1 (1.6%)	0 .	1 (0.8%)

1. SAMPLE SIZE IS BASEED ON NUMBER OF RANDOMISED PATIENTS ASSESSED FOR COPD EXACERBATIONS MEDICATIONS
2. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL
GM2004/00090/00
SB-207499/181

SB 207499

TABLE 13.13D

SUMMARY OF MEDICATIONS GIVEN FOR COPD EXACERBATIONS BY GENERIC TERM AND TREATMENT GROUP

PROTOCOL 181

GENERIC TERM	TREATMENT GROUP PLACEBO (N=62)	SB 207499 (N=65)	Total (N=127)
TERBUTALINE SULFATE	1 (1.6%)	0 .	1 (0.8%)
TIOTROPIUM BROMIDE	1 (1.6%)	0 .	1 (0.8%)

1. SAMPLE SIZE IS BASEED ON NUMBER OF RANDOMISED PATIENTS ASSESSED FOR COPD EXACERBATIONS MEDICATIONS
2. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

CONFIDENTIAL
GM2004/00090/00
SB-207499/181

SB 207499

TABLE 13.14A

SUMMARY OF STUDY MEDICATION COMPLIANCE (%) BY TREATMENT GROUP AND VISIT/WEEK

PROTOCOL 181

VISIT/WEEK	COMPLIANCE	TREATMENT GROUP PLACEBO		SB 207499	
SINGLE BLIND RUN-IN	< 80%	1	(1.6%)	2	(3.1%)
	80-120%	56	(91.8%)	60	(93.8%)
	> 120%	4	(6.6%)	2	(3.1%)
	NUMBER EVALUATED	61		64	
VISIT 3/WEEK 0	< 80%	5	(8.8%)	5	(8.3%)
	80-120%	50	(87.7%)	54	(90.0%)
	> 120%	2	(3.5%)	1	(1.7%)
	NUMBER EVALUATED	57		60	
VISIT 4/WEEK 4	< 80%	3	(5.0%)	2	(3.3%)
	80-120%	57	(95.0%)	58	(96.7%)
	> 120%	0	.	0	.
	NUMBER EVALUATED	60		60	
VISIT 5/WEEK 8	< 80%	1	(1.7%)	3	(5.1%)
	80-120%	58	(98.3%)	55	(93.2%)
	> 120%	0	.	1	(1.7%)
	NUMBER EVALUATED	59		59	
VISIT 6/WEEK 12	< 80%	0	.	0	.
	80-120%	54	(98.2%)	57	(100.0%)
	> 120%	1	(1.8%)	0	.
	NUMBER EVALUATED	55		57	
VISIT 6A/WEEK 12	< 80%	1	(50.0%)	0	.
	80-120%	1	(50.0%)	2	(100.0%)
	> 120%	0	.	0	.
	NUMBER EVALUATED	2		2	
VISIT 7/WEEK 13	< 80%	3	(5.6%)	2	(3.6%)
	80-120%	51	(94.4%)	53	(94.6%)
	> 120%	0	.	1	(1.8%)
	NUMBER EVALUATED	54		56	
OVERALL	< 80%	3	(4.9%)	3	(4.8%)
	80-120%	57	(93.4%)	58	(92.1%)
	> 120%	1	(1.6%)	2	(3.2%)
	NUMBER EVALUATED	61		63	

1. SINGLE-BLIND RUN-IN REPRESENTS COMPLIANCE DURING THE PLACEBO RUN-IN PERIOD
2. OVERALL REPRESENTS COMPLIANCE OVER 13 WEEK DOUBLE-BLIND PERIOD
3. TABLE INCLUDES RANDOMISED PATIENTS WITH NON-MISSING COMPLIANCE DATA

CONFIDENTIAL

GM2004/00090/00
SB-207499/181

SB 207499

TABLE 13.14B

DESCRIPTIVE STATISTICS FOR STUDY MEDICATION COMPLIANCE (%) BY TREATMENT GROUP AND VISIT/WEEK

PROTOCOL 181

VISIT/WEEK	Statistic	TREATMENT GROUP PLACEBO (N=62)	SB 207499 (N=65)
SINGLE BLIND RUN-IN	N	61	64
	MEAN	98.66	96.58
	STD	15.31	13.05
	MEDIAN	98.08	98.21
	MIN	51.92	24.14
	MAX	167.86	130.00
VISIT 3/WEEK 0	N	57	60
	MEAN	102.90	95.56
	STD	60.09	15.40
	MEDIAN	100.00	100.00
	MIN	50.00	24.14
	MAX	540.00	150.00
VISIT 4/WEEK 4	N	60	60
	MEAN	96.18	96.09
	STD	7.41	6.77
	MEDIAN	98.21	98.15
	MIN	67.86	68.06
	MAX	105.36	107.14
VISIT 5/WEEK 8	N	59	59
	MEAN	96.41	95.85
	STD	8.28	8.62
	MEDIAN	100.00	98.21
	MIN	40.91	52.17
	MAX	100.00	123.81
VISIT 6/WEEK 12	N	55	57
	MEAN	97.92	96.65
	STD	5.32	4.07
	MEDIAN	98.21	98.21
	MIN	81.82	83.93
	MAX	120.69	103.57
VISIT 6A/WEEK 12	N	2	2
	MEAN	85.0	94.1
	STD	21.2	8.4
	MEDIAN	85.0	94.1
	MIN	70.0	88.1
	MAX	100.0	100.0
VISIT 7/WEEK 13	N	54	56

1. SINGLE-BLIND RUN-IN REPRESENTS COMPLIANCE DURING THE PLACEBO RUN-IN PERIOD
2. OVERALL REPRESENTS COMPLIANCE OVER 13 WEEK DOUBLE-BLIND PERIOD
3. TABLE INCLUDES RANDOMISED PATIENTS WITH NON-MISSING COMPLIANCE DATA

CONFIDENTIAL

SB 207499

TABLE 13.14B

DESCRIPTIVE STATISTICS FOR STUDY MEDICATION COMPLIANCE (%) BY TREATMENT GROUP AND VISIT/WEEK

PROTOCOL 181

		TREATMENT GROUP	
		PLACEBO	SB 207499
VISIT/WEEK	Statistic	(N=62)	(N=65)
VISIT 7/WEEK 13	MEAN	95.00	98.19
	STD	13.15	9.40
	MEDIAN	100.00	100.00
	MIN	33.33	64.29
	MAX	110.00	121.43
OVERALL	N	61	63
	MEAN	96.54	96.46
	STD	10.31	14.12
	MEDIAN	98.86	97.65
	MIN	50.00	27.14
	MAX	140.00	151.79

1. SINGLE-BLIND RUN-IN REPRESENTS COMPLIANCE DURING THE PLACEBO RUN-IN PERIOD
2. OVERALL REPRESENTS COMPLIANCE OVER 13 WEEK DOUBLE-BLIND PERIOD
3. TABLE INCLUDES RANDOMISED PATIENTS WITH NON-MISSING COMPLIANCE DATA

CONFIDENTIAL

SB 207499

TABLE 13.15

SUMMARY OF PATIENT SMOKING STATUS BY BASELINE STATUS AND TREATMENT GROUP AT VISIT 7

PROTOCOL 181

Treatment Group	Number Assessed	Baseline Status	Smoking Status at Visit 7	Not Smoking at Visit 7
PLACEBO	28	Smoking	21 (75.00%)	4 (14.29%)
	34	Not Smoking	0 (0.00%)	31 (91.18%)
	62	Total	21 (33.87%)	35 (56.45%)
SB 207499	32	Smoking	26 (81.25%)	1 (3.13%)
	33	Not Smoking	1 (3.03%)	29 (87.88%)
	65	Total	27 (41.54%)	30 (46.15%)

1. PERCENTAGES MAY NOT TOTAL TO 100% DUE TO MISSING SMOKING STATUS AT VISIT 7.

CONFIDENTIAL
GM2004/00090/00
SB-207499/181

EFFICACY DATA SOURCE TABLES

Page

TABLE 14.1A - SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL CD68+ (MACROPHAGES) (CELL/MM2) BY TREATMENT GROUP - PP 212
TABLE 14.1B - DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL CD68+ (MACROPHAGES) (CELL/MM2) BY TREATMENT GROUP - - PP 213
TABLE 14.1C - SUMMARY OF TEST OF SIGNIFICANCE FOR INTERACTION TERMS AND COVARIATES FOR CHANGE FROM BASELINE IN - SUB-EPITHELIAL CD68+ (MACROPHAGES)/MM^2 - PP 214
TABLE 14.1D - SUMMARY OF POISSON REGRESSION MODEL USING GEE FOR CHANGE IN CD68 - PP 215
TABLE 14.1E - SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL CD68+ (MACROPHAGES) (CELL/MM2) BY TREATMENT GROUP - - PP (SMOKERS) 216
TABLE 14.1F - SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL CD68+ (MACROPHAGES) (CELL/MM2) BY TREATMENT GROUP - - PP (NON-SMOKERS) 217
TABLE 14.1G - DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL CD68+ (MACROPHAGES) (CELL/MM2) BY TREATMENT GROUP - - PP (SMOKERS) 218
TABLE 14.1H - DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL CD68+ (MACROPHAGES) (CELL/MM2) BY TREATMENT GROUP - - PP (NON-SMOKERS) 219
TABLE 14.2A - SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL CD8+ T-LYMPHOCYTES (CELL/MM2) TISSUE BY TREATMENT GROUP - - PP 220
TABLE 14.2B - DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL CD8+ T-LYMPHOCYTES (CELL/MM2) TISSUE BY TREATMENT GROUP - - PP 221
TABLE 14.2C - SUMMARY OF TEST OF SIGNIFICANCE FOR INTERACTION TERMS AND COVARIATES FOR CHANGE FROM BASELINE IN - SUB-EPITHELIAL CD8+ (T-LYMPHOCYTES)/MM^2 - PP 222
TABLE 14.2D - SUMMARY OF POISSON REGRESSION MODEL USING GEE FOR CHANGE IN CD8 - PP 223

TABLE 14.2E - SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL CD8+ T-LYMPHOCYTES (CELL/MM2) TISSUE BY TREATMENT GROUP - - PP (SMOKERS) 224
TABLE 14.2F - SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL CD8+ T-LYMPHOCYTES (CELL/MM2) TISSUE BY TREATMENT GROUP - - PP (NON-SMOKERS) 225
TABLE 14.2G - DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL CD8+ T-LYMPHOCYTES (CELL/MM2) TISSUE BY TREATMENT GROUP - - PP (SMOKERS) 226
TABLE 14.2H - DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL CD8+ T-LYMPHOCYTES (CELL/MM2) TISSUE BY TREATMENT GROUP - - PP (NON-SMOKERS) 227
TABLE 14.3A - SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL NEUTROPHILS (NE+) (CELL/MM2) TISSUE BY TREATMENT GROUP - - PP 228
TABLE 14.3B - DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL NEUTROPHILS (NE+) (CELL/MM2) TISSUE BY TREATMENT GROUP - - PP 229
TABLE 14.4A - SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL CD4+ LYMPHOCYTES (CELL/MM2) TISSUE BY TREATMENT GROUP - - PP 230
TABLE 14.4B - DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL CD4+ LYMPHOCYTES (CELL/MM2) TISSUE BY TREATMENT GROUP - - PP 231
TABLE 14.5A - SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL IL-8+ MRNA (CELL/MM2) TISSUE BY TREATMENT GROUP - - PP 232
TABLE 14.5B - DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL IL-8+ MRNA (CELL/MM2) TISSUE BY TREATMENT GROUP - - PP 233
TABLE 14.6A - SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL TNF-ALPHA +MRNA (CELL/MM2) TISSUE BY TREATMENT GROUP - - PP 234
TABLE 14.6B - DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL TNF-ALPHA +MRNA (CELL/MM2) TISSUE BY TREATMENT GROUP - - PP 235
TABLE 14.7A - SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL CD45 POSITIVE (CELL/MM2) TISSUE BY TREATMENT GROUP - - PP 236

TABLE 14.7B - DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL CD45 POSITIVE (CELL/MM2) TISSUE BY TREATMENT GROUP - - PP 237
TABLE 14.8A1 - SUMMARY OF CHANGE FROM BASELINE IN EPITHELIAL MUCIN EXPRESSION (MUC5AC) (CELL/MM2) TISSUE BY TREATMENT GROUP - - PP 238
TABLE 14.8A2 - SUMMARY OF CHANGE FROM BASELINE IN SUB-MUCOSA MUCIN EXPRESSION (MUC5AC) (CELL/MM2) TISSUE BY TREATMENT GROUP - - PP 239
TABLE 14.8A3 - SUMMARY OF CHANGE FROM BASELINE IN EPITHELIAL MUCIN EXPRESSION (MUC5B) (CELL/MM2) TISSUE BY TREATMENT GROUP - - PP 240
TABLE 14.8A4 - SUMMARY OF CHANGE FROM BASELINE IN SUB-MUCOSA MUCIN EXPRESSION (MUC5B) (CELL/MM2) TISSUE BY TREATMENT GROUP - - PP 241
TABLE 14.8B1 - DESCRIPTIVE STATISTICS FOR EPITHELIAL MUCIN EXPRESSION (MUC5AC) (CELL/MM2) TISSUE BY TREATMENT GROUP - - PP 242
TABLE 14.8B2 - DESCRIPTIVE STATISTICS FOR SUB-MUCOSA MUCIN EXPRESSION (MUC5AC) (CELL/MM2) TISSUE BY TREATMENT GROUP - - PP 243
TABLE 14.8B3 - DESCRIPTIVE STATISTICS FOR EPITHELIAL MUCIN EXPRESSION (MUC5B) (CELL/MM2) TISSUE BY TREATMENT GROUP - - PP 244
TABLE 14.8B4 - DESCRIPTIVE STATISTICS FOR SUB-MUCOSA MUCIN EXPRESSION (MUC5B) (CELL/MM2) TISSUE BY TREATMENT GROUP - - PP 245
TABLE 14.10A - SUMMARY OF CHANGE FROM BASELINE IN SPUTUM TOTAL CELL COUNTS (10^6/ML) BY TREATMENT GROUP - - PP . . . 246
TABLE 14.10B - DESCRIPTIVE STATISTICS FOR SPUTUM TOTAL CELL COUNTS (10^6/ML) BY TREATMENT GROUP - - PP 247
TABLE 14.11A - SUMMARY OF CHANGE FROM BASELINE IN SPUTUM MACROPHAGES AS A PERCENTAGE OF TOTAL CELLS BY TREATMENT GROUP - - PP 248
TABLE 14.11B - DESCRIPTIVE STATISTICS FOR SPUTUM MACROPHAGES AS A PERCENTAGE OF TOTAL CELLS BY TREATMENT GROUP - - PP 249
TABLE 14.12A - SUMMARY OF CHANGE FROM BASELINE IN SPUTUM NEUTROPHIL ELASTASE (NG/ML) BY TREATMENT GROUP - - PP . . 250

TABLE 14.12B - DESCRIPTIVE STATISTICS FOR SPUTUM NEUTROPHIL ELASTASE (NG/ML) BY TREATMENT GROUP - - PP . . 251
TABLE 14.13A - SUMMARY OF CHANGE FROM BASELINE IN SPUTUM EOSINOPHILS (%) BY TREATMENT GROUP - - PP 252
TABLE 14.13B - DESCRIPTIVE STATISTICS FOR SPUTUM EOSINOPHILS (%) BY TREATMENT GROUP - - PP 253
TABLE 14.14A - SUMMARY OF CHANGE FROM BASELINE IN SPUTUM LYMPHOCYTES (%) BY TREATMENT GROUP - - PP 254
TABLE 14.14B - DESCRIPTIVE STATISTICS FOR SPUTUM LYMPHOCYTES (%) BY TREATMENT GROUP - - PP 255
TABLE 14.15A - SUMMARY OF CHANGE FROM BASELINE IN SPUTUM IL-8 (NG/ML) BY TREATMENT GROUP - - PP 256
TABLE 14.15B - DESCRIPTIVE STATISTICS FOR SPUTUM IL-8 (NG/ML) BY TREATMENT GROUP - - PP 257
TABLE 14.16A - SUMMARY OF CHANGE FROM BASELINE IN PULMONARY FUNCTION TEST SVC BY TREATMENT GROUP - - PP 258
TABLE 14.16B - DESCRIPTIVE STATISTICS FOR PULMONARY FUNCTION TEST SVC BY TREATMENT GROUP - - PP 259
TABLE 14A.1A - SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL CD68+ (MACROPHAGES) (CELL/MM2) BY TREATMENT GROUP - ITT 260
TABLE 14A.1B - DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL CD68+ (MACROPHAGES) (CELL/MM2) BY TREATMENT GROUP - ITT - ITT 261
TABLE 14A.1C - SUMMARY OF TEST OF SIGNIFICANCE FOR INTERACTION TERMS AND COVARIATES FOR CHANGE FROM BASELINE IN - SUB-EPITHELIAL CD68+ (MACROPHAGES)/MM^2 - ITT 262
TABLE 14A.1D - SUMMARY OF POISSON REGRESSION MODEL USING GEE FOR CHANGE IN CD68 - ITT 263
TABLE 14A.2A - SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL CD8+ T-LYMPHOCYTES (CELL/MM2) TISSUE BY TREATMENT GROUP - - ITT 264
TABLE 14A.2B - DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL CD8+ T-LYMPHOCYTES (CELL/MM2) TISSUE BY TREATMENT GROUP - - ITT 265

TABLE 14A.2C - SUMMARY OF TEST OF SIGNIFICANCE FOR INTERACTION TERMS AND COVARIATES FOR CHANGE FROM BASELINE IN - SUB-EPITHELIAL CD8+ (T-LYMPHOCYTES)/MM^2 - ITT 266
TABLE 14A.2D - SUMMARY OF POISSON REGRESSION MODEL USING GEE FOR CHANGE IN CD8 - ITT 267
TABLE 14A.3A - SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL NEUTROPHILS (NE+) (CELL/MM2) TISSUE BY TREATMENT GROUP - - ITT 268
TABLE 14A.3B - DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL NEUTROPHILS (NE+) (CELL/MM2) TISSUE BY TREATMENT GROUP - - ITT 269
TABLE 14A.4A - SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL CD4+ LYMPHOCYTES (CELL/MM2) TISSUE BY TREATMENT GROUP - - ITT 270
TABLE 14A.4B - DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL CD4+ LYMPHOCYTES (CELL/MM2) TISSUE BY TREATMENT GROUP - - ITT 271
TABLE 14A.5A - SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL IL-8+ MRNA (CELL/MM2) TISSUE BY TREATMENT GROUP - - ITT 272
TABLE 14A.5B - DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL IL-8+ MRNA (CELL/MM2) TISSUE BY TREATMENT GROUP - - ITT . . . 273
TABLE 14A.6A - SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL TNF-ALPHA +MRNA (CELL/MM2) TISSUE BY TREATMENT GROUP - - ITT 274
TABLE 14A.6B - DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL TNF-ALPHA +MRNA (CELL/MM2) TISSUE BY TREATMENT GROUP - - ITT 275
TABLE 14A.7A - SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL CD45 POSITIVE (CELL/MM2) TISSUE BY TREATMENT GROUP - - ITT 276
TABLE 14A.7B - DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL CD45 POSITIVE (CELL/MM2) TISSUE BY TREATMENT GROUP - - ITT 277
TABLE 14A.8A1 - SUMMARY OF CHANGE FROM BASELINE IN EPITHELIAL MUCIN EXPRESSION (MUC5AC) (CELL/MM2) TISSUE BY TREATMENT GROUP - - ITT 278

TABLE 14A.8A2 - SUMMARY OF CHANGE FROM BASELINE IN SUB-MUCOSA MUCIN EXPRESSION (MUC5AC) (CELL/MM2) TISSUE BY TREATMENT GROUP - - ITT 279
TABLE 14A.8A3 - SUMMARY OF CHANGE FROM BASELINE IN EPITHELIAL MUCIN EXPRESSION (MUC5B) (CELL/MM2) TISSUE BY TREATMENT GROUP - - ITT 280
TABLE 14A.8A4 - SUMMARY OF CHANGE FROM BASELINE IN SUB-MUCOSA MUCIN EXPRESSION (MUC5B) (CELL/MM2) TISSUE BY TREATMENT GROUP - - ITT 281
TABLE 14A.8B1 - DESCRIPTIVE STATISTICS FOR EPITHELIAL MUCIN EXPRESSION (MUC5AC) (CELL/MM2) TISSUE BY TREATMENT GROUP - - ITT 282
TABLE 14A.8B2 - DESCRIPTIVE STATISTICS FOR SUB-MUCOSA MUCIN EXPRESSION (MUC5AC) (CELL/MM2) TISSUE BY TREATMENT GROUP - - ITT 283
TABLE 14A.8B3 - DESCRIPTIVE STATISTICS FOR EPITHELIAL MUCIN EXPRESSION (MUC5B) (CELL/MM2) TISSUE BY TREATMENT GROUP - - ITT 284
TABLE 14A.8B4 - DESCRIPTIVE STATISTICS FOR SUB-MUCOSA MUCIN EXPRESSION (MUC5B) (CELL/MM2) TISSUE BY TREATMENT GROUP - - ITT 285
TABLE 14A.10A - SUMMARY OF CHANGE FROM BASELINE IN SPUTUM TOTAL CELL COUNTS (10^6/ML) BY TREATMENT GROUP - - ITT. 286
TABLE 14A.10B - DESCRIPTIVE STATISTICS FOR SPUTUM TOTAL CELL COUNTS (10^6/ML) BY TREATMENT GROUP - - ITT 287
TABLE 14A.11A - SUMMARY OF CHANGE FROM BASELINE IN SPUTUM MACROPHAGES AS A PERCENTAGE OF TOTAL CELLS BY TREATMENT GROUP - - ITT 288
TABLE 14A.11B - DESCRIPTIVE STATISTICS FOR SPUTUM MACROPHAGES AS A PERCENTAGE OF TOTAL CELLS BY TREATMENT GROUP - - ITT 289
TABLE 14A.12A - SUMMARY OF CHANGE FROM BASELINE IN SPUTUM NEUTROPHIL ELASTASE (NG/ML) BY TREATMENT GROUP - - ITT 290
TABLE 14A.12B - DESCRIPTIVE STATISTICS FOR SPUTUM NEUTROPHIL ELASTASE (NG/ML) BY TREATMENT GROUP - - ITT . 291
TABLE 14A.13A - SUMMARY OF CHANGE FROM BASELINE IN SPUTUM EOSINOPHILS (%) BY TREATMENT GROUP - - ITT 292

TABLE 14A.13B - DESCRIPTIVE STATISTICS FOR SPUTUM EOSINOPHILS (%) BY TREATMENT GROUP - - ITT 293
TABLE 14A.14A - SUMMARY OF CHANGE FROM BASELINE IN SPUTUM LYMPHOCYTES (%) BY TREATMENT GROUP - - ITT 294
TABLE 14A.14B - DESCRIPTIVE STATISTICS FOR SPUTUM LYMPHOCYTES (%) BY TREATMENT GROUP - - ITT 295
TABLE 14A.15A - SUMMARY OF CHANGE FROM BASELINE IN SPUTUM IL-8 (NG/ML) BY TREATMENT GROUP - - ITT 296
TABLE 14A.15B - DESCRIPTIVE STATISTICS FOR SPUTUM IL-8 (NG/ML) BY TREATMENT GROUP - - ITT 297
TABLE 14A.16A - SUMMARY OF CHANGE FROM BASELINE IN PULMONARY FUNCTION TEST SVC BY TREATMENT GROUP - - ITT 298
TABLE 14A.16B - DESCRIPTIVE STATISTICS FOR PULMONARY FUNCTION TEST SVC BY TREATMENT GROUP - - ITT 299

SB 207499

TABLE 14.1A

SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL CD68+ (MACROPHAGES) (CELL/MM2) BY TREATMENT GROUP - PP

PROTOCOL 181

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	ADJ MEAN	SEM	ADJ MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	49	143.55	11.88	.	.	.	.	.	.	.	.
	SB 207499	54	121.44	10.50	.	.	.	.	.	.	.	.
WEEK 12	PLACEBO	49	93.58	8.61	-49.97	13.76	-77.37	-22.57	.	.	.	.
	SB 207499	54	100.63	7.61	-20.82	12.16	-45.04	3.40	29.15	-4.97	63.27	0.093
ENDPOINT	PLACEBO	49	93.58	8.61	-49.97	13.76	-77.37	-22.57	.	.	.	.
	SB 207499	54	100.63	7.61	-20.82	12.16	-45.04	3.40	29.15	-4.97	63.27	0.093

1. ADJUSTED MEANS ARE ADJUSTED FOR CENTRE
2. BASELINE = VISIT 2/2A, WEEK 12 = VISIT 6/6A, ENDPOINT = VISIT 6 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

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SB 207499

TABLE 14.1B

DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL CD68+ (MACROPHAGES) (CELL/MM2) BY TREATMENT GROUP - PP
PROTOCOL 181

		BASELINE			WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	49	.	.	132.45	92.79	120.00	9.65	382.50	.	.	.	.	.
	SB 207499	54	.	.	121.67	83.38	103.20	14.50	355.00	.	.	.	.	.
WEEK 12	PLACEBO	49	132.45	92.79	93.04	49.35	88.50	12.00	219.50	-39.40	94.24	-16.00	-267.00	121.95
	SB 207499	54	121.67	83.38	101.17	63.82	88.75	6.75	250.00	-20.50	86.93	-5.58	-274.70	127.00
ENDPOINT	PLACEBO	49	132.45	92.79	93.04	49.35	88.50	12.00	219.50	-39.40	94.24	-16.00	-267.00	121.95
	SB 207499	54	121.67	83.38	101.17	63.82	88.75	6.75	250.00	-20.50	86.93	-5.58	-274.70	127.00

1. MEAN VALUES ARE THE SAMPLE MEAN
2. BASELINE = VISIT 2/2A, WEEK 12 = VISIT 6/6A, ENDPOINT = VISIT 6 AND EWA

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SB 207499

TABLE 14.1C

SUMMARY OF TEST OF SIGNIFICANCE FOR INTERACTION TERMS AND COVARIATES FOR CHANGE FROM BASELINE IN SUB-EPITHELIAL CD68+ (MACROPHAGES)/MM^2 - PP
PROTOCOL 181

FACTOR	F-STATISTIC	P-VALUE
AGE	0.16	0.6897
SMOKING STATUS	5.07	0.0275
% PREDICTED FEV1	0.43	0.5154
GENDER	0.15	0.7039
CENTRE	1.46	0.1229
TREATMENT	1.43	0.2367
TREATMENT BY CENTRE	0.64	0.8701

1. TESTS FOR COVARIATES WAS BASED ON MODEL WITH EFFECTS: TREATMENT, CENTRE AND EACH OF THE COVARIATES
2. TESTS FOR TREATMENT-BY-CENTRE INTERACTION WAS BASED ON MODEL WITH EFFECTS: TREATMENT, CENTRE AND THE INTERACTION.

CONFIDENTIAL
GM2004/00090/00
SB-207499/181

SB 207499

TABLE 14.1D

SUMMARY OF POISSON REGRESSION MODEL USING GEE FOR CHANGE IN CD68 - PP

PROTOCOL 181

TREATMENT	CELLS PER UNIT AREA	95% CI	INCIDENCE DENSITY RATIO	95% CI	P-VALUE
PLACEBO	72.474	(52.44, 100.16)	.		.
SB 207499	76.405	(55.41, 105.36)	1.0542	(0.84, 1.32)	0.6499

1. MODEL ADJUSTS FOR CENTRE, BASELINE SMOKING STATUS AND BASELINE VALUE

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GM2004/00090/00
SB-207499/181

SB 207499

TABLE 14.1E

SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL CD68+ (MACROPHAGES) (CELL/MM2) BY TREATMENT GROUP - PP (SMOKERS)
PROTOCOL 181

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	ADJ MEAN	SEM	ADJ MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	21	116.40	16.37	.	.	.	.	.	.	.	.
	SB 207499	26	109.05	13.30	.	.	.	.	.	.	.	.
WEEK 12	PLACEBO	21	84.57	14.86	-31.83	15.89	-64.63	0.97	.	.	.	.
	SB 207499	26	112.65	12.07	3.60	12.91	-23.04	30.25	35.43	-7.66	78.52	0.103
ENDPOINT	PLACEBO	21	84.57	14.86	-31.83	15.89	-64.63	0.97	.	.	.	.
	SB 207499	26	112.65	12.07	3.60	12.91	-23.04	30.25	35.43	-7.66	78.52	0.103

1. ADJUSTED MEANS ARE ADJUSTED FOR CENTRE
2. BASELINE = VISIT 2/2A, WEEK 12 = VISIT 6/6A, ENDPOINT = VISIT 6 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14.1F

SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL CD68+ (MACROPHAGES) (CELL/MM2) BY TREATMENT GROUP - PP (NON-SMOKERS)
PROTOCOL 181

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	ADJ MEAN	SEM	ADJ MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	28	162.65	14.78	.	.	.	.	.	.	.	.
	SB 207499	28	116.84	15.33	.	.	.	.	.	.	.	.
WEEK 12	PLACEBO	28	98.64	11.19	-64.00	17.98	-100.59	-27.42	.	.	.	.
	SB 207499	28	92.59	11.60	-24.25	18.65	-62.19	13.68	39.75	-10.81	90.31	0.119
ENDPOINT	PLACEBO	28	98.64	11.19	-64.00	17.98	-100.59	-27.42	.	.	.	.
	SB 207499	28	92.59	11.60	-24.25	18.65	-62.19	13.68	39.75	-10.81	90.31	0.119

1. ADJUSTED MEANS ARE ADJUSTED FOR CENTRE
2. BASELINE = VISIT 2/2A, WEEK 12 = VISIT 6/6A, ENDPOINT = VISIT 6 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14.1G

DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL CD68+ (MACROPHAGES) (CELL/MM2) BY TREATMENT GROUP - PP (SMOKERS)
PROTOCOL 181

		BASELINE			WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	21	.	.	96.46	52.46	106.50	24.50	175.50	.	.	.	.	.
	SB 207499	26	.	.	111.17	74.18	95.58	18.65	292.00	.	.	.	.	.
WEEK 12	PLACEBO	21	96.46	52.46	78.85	49.72	80.00	12.00	165.00	-17.62	51.10	-16.00	-111.50	120.00
	SB 207499	26	111.17	74.18	108.66	65.59	97.75	6.85	250.00	-2.51	74.25	8.28	-139.50	116.30
ENDPOINT	PLACEBO	21	96.46	52.46	78.85	49.72	80.00	12.00	165.00	-17.62	51.10	-16.00	-111.50	120.00
	SB 207499	26	111.17	74.18	108.66	65.59	97.75	6.85	250.00	-2.51	74.25	8.28	-139.50	116.30

1. MEAN VALUES ARE THE SAMPLE MEAN
2. BASELINE = VISIT 2/2A, WEEK 12 = VISIT 6/6A, ENDPOINT = VISIT 6 AND EWA

CONFIDENTIAL

SB 207499

TABLE 14.1H

DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL CD68+ (MACROPHAGES) (CELL/MM2) BY TREATMENT GROUP - PP (NON-SMOKERS)
PROTOCOL 181

		BASELINE			WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	28	.	.	159.43	107.27	142.63	9.65	382.50	.	.	.	.	.
	SB 207499	28	.	.	131.43	91.36	107.75	14.50	355.00	.	.	.	.	.
WEEK 12	PLACEBO	28	159.43	107.27	103.69	47.16	100.08	20.00	219.50	-55.74	114.93	-22.50	-267.00	121.95
	SB 207499	28	131.43	91.36	94.22	62.52	83.25	6.75	234.00	-37.21	95.54	-21.15	-274.70	127.00
ENDPOINT	PLACEBO	28	159.43	107.27	103.69	47.16	100.08	20.00	219.50	-55.74	114.93	-22.50	-267.00	121.95
	SB 207499	28	131.43	91.36	94.22	62.52	83.25	6.75	234.00	-37.21	95.54	-21.15	-274.70	127.00

1. MEAN VALUES ARE THE SAMPLE MEAN
2. BASELINE = VISIT 2/2A, WEEK 12 = VISIT 6/6A, ENDPOINT = VISIT 6 AND EWA

CONFIDENTIAL

SB 207499

TABLE 14.2A

SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL CD8+ T-LYMPHOCYTES (CELL/MM2) TISSUE BY TREATMENT GROUP - PP
PROTOCOL 181

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	ADJ MEAN	SEM	ADJ MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	49	213.49	10.87	.	.	.	.	.	.	.	.
	SB 207499	54	201.90	9.61	.	.	.	.	.	.	.	.
WEEK 12	PLACEBO	49	143.73	11.20	-69.76	13.59	-96.83	-42.69	.	.	.	.
	SB 207499	54	126.60	9.90	-75.30	12.01	-99.23	-51.37	-5.54	-39.25	28.17	0.744
ENDPOINT	PLACEBO	49	143.73	11.20	-69.76	13.59	-96.83	-42.69	.	.	.	.
	SB 207499	54	126.60	9.90	-75.30	12.01	-99.23	-51.37	-5.54	-39.25	28.17	0.744

1. ADJUSTED MEANS ARE ADJUSTED FOR CENTRE
2. BASELINE = VISIT 2/2A, WEEK 12 = VISIT 6/6A, ENDPOINT = VISIT 6 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

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SB 207499

TABLE 14.2B

DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL CD8+ T-LYMPHOCYTES (CELL/MM2) TISSUE BY TREATMENT GROUP - PP
PROTOCOL 181

		BASELINE			WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	49	.	.	210.11	62.52	212.40	68.00	345.60	.	.	.	.	.
	SB 207499	54	.	.	200.14	62.31	189.05	109.50	392.55	.	.	.	.	.
WEEK 12	PLACEBO	49	210.11	62.52	148.42	72.17	137.65	30.45	356.55	-61.69	76.88	-62.60	-208.30	86.60
	SB 207499	54	200.14	62.31	130.65	73.27	108.30	19.20	308.85	-69.49	86.28	-65.32	-293.85	172.95
ENDPOINT	PLACEBO	49	210.11	62.52	148.42	72.17	137.65	30.45	356.55	-61.69	76.88	-62.60	-208.30	86.60
	SB 207499	54	200.14	62.31	130.65	73.27	108.30	19.20	308.85	-69.49	86.28	-65.32	-293.85	172.95

1. MEAN VALUES ARE THE SAMPLE MEAN
2. BASELINE = VISIT 2/2A, WEEK 12 = VISIT 6/6A, ENDPOINT = VISIT 6 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

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SB 207499

TABLE 14.2C

SUMMARY OF TEST OF SIGNIFICANCE FOR INTERACTION TERMS AND COVARIATES FOR CHANGE FROM BASELINE IN SUB-EPITHELIAL CD8+ (T-LYMPHOCYTES)/MM^2 - PP
PROTOCOL 181

FACTOR	F-STATISTIC	P-VALUE
AGE	0.21	0.6458
SMOKING STATUS	0.00	0.9533
% PREDICTED FEV1	0.21	0.6498
GENDER	2.94	0.0907
CENTRE	1.05	0.4283
TREATMENT	0.24	0.6264
TREATMENT BY CENTRE	0.87	0.6274

1. TESTS FOR COVARIATES WAS BASED ON MODEL WITH EFFECTS: TREATMENT, CENTRE AND EACH OF THE COVARIATES
2. TESTS FOR TREATMENT-BY-CENTRE INTERACTION WAS BASED ON MODEL WITH EFFECTS: TREATMENT, CENTRE AND THE INTERACTION.

CONFIDENTIAL
GM2004/00090/00
SB-207499/181

SB 207499

TABLE 14.2D

SUMMARY OF POISSON REGRESSION MODEL USING GEE FOR CHANGE IN CD8 - PP

PROTOCOL 181

TREATMENT	CELLS PER UNIT AREA	95% CI	INCIDENCE DENSITY RATIO	95% CI	P-VALUE
PLACEBO	120.550	(93.00, 156.26)	.		.
SB 207499	108.801	(84.41, 140.24)	0.9025	(0.74, 1.09)	0.2967

1. MODEL ADJUSTS FOR CENTRE, BASELINE SMOKING STATUS AND BASELINE VALUE

CONFIDENTIAL

SB 207499

TABLE 14.2E

SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL CD8+ T-LYMPHOCYTES (CELL/MM2) TISSUE BY TREATMENT GROUP - PP (SMOKERS)
PROTOCOL 181

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	ADJ MEAN	SEM	ADJ MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	21	188.56	20.63	.	.	.	.	.	.	.	.
	SB 207499	26	202.12	16.76	.	.	.	.	.	.	.	.
WEEK 12	PLACEBO	21	126.49	16.19	-62.07	26.68	-117.15	-7.00	.	.	.	.
	SB 207499	26	135.98	13.15	-66.14	21.68	-110.88	-21.40	-4.06	-76.42	68.29	0.909
ENDPOINT	PLACEBO	21	126.49	16.19	-62.07	26.68	-117.15	-7.00	.	.	.	.
	SB 207499	26	135.98	13.15	-66.14	21.68	-110.88	-21.40	-4.06	-76.42	68.29	0.909

1. ADJUSTED MEANS ARE ADJUSTED FOR CENTRE
2. BASELINE = VISIT 2/2A, WEEK 12 = VISIT 6/6A, ENDPOINT = VISIT 6 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

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SB 207499

TABLE 14.2F

SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL CD8+ T-LYMPHOCYTES (CELL/MM2) TISSUE BY TREATMENT GROUP - PP (NON-SMOKERS)
PROTOCOL 181

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	ADJ MEAN	SEM	ADJ MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	28	226.92	11.65	.	.	.	.	.	.	.	.
	SB 207499	28	195.34	12.08	.	.	.	.	.	.	.	.
WEEK 12	PLACEBO	28	156.00	16.53	-70.92	16.92	-105.35	-36.49	.	.	.	.
	SB 207499	28	116.96	17.14	-78.38	17.55	-114.08	-42.68	-7.46	-55.04	40.13	0.752
ENDPOINT	PLACEBO	28	156.00	16.53	-70.92	16.92	-105.35	-36.49	.	.	.	.
	SB 207499	28	116.96	17.14	-78.38	17.55	-114.08	-42.68	-7.46	-55.04	40.13	0.752

1. ADJUSTED MEANS ARE ADJUSTED FOR CENTRE
2. BASELINE = VISIT 2/2A, WEEK 12 = VISIT 6/6A, ENDPOINT = VISIT 6 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

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SB 207499

TABLE 14.2G

DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL CD8+ T-LYMPHOCYTES (CELL/MM2) TISSUE BY TREATMENT GROUP - PP (SMOKERS)
PROTOCOL 181

		BASELINE			WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	21	.	.	200.71	66.48	188.50	68.00	345.60	.	.	.	.	.
	SB 207499	26	.	.	203.63	65.67	207.50	109.50	363.35	.	.	.	.	.
WEEK 12	PLACEBO	21	200.71	66.48	123.27	58.42	109.20	30.45	210.10	-77.44	82.51	-77.35	-208.30	69.65
	SB 207499	26	203.63	65.67	130.13	61.75	111.73	58.25	288.50	-73.50	80.14	-62.90	-293.85	79.25
ENDPOINT	PLACEBO	21	200.71	66.48	123.27	58.42	109.20	30.45	210.10	-77.44	82.51	-77.35	-208.30	69.65
	SB 207499	26	203.63	65.67	130.13	61.75	111.73	58.25	288.50	-73.50	80.14	-62.90	-293.85	79.25

1. MEAN VALUES ARE THE SAMPLE MEAN
2. BASELINE = VISIT 2/2A, WEEK 12 = VISIT 6/6A, ENDPOINT = VISIT 6 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14.2H

DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL CD8+ T-LYMPHOCYTES (CELL/MM2) TISSUE BY TREATMENT GROUP - PP (NON-SMOKERS)
PROTOCOL 181

		BASELINE			WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	28	.	.	217.16	59.61	231.05	80.50	344.25	.	.	.	.	.
	SB 207499	28	.	.	196.89	60.05	187.05	123.40	392.55	.	.	.	.	.
WEEK 12	PLACEBO	28	217.16	59.61	167.28	76.62	153.05	31.45	356.55	-49.88	71.60	-49.20	-198.65	86.60
	SB 207499	28	196.89	60.05	131.13	83.70	101.08	19.20	308.85	-65.76	92.93	-72.23	-200.35	172.95
ENDPOINT	PLACEBO	28	217.16	59.61	167.28	76.62	153.05	31.45	356.55	-49.88	71.60	-49.20	-198.65	86.60
	SB 207499	28	196.89	60.05	131.13	83.70	101.08	19.20	308.85	-65.76	92.93	-72.23	-200.35	172.95

1. MEAN VALUES ARE THE SAMPLE MEAN
2. BASELINE = VISIT 2/2A, WEEK 12 = VISIT 6/6A, ENDPOINT = VISIT 6 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

GM2004/00090/00
SB-207499/181

SB 207499

TABLE 14.3A

SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL NEUTROPHILS (NE+) (CELL/MM2) TISSUE BY TREATMENT GROUP - PP
PROTOCOL 181

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	ADJ MEAN	SEM	ADJ MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	49	46.85	5.01	.	.	.	.	.	.	.	.
	SB 207499	54	38.01	4.43	.	.	.	.	.	.	.	.
WEEK 12	PLACEBO	49	25.21	4.12	-21.64	6.52	-34.63	-8.65	.	.	.	.
	SB 207499	54	35.81	3.64	-2.20	5.76	-13.68	9.28	19.44	3.27	35.62	0.019
ENDPOINT	PLACEBO	49	25.21	4.12	-21.64	6.52	-34.63	-8.65	.	.	.	.
	SB 207499	54	35.81	3.64	-2.20	5.76	-13.68	9.28	19.44	3.27	35.62	0.019

1. ADJUSTED MEANS ARE ADJUSTED FOR CENTRE
2. BASELINE = VISIT 2/2A, WEEK 12 = VISIT 6/6A, ENDPOINT = VISIT 6 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14.3B

DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL NEUTROPHILS (NE+) (CELL/MM2) TISSUE BY TREATMENT GROUP - PP
PROTOCOL 181

		BASELINE			WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	49	.	.	46.94	38.93	36.75	1.75	198.50	.	.	.	.	.
	SB 207499	54	.	.	36.73	23.07	35.10	0.55	111.55	.	.	.	.	.
WEEK 12	PLACEBO	49	46.94	38.93	26.24	23.29	19.90	1.55	120.25	-20.70	40.66	-10.60	-185.70	72.00
	SB 207499	54	36.73	23.07	35.91	29.06	25.45	2.30	128.90	-0.82	34.46	-3.03	-93.60	77.10
ENDPOINT	PLACEBO	49	46.94	38.93	26.24	23.29	19.90	1.55	120.25	-20.70	40.66	-10.60	-185.70	72.00
	SB 207499	54	36.73	23.07	35.91	29.06	25.45	2.30	128.90	-0.82	34.46	-3.03	-93.60	77.10

1. MEAN VALUES ARE THE SAMPLE MEAN
2. BASELINE = VISIT 2/2A, WEEK 12 = VISIT 6/6A, ENDPOINT = VISIT 6 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14.4A

SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL CD4+ LYMPHOCYTES (CELL/MM2) TISSUE BY TREATMENT GROUP - PP
PROTOCOL 181

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	ADJ MEAN	SEM	ADJ MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	49	122.87	8.55	.	.	.	.	.	.	.	.
	SB 207499	54	102.28	7.56	.	.	.	.	.	.	.	.
WEEK 12	PLACEBO	49	101.25	8.27	-21.62	11.99	-45.49	2.26	.	.	.	.
	SB 207499	54	94.22	7.31	-8.06	10.60	-29.16	13.04	13.56	-16.18	43.29	0.367
ENDPOINT	PLACEBO	49	101.25	8.27	-21.62	11.99	-45.49	2.26	.	.	.	.
	SB 207499	54	94.22	7.31	-8.06	10.60	-29.16	13.04	13.56	-16.18	43.29	0.367

1. ADJUSTED MEANS ARE ADJUSTED FOR CENTRE
2. BASELINE = VISIT 2/2A, WEEK 12 = VISIT 6/6A, ENDPOINT = VISIT 6 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

GM2004/00090/00
SB-207499/181

SB 207499

TABLE 14.4B

DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL CD4+ LYMPHOCYTES (CELL/MM2) TISSUE BY TREATMENT GROUP - PP
PROTOCOL 181

		BASELINE			WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	49	.	.	121.45	57.07	110.40	37.55	287.45	.	.	.	.	.
	SB 207499	54	.	.	101.81	46.61	96.53	31.75	219.15	.	.	.	.	.
WEEK 12	PLACEBO	49	121.45	57.07	93.43	48.56	81.60	12.10	223.60	-28.02	71.94	-21.90	-201.85	133.25
	SB 207499	54	101.81	46.61	88.64	56.36	81.83	13.25	259.00	-13.17	68.08	-11.60	-205.60	112.35
ENDPOINT	PLACEBO	49	121.45	57.07	93.43	48.56	81.60	12.10	223.60	-28.02	71.94	-21.90	-201.85	133.25
	SB 207499	54	101.81	46.61	88.64	56.36	81.83	13.25	259.00	-13.17	68.08	-11.60	-205.60	112.35

1. MEAN VALUES ARE THE SAMPLE MEAN
2. BASELINE = VISIT 2/2A, WEEK 12 = VISIT 6/6A, ENDPOINT = VISIT 6 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

GM2004/00090/00
SB-207499/181

SB 207499

TABLE 14.5A

SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL IL-8+ MRNA (CELL/MM2) TISSUE BY TREATMENT GROUP - PP
PROTOCOL 181

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	ADJ MEAN	SEM	ADJ MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	49	44.36	4.73	.	.	.	.	.	.	.	.
	SB 207499	54	36.08	4.18	.	.	.	.	.	.	.	.
WEEK 12	PLACEBO	49	19.60	2.34	-24.76	4.71	-34.15	-15.37	.	.	.	.
	SB 207499	54	22.90	2.07	-13.18	4.17	-21.48	-4.88	11.58	-0.12	23.27	0.052
ENDPOINT	PLACEBO	49	19.60	2.34	-24.76	4.71	-34.15	-15.37	.	.	.	.
	SB 207499	54	22.90	2.07	-13.18	4.17	-21.48	-4.88	11.58	-0.12	23.27	0.052

1. ADJUSTED MEANS ARE ADJUSTED FOR CENTRE
2. BASELINE = VISIT 2/2A, WEEK 12 = VISIT 6/6A, ENDPOINT = VISIT 6 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14.5B

DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL IL-8+ MRNA (CELL/MM2) TISSUE BY TREATMENT GROUP - PP
PROTOCOL 181

		BASELINE			WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	49	.	.	43.55	33.98	34.00	7.10	211.70	.	.	.	.	.
	SB 207499	54	.	.	36.43	18.86	32.65	7.65	92.90	.	.	.	.	.
WEEK 12	PLACEBO	49	43.55	33.98	19.43	13.68	16.00	5.00	78.80	-24.12	33.27	-19.65	-202.15	15.40
	SB 207499	54	36.43	18.86	23.07	16.58	19.50	4.15	84.55	-13.36	21.34	-13.58	-65.35	65.15
ENDPOINT	PLACEBO	49	43.55	33.98	19.43	13.68	16.00	5.00	78.80	-24.12	33.27	-19.65	-202.15	15.40
	SB 207499	54	36.43	18.86	23.07	16.58	19.50	4.15	84.55	-13.36	21.34	-13.58	-65.35	65.15

1. MEAN VALUES ARE THE SAMPLE MEAN
2. BASELINE = VISIT 2/2A, WEEK 12 = VISIT 6/6A, ENDPOINT = VISIT 6 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14.6A

SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL TNF-ALPHA +MRNA (CELL/MM2) TISSUE BY TREATMENT GROUP - PP
PROTOCOL 181

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	ADJ MEAN	SEM	ADJ MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	49	70.34	5.16	.	.	.	.	.	.	.	.
	SB 207499	54	63.46	4.56	.	.	.	.	.	.	.	.
WEEK 12	PLACEBO	49	27.81	2.90	-42.53	5.73	-53.95	-31.11	.	.	.	.
	SB 207499	54	28.56	2.57	-34.90	5.07	-44.99	-24.81	7.63	-6.59	21.84	0.289
ENDPOINT	PLACEBO	49	27.81	2.90	-42.53	5.73	-53.95	-31.11	.	.	.	.
	SB 207499	54	28.56	2.57	-34.90	5.07	-44.99	-24.81	7.63	-6.59	21.84	0.289

1. ADJUSTED MEANS ARE ADJUSTED FOR CENTRE
2. BASELINE = VISIT 2/2A, WEEK 12 = VISIT 6/6A, ENDPOINT = VISIT 6 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL
GM2004/00090/00
SB-207499/181

SB 207499

TABLE 14.6B

DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL TNF-ALPHA +MRNA (CELL/MM2) TISSUE BY TREATMENT GROUP - PP
PROTOCOL 181

		BASELINE			WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	49	.	.	66.76	32.74	67.30	13.90	142.15	.	.	.	.	.
	SB 207499	54	.	.	62.90	32.95	57.50	11.80	134.20	.	.	.	.	.
WEEK 12	PLACEBO	49	66.76	32.74	28.21	19.69	23.30	9.75	108.00	-38.55	35.87	-40.05	-117.70	54.55
	SB 207499	54	62.90	32.95	29.20	17.96	25.33	8.75	109.75	-33.70	35.32	-29.13	-119.75	27.90
ENDPOINT	PLACEBO	49	66.76	32.74	28.21	19.69	23.30	9.75	108.00	-38.55	35.87	-40.05	-117.70	54.55
	SB 207499	54	62.90	32.95	29.20	17.96	25.33	8.75	109.75	-33.70	35.32	-29.13	-119.75	27.90

1. MEAN VALUES ARE THE SAMPLE MEAN
2. BASELINE = VISIT 2/2A, WEEK 12 = VISIT 6/6A, ENDPOINT = VISIT 6 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14.7A

SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL CD45 POSITIVE (CELL/MM2) TISSUE BY TREATMENT GROUP - PP
PROTOCOL 181

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	ADJ MEAN	SEM	ADJ MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	49	393.12	17.13	.	.	.	.	.	.	.	.
	SB 207499	54	396.14	15.14	.	.	.	.	.	.	.	.
WEEK 12	PLACEBO	49	302.39	17.68	-90.73	18.77	-128.12	-53.34	.	.	.	.
	SB 207499	54	296.79	15.62	-99.35	16.59	-132.40	-66.30	-8.62	-55.18	37.94	0.713
ENDPOINT	PLACEBO	49	302.39	17.68	-90.73	18.77	-128.12	-53.34	.	.	.	.
	SB 207499	54	296.79	15.62	-99.35	16.59	-132.40	-66.30	-8.62	-55.18	37.94	0.713

1. ADJUSTED MEANS ARE ADJUSTED FOR CENTRE
2. BASELINE = VISIT 2/2A, WEEK 12 = VISIT 6/6A, ENDPOINT = VISIT 6 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14.7B

DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL CD45 POSITIVE (CELL/MM2) TISSUE BY TREATMENT GROUP - PP
PROTOCOL 181

		BASELINE			WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	49	.	.	380.39	110.78	401.05	36.50	591.00	.	.	.	.	.
	SB 207499	54	.	.	391.38	104.75	402.85	170.80	607.10	.	.	.	.	.
WEEK 12	PLACEBO	49	380.39	110.78	291.89	99.18	266.30	124.30	545.30	-88.51	102.21	-75.40	-352.40	130.25
	SB 207499	54	391.38	104.75	291.04	136.33	247.15	43.65	627.65	-100.34	140.00	-104.33	-437.60	302.25
ENDPOINT	PLACEBO	49	380.39	110.78	291.89	99.18	266.30	124.30	545.30	-88.51	102.21	-75.40	-352.40	130.25
	SB 207499	54	391.38	104.75	291.04	136.33	247.15	43.65	627.65	-100.34	140.00	-104.33	-437.60	302.25

1. MEAN VALUES ARE THE SAMPLE MEAN
2. BASELINE = VISIT 2/2A, WEEK 12 = VISIT 6/6A, ENDPOINT = VISIT 6 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14.8A1

SUMMARY OF CHANGE FROM BASELINE IN EPITHELIAL MUCIN EXPRESSION (MUC5AC) (CELL/MM2) TISSUE BY TREATMENT GROUP - PP
PROTOCOL 181

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	ADJ MEAN	SEM	ADJ MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	18	47.80	4.94	.	.	.	.	.	.	.	.
	SB 207499	21	41.19	4.65	.	.	.	.	.	.	.	.
WEEK 12	PLACEBO	18	46.50	3.94	-1.30	5.15	-12.03	9.44	.	.	.	.
	SB 207499	21	40.70	3.71	-0.48	4.84	-10.59	9.62	0.81	-14.84	16.47	0.915
ENDPOINT	PLACEBO	18	46.50	3.94	-1.30	5.15	-12.03	9.44	.	.	.	.
	SB 207499	21	40.70	3.71	-0.48	4.84	-10.59	9.62	0.81	-14.84	16.47	0.915

1. ADJUSTED MEANS ARE ADJUSTED FOR CENTRE
2. BASELINE = VISIT 2/2A, WEEK 12 = VISIT 6/6A, ENDPOINT = VISIT 6 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

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GM2004/00090/00
SB-207499/181

SB 207499

TABLE 14.8A2

SUMMARY OF CHANGE FROM BASELINE IN SUB-MUCOSA MUCIN EXPRESSION (MUC5AC) (CELL/MM2) TISSUE BY TREATMENT GROUP - PP
PROTOCOL 181

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	ADJ MEAN	SEM	ADJ MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	10	5.30	0.62	.	.	.	.	.	.	.	.
	SB 207499	14	4.34	0.41	.	.	.	.	.	.	.	.
WEEK 12	PLACEBO	10	7.97	1.01	2.67	1.02	0.40	4.94	.	.	.	.
	SB 207499	14	8.15	0.68	3.82	0.68	2.29	5.34	1.15	-1.71	4.01	0.393
ENDPOINT	PLACEBO	10	7.97	1.01	2.67	1.02	0.40	4.94	.	.	.	.
	SB 207499	14	8.15	0.68	3.82	0.68	2.29	5.34	1.15	-1.71	4.01	0.393

1. MEAN VALUES ARE THE SAMPLE MEAN
2. BASELINE = VISIT 2/2A, WEEK 12 = VISIT 6/6A, ENDPOINT = VISIT 6 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

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SB 207499

TABLE 14.8A3

SUMMARY OF CHANGE FROM BASELINE IN EPITHELIAL MUCIN EXPRESSION (MUC5B) (CELL/MM2) TISSUE BY TREATMENT GROUP - PP
PROTOCOL 181

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	ADJ MEAN	SEM	ADJ MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	16	33.23	4.77	.	.	.	.	.	.	.	.
	SB 207499	20	32.86	4.71	.	.	.	.	.	.	.	.
WEEK 12	PLACEBO	16	32.06	4.73	-1.17	6.26	-14.23	11.89	.	.	.	.
	SB 207499	20	23.61	4.68	-9.26	6.19	-22.16	3.65	-8.09	-27.00	10.82	0.383
ENDPOINT	PLACEBO	16	32.06	4.73	-1.17	6.26	-14.23	11.89	.	.	.	.
	SB 207499	20	23.61	4.68	-9.26	6.19	-22.16	3.65	-8.09	-27.00	10.82	0.383

1. ADJUSTED MEANS ARE ADJUSTED FOR CENTRE
2. BASELINE = VISIT 2/2A, WEEK 12 = VISIT 6/6A, ENDPOINT = VISIT 6 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

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GM2004/00090/00
SB-207499/181

SB 207499

TABLE 14.8A4

SUMMARY OF CHANGE FROM BASELINE IN SUB-MUCOSA MUCIN EXPRESSION (MUC5B) (CELL/MM2) TISSUE BY TREATMENT GROUP - PP
PROTOCOL 181

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	ADJ MEAN	SEM	ADJ MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	18	54.54	4.46	.	.	.	.	.	.	.	.
	SB 207499	19	56.75	4.33	.	.	.	.	.	.	.	.
WEEK 12	PLACEBO	18	45.04	4.62	-9.50	6.54	-23.24	4.24	.	.	.	.
	SB 207499	19	57.77	4.49	1.02	6.35	-12.33	14.36	10.52	-9.09	30.13	0.275
ENDPOINT	PLACEBO	18	45.04	4.62	-9.50	6.54	-23.24	4.24	.	.	.	.
	SB 207499	19	57.77	4.49	1.02	6.35	-12.33	14.36	10.52	-9.09	30.13	0.275

1. ADJUSTED MEANS ARE ADJUSTED FOR CENTRE
2. BASELINE = VISIT 2/2A, WEEK 12 = VISIT 6/6A, ENDPOINT = VISIT 6 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14.8B1

DESCRIPTIVE STATISTICS FOR EPITHELIAL MUCIN EXPRESSION (MUC5AC) (CELL/MM2) TISSUE BY TREATMENT GROUP - PP
PROTOCOL 181

		BASELINE			WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	18	.	.	45.61	17.32	42.45	19.60	84.85	.	.	.	.	.
	SB 207499	21	.	.	42.59	14.56	40.67	26.61	75.63	.	.	.	.	.
WEEK 12	PLACEBO	18	45.61	17.32	42.50	14.01	42.99	16.99	68.02	-3.11	19.45	-1.68	-48.24	36.07
	SB 207499	21	42.59	14.56	45.21	14.53	41.96	16.74	69.83	2.62	18.51	-1.61	-38.09	37.93
ENDPOINT	PLACEBO	18	45.61	17.32	42.50	14.01	42.99	16.99	68.02	-3.11	19.45	-1.68	-48.24	36.07
	SB 207499	21	42.59	14.56	45.21	14.53	41.96	16.74	69.83	2.62	18.51	-1.61	-38.09	37.93

1. MEAN VALUES ARE THE SAMPLE MEAN
2. BASELINE = VISIT 2/2A, WEEK 12 = VISIT 6/6A, ENDPOINT = VISIT 6 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14.8B2

DESCRIPTIVE STATISTICS FOR SUB-MUCOSA MUCIN EXPRESSION (MUC5AC) (CELL/MM2) TISSUE BY TREATMENT GROUP - PP
PROTOCOL 181

		BASELINE			WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	10	.	.	1.40	1.83	0.55	0.05	6.11	.	.	.	.	.
	SB 207499	14	.	.	4.49	9.41	1.53	0.19	36.46	.	.	.	.	.
WEEK 12	PLACEBO	10	1.40	1.83	1.62	2.53	0.98	0.00	8.59	0.21	2.64	-0.02	-4.69	6.22
	SB 207499	14	4.49	9.41	7.66	14.41	1.34	0.00	46.34	3.17	7.89	-0.05	-3.40	27.34
ENDPOINT	PLACEBO	10	1.40	1.83	1.62	2.53	0.98	0.00	8.59	0.21	2.64	-0.02	-4.69	6.22
	SB 207499	14	4.49	9.41	7.66	14.41	1.34	0.00	46.34	3.17	7.89	-0.05	-3.40	27.34

1. MEAN VALUES ARE THE SAMPLE MEAN
2. BASELINE = VISIT 2/2A, WEEK 12 = VISIT 6/6A, ENDPOINT = VISIT 6 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14.8B3

DESCRIPTIVE STATISTICS FOR EPITHELIAL MUCIN EXPRESSION (MUC5B) (CELL/MM2) TISSUE BY TREATMENT GROUP - PP
PROTOCOL 181

		BASELINE			WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	16	.	.	36.37	16.94	35.42	4.71	59.22	.	.	.	.	.
	SB 207499	20	.	.	35.20	20.01	32.03	0.72	71.04	.	.	.	.	.
WEEK 12	PLACEBO	16	36.37	16.94	31.94	18.15	33.75	0.89	61.06	-4.43	20.83	-2.78	-40.95	29.17
	SB 207499	20	35.20	20.01	29.03	18.87	31.33	2.35	66.40	-6.17	21.34	-3.18	-54.06	29.92
ENDPOINT	PLACEBO	16	36.37	16.94	31.94	18.15	33.75	0.89	61.06	-4.43	20.83	-2.78	-40.95	29.17
	SB 207499	20	35.20	20.01	29.03	18.87	31.33	2.35	66.40	-6.17	21.34	-3.18	-54.06	29.92

1. MEAN VALUES ARE THE SAMPLE MEAN
2. BASELINE = VISIT 2/2A, WEEK 12 = VISIT 6/6A, ENDPOINT = VISIT 6 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14.8B4

DESCRIPTIVE STATISTICS FOR SUB-MUCOSA MUCIN EXPRESSION (MUC5B) (CELL/MM2) TISSUE BY TREATMENT GROUP - PP
PROTOCOL 181

		BASELINE			WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	18	.	.	51.34	11.46	49.82	34.13	74.05	.	.	.	.	.
	SB 207499	19	.	.	59.03	18.27	58.52	24.98	98.13	.	.	.	.	.
WEEK 12	PLACEBO	18	51.34	11.46	46.27	14.58	45.53	18.25	75.60	-5.07	17.56	-4.35	-44.92	32.62
	SB 207499	19	59.03	18.27	58.64	17.22	58.82	17.82	94.48	-0.40	25.28	-0.79	-44.67	50.13
ENDPOINT	PLACEBO	18	51.34	11.46	46.27	14.58	45.53	18.25	75.60	-5.07	17.56	-4.35	-44.92	32.62
	SB 207499	19	59.03	18.27	58.64	17.22	58.82	17.82	94.48	-0.40	25.28	-0.79	-44.67	50.13

1. MEAN VALUES ARE THE SAMPLE MEAN
2. BASELINE = VISIT 2/2A, WEEK 12 = VISIT 6/6A, ENDPOINT = VISIT 6 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14.10A

SUMMARY OF CHANGE FROM BASELINE IN SPUTUM TOTAL CELL COUNTS (10^6/ML) BY TREATMENT GROUP - PP
PROTOCOL 181

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	ADJ MEAN	SEM	ADJ MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	42	14.48	2.94	.	.	.	.	.	.	.	.
	SB 207499	43	9.41	2.73	.	.	.	.	.	.	.	.
WEEK 13	PLACEBO	42	6.50	0.77	-7.98	2.69	-13.36	-2.61	.	.	.	.
	SB 207499	43	4.12	0.71	-5.29	2.49	-10.28	-0.30	2.69	-4.22	9.60	0.439
ENDPOINT	PLACEBO	42	6.50	0.77	-7.98	2.69	-13.36	-2.61	.	.	.	.
	SB 207499	43	4.12	0.71	-5.29	2.49	-10.28	-0.30	2.69	-4.22	9.60	0.439

1. ADJUSTED MEANS ARE ADJUSTED FOR CENTRE
2. BASELINE = VISIT 2/2A, WEEK 13 = VISIT 7/7A, ENDPOINT = VISIT 7 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14.10B

DESCRIPTIVE STATISTICS FOR SPUTUM TOTAL CELL COUNTS (10^6/ML) BY TREATMENT GROUP - PP
PROTOCOL 181

		BASELINE			WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	42	.	.	12.04	20.82	4.03	0.08	111.44	.	.	.	.	.
	SB 207499	43	.	.	8.49	13.35	3.74	0.20	78.38	.	.	.	.	.
WEEK 13	PLACEBO	42	12.04	20.82	6.21	6.37	4.07	0.16	29.88	-5.83	17.08	-0.56	-81.56	11.40
	SB 207499	43	8.49	13.35	4.31	4.44	3.50	0.23	19.61	-4.18	13.17	-0.87	-77.30	15.46
ENDPOINT	PLACEBO	42	12.04	20.82	6.21	6.37	4.07	0.16	29.88	-5.83	17.08	-0.56	-81.56	11.40
	SB 207499	43	8.49	13.35	4.31	4.44	3.50	0.23	19.61	-4.18	13.17	-0.87	-77.30	15.46

1. MEAN VALUES ARE THE SAMPLE MEAN
2. BASELINE = VISIT 2/2A, WEEK 13 = VISIT 7/7A, ENDPOINT = VISIT 7 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14.11A

SUMMARY OF CHANGE FROM BASELINE IN SPUTUM MACROPHAGES AS A PERCENTAGE OF TOTAL CELLS BY TREATMENT GROUP - PP
PROTOCOL 181

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	ADJ MEAN	SEM	ADJ MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	33	44.30	4.19	.	.	.	.	.	.	.	.
	SB 207499	33	44.52	3.95	.	.	.	.	.	.	.	.
WEEK 13	PLACEBO	33	40.44	3.41	-3.86	5.40	-14.78	7.05	.	.	.	.
	SB 207499	33	49.28	3.22	4.76	5.10	-5.54	15.06	8.63	-5.55	22.80	0.226
ENDPOINT	PLACEBO	33	40.44	3.41	-3.86	5.40	-14.78	7.05	.	.	.	.
	SB 207499	33	49.28	3.22	4.76	5.10	-5.54	15.06	8.63	-5.55	22.80	0.226

1. ADJUSTED MEANS ARE ADJUSTED FOR CENTRE
2. BASELINE = VISIT 2/2A, WEEK 13 = VISIT 7/7A, ENDPOINT = VISIT 7 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14.11B

DESCRIPTIVE STATISTICS FOR SPUTUM MACROPHAGES AS A PERCENTAGE OF TOTAL CELLS BY TREATMENT GROUP - PP
PROTOCOL 181

		BASELINE			WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	33	.	.	43.27	20.48	43.00	6.25	91.50	.	.	.	.	.
	SB 207499	33	.	.	43.63	21.89	41.50	8.88	91.50	.	.	.	.	.
WEEK 13	PLACEBO	33	43.27	20.48	35.84	20.71	29.25	3.50	90.00	-7.43	26.71	-4.25	-62.50	73.50
	SB 207499	33	43.63	21.89	43.44	27.23	34.75	8.75	90.97	-0.19	29.77	0.00	-79.50	71.38
ENDPOINT	PLACEBO	33	43.27	20.48	35.84	20.71	29.25	3.50	90.00	-7.43	26.71	-4.25	-62.50	73.50
	SB 207499	33	43.63	21.89	43.44	27.23	34.75	8.75	90.97	-0.19	29.77	0.00	-79.50	71.38

1. MEAN VALUES ARE THE SAMPLE MEAN
2. BASELINE = VISIT 2/2A, WEEK 13 = VISIT 7/7A, ENDPOINT = VISIT 7 AND EWA

CONFIDENTIAL

SB 207499

TABLE 14.12A

SUMMARY OF CHANGE FROM BASELINE IN SPUTUM NEUTROPHIL ELASTASE (NG/ML) BY TREATMENT GROUP - PP
PROTOCOL 181

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	ADJ MEAN	SEM	ADJ MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	40	49781.33	32771.16	.	.	.	.	.	.	.	.
	SB 207499	41	61218.48	30969.87	.	.	.	.	.	.	.	.
WEEK 13	PLACEBO	40	40769.03	40070.34	-9012.30	36206.43	-81571.6	63547.01	.	.	.	.
	SB 207499	41	66272.22	37867.85	5053.74	34216.32	-63517.3	73624.77	14066.04	-80706.9	108839.0	0.767
ENDPOINT	PLACEBO	40	40769.03	40070.34	-9012.30	36206.43	-81571.6	63547.01	.	.	.	.
	SB 207499	41	66272.22	37867.85	5053.74	34216.32	-63517.3	73624.77	14066.04	-80706.9	108839.0	0.767

1. ADJUSTED MEANS ARE ADJUSTED FOR CENTRE
2. BASELINE = VISIT 2/2A, WEEK 13 = VISIT 7/7A, ENDPOINT = VISIT 7 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14.12B

DESCRIPTIVE STATISTICS FOR SPUTUM NEUTROPHIL ELASTASE (NG/ML) BY TREATMENT GROUP - PP
PROTOCOL 181

		BASELINE			WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	40	.	.	53800.9	192768	1006.04	7.80	1133138	.	.	.	.	.
	SB 207499	41	.	.	52608.4	157562	163.80	15.60	898650	.	.	.	.	.
WEEK 13	PLACEBO	40	53800.9	192768	52935.7	145776	1761.89	48.75	762000	-865.25	134314	22.42	-492676	483329
	SB 207499	41	52608.4	157562	68703.3	253602	759.44	42.90	1335938	16094.9	223414	3.90	-400462	1308890
ENDPOINT	PLACEBO	40	53800.9	192768	52935.7	145776	1761.89	48.75	762000	-865.25	134314	22.42	-492676	483329
	SB 207499	41	52608.4	157562	68703.3	253602	759.44	42.90	1335938	16094.9	223414	3.90	-400462	1308890

1. MEAN VALUES ARE THE SAMPLE MEAN
2. BASELINE = VISIT 2/2A, WEEK 13 = VISIT 7/7A, ENDPOINT = VISIT 7 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL
GM2004/00090/00
SB-207499/181

SB 207499

TABLE 14.13A

SUMMARY OF CHANGE FROM BASELINE IN SPUTUM EOSINOPHILS (%) BY TREATMENT GROUP - PP
PROTOCOL 181

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	ADJ MEAN	SEM	ADJ MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	33	3.47	2.42	.	.	.	.	.	.	.	.
	SB 207499	33	3.57	2.28	.	.	.	.	.	.	.	.
WEEK 13	PLACEBO	33	3.84	1.73	0.37	2.48	-4.65	5.39	.	.	.	.
	SB 207499	33	3.04	1.64	-0.53	2.34	-5.27	4.21	-0.90	-7.42	5.62	0.782
ENDPOINT	PLACEBO	33	3.84	1.73	0.37	2.48	-4.65	5.39	.	.	.	.
	SB 207499	33	3.04	1.64	-0.53	2.34	-5.27	4.21	-0.90	-7.42	5.62	0.782

1. ADJUSTED MEANS ARE ADJUSTED FOR CENTRE
2. BASELINE = VISIT 2/2A, WEEK 13 = VISIT 7/7A, ENDPOINT = VISIT 7 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

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SB 207499

TABLE 14.13B

DESCRIPTIVE STATISTICS FOR SPUTUM EOSINOPHILS (%) BY TREATMENT GROUP - PP
PROTOCOL 181

		BASELINE			WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	33	.	.	3.80	6.93	1.25	0.00	30.25	.	.	.	.	.
	SB 207499	33	.	.	4.45	13.70	0.88	0.00	78.25	.	.	.	.	.
WEEK 13	PLACEBO	33	3.80	6.93	3.80	6.86	2.00	0.25	35.00	0.00	8.34	0.25	-25.50	33.75
	SB 207499	33	4.45	13.70	3.44	8.48	1.25	0.00	48.00	-1.01	14.29	0.25	-66.00	44.75
ENDPOINT	PLACEBO	33	3.80	6.93	3.80	6.86	2.00	0.25	35.00	0.00	8.34	0.25	-25.50	33.75
	SB 207499	33	4.45	13.70	3.44	8.48	1.25	0.00	48.00	-1.01	14.29	0.25	-66.00	44.75

1. MEAN VALUES ARE THE SAMPLE MEAN
2. BASELINE = VISIT 2/2A, WEEK 13 = VISIT 7/7A, ENDPOINT = VISIT 7 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

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SB 207499

TABLE 14.14A

SUMMARY OF CHANGE FROM BASELINE IN SPUTUM LYMPHOCYTES (%) BY TREATMENT GROUP - PP
PROTOCOL 181

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	ADJ MEAN	SEM	ADJ MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	33	0.89	0.33	.	.	.	.	.	.	.	.
	SB 207499	33	0.60	0.31	.	.	.	.	.	.	.	.
WEEK 13	PLACEBO	33	0.90	0.21	0.01	0.32	-0.64	0.66	.	.	.	.
	SB 207499	33	0.60	0.20	-0.00	0.30	-0.62	0.61	-0.01	-0.85	0.83	0.980
ENDPOINT	PLACEBO	33	0.90	0.21	0.01	0.32	-0.64	0.66	.	.	.	.
	SB 207499	33	0.60	0.20	-0.00	0.30	-0.62	0.61	-0.01	-0.85	0.83	0.980

1. ADJUSTED MEANS ARE ADJUSTED FOR CENTRE
2. BASELINE = VISIT 2/2A, WEEK 13 = VISIT 7/7A, ENDPOINT = VISIT 7 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14.14B

DESCRIPTIVE STATISTICS FOR SPUTUM LYMPHOCYTES (%) BY TREATMENT GROUP - PP
PROTOCOL 181

		BASELINE			WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	33	.	.	1.03	1.49	0.25	0.00	5.00	.	.	.	.	.
	SB 207499	33	.	.	0.77	1.23	0.50	0.00	6.25	.	.	.	.	.
WEEK 13	PLACEBO	33	1.03	1.49	0.85	1.00	0.50	0.00	3.79	-0.19	1.16	0.00	-4.38	1.25
	SB 207499	33	0.77	1.23	0.66	0.93	0.25	0.00	4.00	-0.11	1.56	0.00	-5.25	4.00
ENDPOINT	PLACEBO	33	1.03	1.49	0.85	1.00	0.50	0.00	3.79	-0.19	1.16	0.00	-4.38	1.25
	SB 207499	33	0.77	1.23	0.66	0.93	0.25	0.00	4.00	-0.11	1.56	0.00	-5.25	4.00

1. MEAN VALUES ARE THE SAMPLE MEAN
2. BASELINE = VISIT 2/2A, WEEK 13 = VISIT 7/7A, ENDPOINT = VISIT 7 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14.15A

SUMMARY OF CHANGE FROM BASELINE IN SPUTUM IL-8 (NG/ML) BY TREATMENT GROUP - PP
PROTOCOL 181

WEEK	TREATMENT GROUP	N	WEEKLY ASSESSMENT ADJ MEAN	WEEKLY ASSESSMENT SEM	CHANGE FROM BASELINE ADJ MEAN	CHANGE FROM BASELINE SEM	CHANGE FROM BASELINE LOWER 95% CI	CHANGE FROM BASELINE UPPER 95% CI	COMPARISON WITH PLACEBO MEAN DIFFERENCE	COMPARISON WITH PLACEBO LOWER 95% CI	COMPARISON WITH PLACEBO UPPER 95% CI	COMPARISON WITH PLACEBO P-VALUE
BASELINE	PLACEBO	40	71.92	8.55	.	.	.	.	.	.	.	.
	SB 207499	41	45.77	8.08	.	.	.	.	.	.	.	.
WEEK 13	PLACEBO	40	50.37	7.95	-21.55	9.71	-41.02	-2.09	.	.	.	.
	SB 207499	41	27.15	7.51	-18.61	9.18	-37.01	-0.22	2.94	-22.48	28.36	0.818
ENDPOINT	PLACEBO	40	50.37	7.95	-21.55	9.71	-41.02	-2.09	.	.	.	.
	SB 207499	41	27.15	7.51	-18.61	9.18	-37.01	-0.22	2.94	-22.48	28.36	0.818

1. ADJUSTED MEANS ARE ADJUSTED FOR CENTRE
2. BASELINE = VISIT 2/2A, WEEK 13 = VISIT 7/7A, ENDPOINT = VISIT 7 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14.15B

DESCRIPTIVE STATISTICS FOR SPUTUM IL-8 (NG/ML) BY TREATMENT GROUP - PP
PROTOCOL 181

		BASELINE			WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	40	.	.	61.47	99.69	24.68	0.37	531.62	.	.	.	.	.
	SB 207499	41	.	.	22.93	26.78	10.67	0.13	142.37	.	.	.	.	.
WEEK 13	PLACEBO	40	61.47	99.69	55.76	65.19	36.43	0.13	343.39	-5.72	105.88	7.49	-500.01	269.10
	SB 207499	41	22.93	26.78	30.56	40.51	13.82	1.73	178.81	7.63	39.98	0.17	-81.70	147.19
ENDPOINT	PLACEBO	40	61.47	99.69	55.76	65.19	36.43	0.13	343.39	-5.72	105.88	7.49	-500.01	269.10
	SB 207499	41	22.93	26.78	30.56	40.51	13.82	1.73	178.81	7.63	39.98	0.17	-81.70	147.19

1. MEAN VALUES ARE THE SAMPLE MEAN
2. BASELINE = VISIT 2/2A, WEEK 13 = VISIT 7/7A, ENDPOINT = VISIT 7 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14.16A

SUMMARY OF CHANGE FROM BASELINE IN PULMONARY FUNCTION TEST SVC BY TREATMENT GROUP - PP
PROTOCOL 181

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	ADJ MEAN	SEM	ADJ MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	59	3.12	0.13	.	.	.	.	.	.	.	.
	SB 207499	58	3.30	0.12	.	.	.	.	.	.	.	.
WEEK 4	PLACEBO	57	3.10	0.12	-0.02	0.06	-0.14	0.10	.	.	.	.
	SB 207499	58	3.43	0.11	0.13	0.06	0.02	0.24	0.15	-0.00	0.31	0.054
WEEK 8	PLACEBO	57	3.08	0.12	-0.02	0.07	-0.15	0.12	.	.	.	.
	SB 207499	55	3.42	0.11	0.08	0.06	-0.05	0.20	0.09	-0.08	0.27	0.283
WEEK 12	PLACEBO	52	3.07	0.12	-0.01	0.07	-0.14	0.13	.	.	.	.
	SB 207499	54	3.25	0.11	-0.06	0.06	-0.18	0.07	-0.05	-0.22	0.12	0.586
WEEK 13	PLACEBO	49	3.18	0.12	0.04	0.06	-0.09	0.17	.	.	.	.
	SB 207499	51	3.30	0.11	0.03	0.06	-0.08	0.15	-0.00	-0.16	0.16	0.952
ENDPOINT	PLACEBO	59	3.16	0.11	0.04	0.07	-0.09	0.17	.	.	.	.
	SB 207499	58	3.33	0.11	0.03	0.06	-0.09	0.15	-0.01	-0.18	0.15	0.900

1. ADJUSTED MEANS ARE ADJUSTED FOR CENTRE
2. BASELINE = VISIT 3, WEEK 4 = VISIT 5, WEEK 12 = VISIT 6/6A, WEEK 13 = VISIT 7, ENDPOINT = LAST ON-THERAPY OBSERVATION CARRIED FORWARD
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL
GM2004/00090/00
SB-207499/181

SB 207499

TABLE 14.16B

DESCRIPTIVE STATISTICS FOR PULMONARY FUNCTION TEST SVC BY TREATMENT GROUP - PP
PROTOCOL 181

		BASELINE			WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	59	.	.	3.12	0.85	3.09	1.58	5.21	.	.	.	.	.
	SB 207499	58	.	.	3.31	0.98	3.31	1.09	5.97	.	.	.	.	.
WEEK 4	PLACEBO	57	3.12	0.86	3.08	0.80	3.15	1.68	4.68	-0.03	0.43	-0.05	-0.76	2.00
	SB 207499	58	3.31	0.98	3.42	1.01	3.36	1.50	6.41	0.10	0.32	0.05	-0.63	1.09
WEEK 8	PLACEBO	57	3.10	0.85	3.08	0.83	3.12	1.20	4.73	-0.02	0.43	-0.04	-1.30	1.90
	SB 207499	55	3.36	0.97	3.43	0.93	3.32	1.57	6.04	0.07	0.43	0.02	-1.07	1.71
WEEK 12	PLACEBO	52	3.12	0.86	3.10	0.80	3.07	1.72	4.64	-0.03	0.45	-0.07	-0.73	2.22
	SB 207499	54	3.35	0.98	3.27	1.00	3.17	1.15	6.20	-0.08	0.43	-0.06	-1.26	0.74
WEEK 13	PLACEBO	49	3.15	0.82	3.15	0.80	3.08	1.70	5.01	0.00	0.30	-0.02	-0.81	0.92
	SB 207499	51	3.33	0.99	3.37	1.00	3.36	1.34	6.04	0.03	0.45	0.00	-1.13	1.29
ENDPOINT	PLACEBO	59	3.12	0.85	3.13	0.82	3.13	1.68	5.01	0.01	0.43	-0.02	-0.81	2.22
	SB 207499	58	3.31	0.98	3.34	0.99	3.36	1.34	6.04	0.02	0.43	-0.01	-1.13	1.29

1. MEAN VALUES ARE THE SAMPLE MEAN
2. BASELINE = VISIT 3, WEEK 4 = VISIT 5, WEEK 12 = VISIT 6/6A, WEEK 13 = VISIT 7, ENDPOINT = LAST ON-THERAPY OBSERVATION CARRIED FORWARD
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

GM2004/00090/00
SB-207499/181

SB 207499

TABLE 14A.1A

SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL CD68+ (MACROPHAGES) (CELL/MM2) BY TREATMENT GROUP - ITT

PROTOCOL 181

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	ADJ MEAN	SEM	ADJ MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	52	137.18	11.69	.	.	.	.	.	.	.	.
	SB 207499	54	119.11	10.90	.	.	.	.	.	.	.	.
WEEK 12	PLACEBO	52	92.61	8.30	-44.57	13.53	-71.50	-17.64	.	.	.	.
	SB 207499	54	99.38	7.74	-19.73	12.61	-44.84	5.38	24.84	-9.34	59.02	0.152
ENDPOINT	PLACEBO	52	92.61	8.30	-44.57	13.53	-71.50	-17.64	.	.	.	.
	SB 207499	54	99.38	7.74	-19.73	12.61	-44.84	5.38	24.84	-9.34	59.02	0.152

1. ADJUSTED MEANS ARE ADJUSTED FOR CENTRE
2. BASELINE = VISIT 2/2A, WEEK 12 = VISIT 6/6A, ENDPOINT = VISIT 6 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

GM2004/00090/00
SB-207499/181

SB 207499

TABLE 14A.1B

DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL CD68+ (MACROPHAGES) (CELL/MM2) BY TREATMENT GROUP - ITT
ITT
PROTOCOL 181

		BASELINE			WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	52	.	.	129.15	91.33	111.40	9.65	382.50	.	.	.	.	.
	SB 207499	54	.	.	121.67	83.38	103.20	14.50	355.00	.	.	.	.	.
WEEK 12	PLACEBO	52	129.15	91.33	92.03	48.27	88.25	12.00	219.50	-37.12	92.43	-17.00	-267.00	121.95
	SB 207499	54	121.67	83.38	101.17	63.82	88.75	6.75	250.00	-20.50	86.93	-5.58	-274.70	127.00
ENDPOINT	PLACEBO	52	129.15	91.33	92.03	48.27	88.25	12.00	219.50	-37.12	92.43	-17.00	-267.00	121.95
	SB 207499	54	121.67	83.38	101.17	63.82	88.75	6.75	250.00	-20.50	86.93	-5.58	-274.70	127.00

1. MEAN VALUES ARE THE SAMPLE MEAN
2. BASELINE = VISIT 2/2A, WEEK 12 = VISIT 6/6A, ENDPOINT = VISIT 6 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

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SB 207499

TABLE 14A.1C

SUMMARY OF TEST OF SIGNIFICANCE FOR INTERACTION TERMS AND COVARIATES FOR CHANGE FROM BASELINE IN SUB-EPITHELIAL CD68+ (MACROPHAGES)/MM^2 - ITT
PROTOCOL 181

FACTOR	F-STATISTIC	P-VALUE
AGE	0.03	0.8729
SMOKING STATUS	5.65	0.0200
% PREDICTED FEV1	0.51	0.4772
GENDER	0.42	0.5194
CENTRE	1.30	0.2048
TREATMENT	0.85	0.3614
TREATMENT BY CENTRE	0.62	0.8837

1. TESTS FOR COVARIATES WAS BASED ON MODEL WITH EFFECTS: TREATMENT, CENTRE AND EACH OF THE COVARIATES
2. TESTS FOR TREATMENT-BY-CENTRE INTERACTION WAS BASED ON MODEL WITH EFFECTS: TREATMENT, CENTRE AND THE INTERACTION.

CONFIDENTIAL
GM2004/00090/00
SB-207499/181

SB 207499

TABLE 14A.1D

SUMMARY OF POISSON REGRESSION MODEL USING GEE FOR CHANGE IN CD68 - ITT

PROTOCOL 181

TREATMENT	CELLS PER UNIT AREA	95% CI	INCIDENCE DENSITY RATIO	95% CI	P-VALUE
PLACEBO	74.232	(54.71, 100.72)	.		.
SB 207499	77.908	(57.25, 106.01)	1.0495	(0.84, 1.31)	0.6726

1. MODEL ADJUSTS FOR CENTRE, BASELINE SMOKING STATUS AND BASELINE VALUE

CONFIDENTIAL
GM2004/00090/00
SB-207499/181

SB 207499

TABLE 14A.2A

SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL CD8+ T-LYMPHOCYTES (CELL/MM2) TISSUE BY TREATMENT GROUP - ITT
PROTOCOL 181

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	ADJ MEAN	SEM	ADJ MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	52	211.36	10.47	.	.	.	.	.	.	.	.
	SB 207499	54	199.13	9.76	.	.	.	.	.	.	.	.
WEEK 12	PLACEBO	52	141.70	10.84	-69.66	13.17	-95.88	-43.43	.	.	.	.
	SB 207499	54	122.77	10.11	-76.35	12.28	-100.80	-51.90	-6.70	-39.98	26.58	0.690
ENDPOINT	PLACEBO	52	141.70	10.84	-69.66	13.17	-95.88	-43.43	.	.	.	.
	SB 207499	54	122.77	10.11	-76.35	12.28	-100.80	-51.90	-6.70	-39.98	26.58	0.690

1. ADJUSTED MEANS ARE ADJUSTED FOR CENTRE
2. BASELINE = VISIT 2/2A, WEEK 12 = VISIT 6/6A, ENDPOINT = VISIT 6 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14A.2B

DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL CD8+ T-LYMPHOCYTES (CELL/MM2) TISSUE BY TREATMENT GROUP - ITT
PROTOCOL 181

		BASELINE			WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	52	.	.	209.68	62.18	213.53	68.00	345.60	.	.	.	.	.
	SB 207499	54	.	.	200.14	62.31	189.05	109.50	392.55	.	.	.	.	.
WEEK 12	PLACEBO	52	209.68	62.18	147.92	74.21	136.58	30.45	356.55	-61.76	78.18	-64.35	-208.30	86.60
	SB 207499	54	200.14	62.31	130.65	73.27	108.30	19.20	308.85	-69.49	86.28	-65.32	-293.85	172.95
ENDPOINT	PLACEBO	52	209.68	62.18	147.92	74.21	136.58	30.45	356.55	-61.76	78.18	-64.35	-208.30	86.60
	SB 207499	54	200.14	62.31	130.65	73.27	108.30	19.20	308.85	-69.49	86.28	-65.32	-293.85	172.95

1. MEAN VALUES ARE THE SAMPLE MEAN
2. BASELINE = VISIT 2/2A, WEEK 12 = VISIT 6/6A, ENDPOINT = VISIT 6 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14A.2C

SUMMARY OF TEST OF SIGNIFICANCE FOR INTERACTION TERMS AND COVARIATES FOR CHANGE FROM BASELINE IN SUB-EPITHELIAL CD8+ (T-LYMPHOCYTES)/MM^2 - ITT
PROTOCOL 181

FACTOR	F-STATISTIC	P-VALUE
AGE	0.24	0.6259
SMOKING STATUS	0.01	0.9326
% PREDICTED FEV1	0.20	0.6551
GENDER	3.51	0.0648
CENTRE	1.09	0.3845
TREATMENT	0.26	0.6121
TREATMENT BY CENTRE	0.95	0.5281

1. TESTS FOR COVARIATES WAS BASED ON MODEL WITH EFFECTS: TREATMENT, CENTRE AND EACH OF THE COVARIATES
2. TESTS FOR TREATMENT-BY-CENTRE INTERACTION WAS BASED ON MODEL WITH EFFECTS: TREATMENT, CENTRE AND THE INTERACTION.

CONFIDENTIAL

SB 207499

TABLE 14A.2D

SUMMARY OF POISSON REGRESSION MODEL USING GEE FOR CHANGE IN CD8 - ITT

PROTOCOL 181

TREATMENT	CELLS PER UNIT AREA	95% CI	INCIDENCE DENSITY RATIO	95% CI	P-VALUE
PLACEBO	118.087	(91.11, 153.06)	.		.
SB 207499	103.724	(80.01, 134.46)	0.8784	(0.73, 1.06)	0.1775

1. MODEL ADJUSTS FOR CENTRE, BASELINE SMOKING STATUS AND BASELINE VALUE

CONFIDENTIAL
GM2004/00090/00
SB-207499/181

SB 207499

TABLE 14A.3A

SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL NEUTROPHILS (NE+) (CELL/MM2) TISSUE BY TREATMENT GROUP - ITT
PROTOCOL 181

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	ADJ MEAN	SEM	ADJ MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	52	44.45	4.93	.	.	.	.	.	.	.	.
	SB 207499	54	37.21	4.59	.	.	.	.	.	.	.	.
WEEK 12	PLACEBO	52	24.38	3.96	-20.07	6.32	-32.64	-7.50	.	.	.	.
	SB 207499	54	35.41	3.69	-1.80	5.89	-13.52	9.93	18.27	2.31	34.23	0.025
ENDPOINT	PLACEBO	52	24.38	3.96	-20.07	6.32	-32.64	-7.50	.	.	.	.
	SB 207499	54	35.41	3.69	-1.80	5.89	-13.52	9.93	18.27	2.31	34.23	0.025

1. ADJUSTED MEANS ARE ADJUSTED FOR CENTRE
2. BASELINE = VISIT 2/2A, WEEK 12 = VISIT 6/6A, ENDPOINT = VISIT 6 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

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GM2004/00090/00
SB-207499/181

SB 207499

TABLE 14A.3B

DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL NEUTROPHILS (NE+) (CELL/MM2) TISSUE BY TREATMENT GROUP - ITT
PROTOCOL 181

		BASELINE			WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	52	.	.	45.23	38.48	35.48	1.75	198.50	.	.	.	.	.
	SB 207499	54	.	.	36.73	23.07	35.10	0.55	111.55	.	.	.	.	.
WEEK 12	PLACEBO	52	45.23	38.48	25.84	22.67	20.10	1.55	120.25	-19.39	39.94	-10.47	-185.70	72.00
	SB 207499	54	36.73	23.07	35.91	29.06	25.45	2.30	128.90	-0.82	34.46	-3.03	-93.60	77.10
ENDPOINT	PLACEBO	52	45.23	38.48	25.84	22.67	20.10	1.55	120.25	-19.39	39.94	-10.47	-185.70	72.00
	SB 207499	54	36.73	23.07	35.91	29.06	25.45	2.30	128.90	-0.82	34.46	-3.03	-93.60	77.10

1. MEAN VALUES ARE THE SAMPLE MEAN
2. BASELINE = VISIT 2/2A, WEEK 12 = VISIT 6/6A, ENDPOINT = VISIT 6 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

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SB 207499

TABLE 14A.4A

SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL CD4+ LYMPHOCYTES (CELL/MM2) TISSUE BY TREATMENT GROUP - ITT
PROTOCOL 181

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	ADJ MEAN	SEM	ADJ MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	52	117.10	8.38	.	.	.	.	.	.	.	.
	SB 207499	54	98.99	7.81	.	.	.	.	.	.	.	.
WEEK 12	PLACEBO	52	99.27	7.99	-17.83	11.73	-41.18	5.51	.	.	.	.
	SB 207499	54	91.14	7.45	-7.85	10.93	-29.62	13.92	9.98	-19.65	39.61	0.505
ENDPOINT	PLACEBO	52	99.27	7.99	-17.83	11.73	-41.18	5.51	.	.	.	.
	SB 207499	54	91.14	7.45	-7.85	10.93	-29.62	13.92	9.98	-19.65	39.61	0.505

1. ADJUSTED MEANS ARE ADJUSTED FOR CENTRE
2. BASELINE = VISIT 2/2A, WEEK 12 = VISIT 6/6A, ENDPOINT = VISIT 6 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

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SB 207499

TABLE 14A.4B

DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL CD4+ LYMPHOCYTES (CELL/MM2) TISSUE BY TREATMENT GROUP - ITT
PROTOCOL 181

		BASELINE			WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	52	.	.	118.02	57.28	104.50	37.55	287.45	.	.	.	.	.
	SB 207499	54	.	.	101.81	46.61	96.53	31.75	219.15	.	.	.	.	.
WEEK 12	PLACEBO	52	118.02	57.28	92.08	48.37	80.28	12.10	223.60	-25.94	70.48	-19.00	-201.85	133.25
	SB 207499	54	101.81	46.61	88.64	56.36	81.83	13.25	259.00	-13.17	68.08	-11.60	-205.60	112.35
ENDPOINT	PLACEBO	52	118.02	57.28	92.08	48.37	80.28	12.10	223.60	-25.94	70.48	-19.00	-201.85	133.25
	SB 207499	54	101.81	46.61	88.64	56.36	81.83	13.25	259.00	-13.17	68.08	-11.60	-205.60	112.35

1. MEAN VALUES ARE THE SAMPLE MEAN
2. BASELINE = VISIT 2/2A, WEEK 12 = VISIT 6/6A, ENDPOINT = VISIT 6 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

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GM2004/00090/00
SB-207499/181

SB 207499

TABLE 14A.5A

SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL IL-8+ MRNA (CELL/MM2) TISSUE BY TREATMENT GROUP - ITT
PROTOCOL 181

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	ADJ MEAN	SEM	ADJ MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	52	45.33	4.54	.	.	.	.	.	.	.	.
	SB 207499	54	37.27	4.23	.	.	.	.	.	.	.	.
WEEK 12	PLACEBO	52	19.26	2.25	-26.07	4.53	-35.08	-17.06	.	.	.	.
	SB 207499	54	22.73	2.10	-14.54	4.22	-22.94	-6.14	11.53	0.09	22.96	0.048
ENDPOINT	PLACEBO	52	19.26	2.25	-26.07	4.53	-35.08	-17.06	.	.	.	.
	SB 207499	54	22.73	2.10	-14.54	4.22	-22.94	-6.14	11.53	0.09	22.96	0.048

1. ADJUSTED MEANS ARE ADJUSTED FOR CENTRE
2. BASELINE = VISIT 2/2A, WEEK 12 = VISIT 6/6A, ENDPOINT = VISIT 6 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

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SB 207499

TABLE 14A.5B

DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL IL-8+ MRNA (CELL/MM2) TISSUE BY TREATMENT GROUP - ITT
PROTOCOL 181

		BASELINE			WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	52	.	.	44.11	33.29	36.48	7.10	211.70	.	.	.	.	.
	SB 207499	54	.	.	36.43	18.86	32.65	7.65	92.90	.	.	.	.	.
WEEK 12	PLACEBO	52	44.11	33.29	19.34	13.34	15.85	5.00	78.80	-24.77	32.75	-19.85	-202.15	15.40
	SB 207499	54	36.43	18.86	23.07	16.58	19.50	4.15	84.55	-13.36	21.34	-13.58	-65.35	65.15
ENDPOINT	PLACEBO	52	44.11	33.29	19.34	13.34	15.85	5.00	78.80	-24.77	32.75	-19.85	-202.15	15.40
	SB 207499	54	36.43	18.86	23.07	16.58	19.50	4.15	84.55	-13.36	21.34	-13.58	-65.35	65.15

1. MEAN VALUES ARE THE SAMPLE MEAN
2. BASELINE = VISIT 2/2A, WEEK 12 = VISIT 6/6A, ENDPOINT = VISIT 6 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

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SB 207499

TABLE 14A.6A

SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL TNF-ALPHA +MRNA (CELL/MM2) TISSUE BY TREATMENT GROUP - ITT
PROTOCOL 181

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	ADJ MEAN	SEM	ADJ MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	52	71.28	5.04	.	.	.	.	.	.	.	.
	SB 207499	54	63.78	4.70	.	.	.	.	.	.	.	.
WEEK 12	PLACEBO	52	27.81	2.79	-43.47	5.56	-54.54	-32.40	.	.	.	.
	SB 207499	54	28.34	2.60	-35.44	5.18	-45.76	-25.12	8.03	-6.02	22.07	0.259
ENDPOINT	PLACEBO	52	27.81	2.79	-43.47	5.56	-54.54	-32.40	.	.	.	.
	SB 207499	54	28.34	2.60	-35.44	5.18	-45.76	-25.12	8.03	-6.02	22.07	0.259

1. ADJUSTED MEANS ARE ADJUSTED FOR CENTRE
2. BASELINE = VISIT 2/2A, WEEK 12 = VISIT 6/6A, ENDPOINT = VISIT 6 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

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SB 207499

TABLE 14A.6B

DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL TNF-ALPHA +MRNA (CELL/MM2) TISSUE BY TREATMENT GROUP - ITT
PROTOCOL 181

		BASELINE			WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	52	.	.	68.32	32.56	68.68	13.90	142.15	.	.	.	.	.
	SB 207499	54	.	.	62.90	32.95	57.50	11.80	134.20	.	.	.	.	.
WEEK 12	PLACEBO	52	68.32	32.56	28.38	19.38	23.25	9.75	108.00	-39.94	35.27	-44.13	-117.70	54.55
	SB 207499	54	62.90	32.95	29.20	17.96	25.33	8.75	109.75	-33.70	35.32	-29.13	-119.75	27.90
ENDPOINT	PLACEBO	52	68.32	32.56	28.38	19.38	23.25	9.75	108.00	-39.94	35.27	-44.13	-117.70	54.55
	SB 207499	54	62.90	32.95	29.20	17.96	25.33	8.75	109.75	-33.70	35.32	-29.13	-119.75	27.90

1. MEAN VALUES ARE THE SAMPLE MEAN
2. BASELINE = VISIT 2/2A, WEEK 12 = VISIT 6/6A, ENDPOINT = VISIT 6 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

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SB 207499

TABLE 14A.7A

SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL CD45 POSITIVE (CELL/MM2) TISSUE BY TREATMENT GROUP - ITT
PROTOCOL 181

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	ADJ MEAN	SEM	ADJ MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	52	384.03	16.63	.	.	.	.	.	.	.	.
	SB 207499	54	391.04	15.51	.	.	.	.	.	.	.	.
WEEK 12	PLACEBO	52	295.87	16.99	-88.17	18.23	-124.46	-51.87	.	.	.	.
	SB 207499	54	290.33	15.84	-100.71	17.00	-134.55	-66.87	-12.54	-58.61	33.53	0.589
ENDPOINT	PLACEBO	52	295.87	16.99	-88.17	18.23	-124.46	-51.87	.	.	.	.
	SB 207499	54	290.33	15.84	-100.71	17.00	-134.55	-66.87	-12.54	-58.61	33.53	0.589

1. ADJUSTED MEANS ARE ADJUSTED FOR CENTRE
2. BASELINE = VISIT 2/2A, WEEK 12 = VISIT 6/6A, ENDPOINT = VISIT 6 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

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SB 207499

TABLE 14A.7B

DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL CD45 POSITIVE (CELL/MM2) TISSUE BY TREATMENT GROUP - ITT
PROTOCOL 181

		BASELINE			WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	52	.	.	377.17	110.08	399.03	36.50	591.00	.	.	.	.	.
	SB 207499	54	.	.	391.38	104.75	402.85	170.80	607.10	.	.	.	.	.
WEEK 12	PLACEBO	52	377.17	110.08	287.88	99.55	266.30	113.70	545.30	-89.30	102.00	-76.68	-352.40	130.25
	SB 207499	54	391.38	104.75	291.04	136.33	247.15	43.65	627.65	-100.34	140.00	-104.33	-437.60	302.25
ENDPOINT	PLACEBO	52	377.17	110.08	287.88	99.55	266.30	113.70	545.30	-89.30	102.00	-76.68	-352.40	130.25
	SB 207499	54	391.38	104.75	291.04	136.33	247.15	43.65	627.65	-100.34	140.00	-104.33	-437.60	302.25

1. MEAN VALUES ARE THE SAMPLE MEAN
2. BASELINE = VISIT 2/2A, WEEK 12 = VISIT 6/6A, ENDPOINT = VISIT 6 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14A.8A1

SUMMARY OF CHANGE FROM BASELINE IN EPITHELIAL MUCIN EXPRESSION (MUC5AC) (CELL/MM2) TISSUE BY TREATMENT GROUP - ITT
PROTOCOL 181

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	ADJ MEAN	SEM	ADJ MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	19	45.56	4.77	.	.	.	.	.	.	.	.
	SB 207499	21	38.94	4.78	.	.	.	.	.	.	.	.
WEEK 12	PLACEBO	19	46.59	3.80	1.03	4.96	-9.33	11.38	.	.	.	.
	SB 207499	21	40.78	3.81	1.84	4.97	-8.54	12.22	0.81	-14.84	16.47	0.915
ENDPOINT	PLACEBO	19	46.59	3.80	1.03	4.96	-9.33	11.38	.	.	.	.
	SB 207499	21	40.78	3.81	1.84	4.97	-8.54	12.22	0.81	-14.84	16.47	0.915

1. ADJUSTED MEANS ARE ADJUSTED FOR CENTRE
2. BASELINE = VISIT 2/2A, WEEK 12 = VISIT 6/6A, ENDPOINT = VISIT 6 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

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SB 207499

TABLE 14A.8A2

SUMMARY OF CHANGE FROM BASELINE IN SUB-MUCOSA MUCIN EXPRESSION (MUC5AC) (CELL/MM2) TISSUE BY TREATMENT GROUP - ITT
PROTOCOL 181

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	ADJ MEAN	SEM	ADJ MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	11	5.16	0.58	.	.	.	.	.	.	.	.
	SB 207499	14	4.19	0.43	.	.	.	.	.	.	.	.
WEEK 12	PLACEBO	11	7.68	0.95	2.53	0.96	0.38	4.67	.	.	.	.
	SB 207499	14	7.87	0.71	3.67	0.72	2.08	5.27	1.15	-1.71	4.01	0.393
ENDPOINT	PLACEBO	11	7.68	0.95	2.53	0.96	0.38	4.67	.	.	.	.
	SB 207499	14	7.87	0.71	3.67	0.72	2.08	5.27	1.15	-1.71	4.01	0.393

1. MEAN VALUES ARE THE SAMPLE MEAN
2. BASELINE = VISIT 2/2A, WEEK 12 = VISIT 6/6A, ENDPOINT = VISIT 6 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14A.8A3

SUMMARY OF CHANGE FROM BASELINE IN EPITHELIAL MUCIN EXPRESSION (MUC5B) (CELL/MM2) TISSUE BY TREATMENT GROUP - ITT
PROTOCOL 181

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	ADJ MEAN	SEM	ADJ MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	17	31.51	4.59	.	.	.	.	.	.	.	.
	SB 207499	20	31.15	4.85	.	.	.	.	.	.	.	.
WEEK 12	PLACEBO	17	30.13	4.56	-1.39	6.03	-13.96	11.19	.	.	.	.
	SB 207499	20	21.67	4.82	-9.47	6.37	-22.77	3.82	-8.09	-27.00	10.82	0.383
ENDPOINT	PLACEBO	17	30.13	4.56	-1.39	6.03	-13.96	11.19	.	.	.	.
	SB 207499	20	21.67	4.82	-9.47	6.37	-22.77	3.82	-8.09	-27.00	10.82	0.383

1. ADJUSTED MEANS ARE ADJUSTED FOR CENTRE
2. BASELINE = VISIT 2/2A, WEEK 12 = VISIT 6/6A, ENDPOINT = VISIT 6 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14A.8A4

SUMMARY OF CHANGE FROM BASELINE IN SUB-MUCOSA MUCIN EXPRESSION (MUC5B) (CELL/MM2) TISSUE BY TREATMENT GROUP - ITT
PROTOCOL 181

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	ADJ MEAN	SEM	ADJ MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	19	55.00	4.31	.	.	.	.	.	.	.	.
	SB 207499	19	57.20	4.43	.	.	.	.	.	.	.	.
WEEK 12	PLACEBO	19	45.79	4.46	-9.21	6.32	-22.48	4.06	.	.	.	.
	SB 207499	19	58.52	4.59	1.31	6.50	-12.33	14.96	10.52	-9.09	30.13	0.275
ENDPOINT	PLACEBO	19	45.79	4.46	-9.21	6.32	-22.48	4.06	.	.	.	.
	SB 207499	19	58.52	4.59	1.31	6.50	-12.33	14.96	10.52	-9.09	30.13	0.275

1. ADJUSTED MEANS ARE ADJUSTED FOR CENTRE
2. BASELINE = VISIT 2/2A, WEEK 12 = VISIT 6/6A, ENDPOINT = VISIT 6 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14A.8B1

DESCRIPTIVE STATISTICS FOR EPITHELIAL MUCIN EXPRESSION (MUC5AC) (CELL/MM2) TISSUE BY TREATMENT GROUP - ITT
PROTOCOL 181

		BASELINE			WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	19	.	.	43.48	19.22	41.78	5.19	84.85	.	.	.	.	.
	SB 207499	21	.	.	42.59	14.56	40.67	26.61	75.63	.	.	.	.	.
WEEK 12	PLACEBO	19	43.48	19.22	42.79	13.67	44.36	16.99	68.02	-0.69	21.65	-0.77	-48.24	42.89
	SB 207499	21	42.59	14.56	45.21	14.53	41.96	16.74	69.83	2.62	18.51	-1.61	-38.09	37.93
ENDPOINT	PLACEBO	19	43.48	19.22	42.79	13.67	44.36	16.99	68.02	-0.69	21.65	-0.77	-48.24	42.89
	SB 207499	21	42.59	14.56	45.21	14.53	41.96	16.74	69.83	2.62	18.51	-1.61	-38.09	37.93

1. MEAN VALUES ARE THE SAMPLE MEAN
2. BASELINE = VISIT 2/2A, WEEK 12 = VISIT 6/6A, ENDPOINT = VISIT 6 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14A.8B2

DESCRIPTIVE STATISTICS FOR SUB-MUCOSA MUCIN EXPRESSION (MUC5AC) (CELL/MM2) TISSUE BY TREATMENT GROUP - ITT
PROTOCOL 181

		BASELINE			WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	11	.	.	1.57	1.83	0.67	0.05	6.11	.	.	.	.	.
	SB 207499	14	.	.	4.49	9.41	1.53	0.19	36.46	.	.	.	.	.
WEEK 12	PLACEBO	11	1.57	1.83	1.83	2.50	1.22	0.00	8.59	0.26	2.51	0.00	-4.69	6.22
	SB 207499	14	4.49	9.41	7.66	14.41	1.34	0.00	46.34	3.17	7.89	-0.05	-3.40	27.34
ENDPOINT	PLACEBO	11	1.57	1.83	1.83	2.50	1.22	0.00	8.59	0.26	2.51	0.00	-4.69	6.22
	SB 207499	14	4.49	9.41	7.66	14.41	1.34	0.00	46.34	3.17	7.89	-0.05	-3.40	27.34

1. MEAN VALUES ARE THE SAMPLE MEAN
2. BASELINE = VISIT 2/2A, WEEK 12 = VISIT 6/6A, ENDPOINT = VISIT 6 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14A.8B3

DESCRIPTIVE STATISTICS FOR EPITHELIAL MUCIN EXPRESSION (MUC5B) (CELL/MM2) TISSUE BY TREATMENT GROUP - ITT
PROTOCOL 181

		BASELINE			WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	17	.	.	34.57	18.00	35.35	4.71	59.22	.	.	.	.	.
	SB 207499	20	.	.	35.20	20.01	32.03	0.72	71.04	.	.	.	.	.
WEEK 12	PLACEBO	17	34.57	18.00	30.13	19.09	27.74	0.89	61.06	-4.44	20.17	-4.66	-40.95	29.17
	SB 207499	20	35.20	20.01	29.03	18.87	31.33	2.35	66.40	-6.17	21.34	-3.18	-54.06	29.92
ENDPOINT	PLACEBO	17	34.57	18.00	30.13	19.09	27.74	0.89	61.06	-4.44	20.17	-4.66	-40.95	29.17
	SB 207499	20	35.20	20.01	29.03	18.87	31.33	2.35	66.40	-6.17	21.34	-3.18	-54.06	29.92

1. MEAN VALUES ARE THE SAMPLE MEAN
2. BASELINE = VISIT 2/2A, WEEK 12 = VISIT 6/6A, ENDPOINT = VISIT 6 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

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SB 207499

TABLE 14A.8B4

DESCRIPTIVE STATISTICS FOR SUB-MUCOSA MUCIN EXPRESSION (MUC5B) (CELL/MM2) TISSUE BY TREATMENT GROUP - ITT
PROTOCOL 181

		BASELINE			WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	19	.	.	51.96	11.47	50.95	34.13	74.05	.	.	.	.	.
	SB 207499	19	.	.	59.03	18.27	58.52	24.98	98.13	.	.	.	.	.
WEEK 12	PLACEBO	19	51.96	11.47	46.95	14.48	46.22	18.25	75.60	-5.01	17.07	-3.86	-44.92	32.62
	SB 207499	19	59.03	18.27	58.64	17.22	58.82	17.82	94.48	-0.40	25.28	-0.79	-44.67	50.13
ENDPOINT	PLACEBO	19	51.96	11.47	46.95	14.48	46.22	18.25	75.60	-5.01	17.07	-3.86	-44.92	32.62
	SB 207499	19	59.03	18.27	58.64	17.22	58.82	17.82	94.48	-0.40	25.28	-0.79	-44.67	50.13

1. MEAN VALUES ARE THE SAMPLE MEAN
2. BASELINE = VISIT 2/2A, WEEK 12 = VISIT 6/6A, ENDPOINT = VISIT 6 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

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SB 207499

TABLE 14A.10A

SUMMARY OF CHANGE FROM BASELINE IN SPUTUM TOTAL CELL COUNTS (10^6/ML) BY TREATMENT GROUP - ITT
PROTOCOL 181

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	ADJ MEAN	SEM	ADJ MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	46	13.09	2.87	.	.	.	.	.	.	.	.
	SB 207499	44	8.79	2.81	.	.	.	.	.	.	.	.
WEEK 13	PLACEBO	46	6.43	0.75	-6.66	2.59	-11.83	-1.49	.	.	.	.
	SB 207499	44	4.07	0.74	-4.72	2.53	-9.77	0.33	1.94	-4.85	8.73	0.570
ENDPOINT	PLACEBO	46	6.43	0.75	-6.66	2.59	-11.83	-1.49	.	.	.	.
	SB 207499	44	4.07	0.74	-4.72	2.53	-9.77	0.33	1.94	-4.85	8.73	0.570

1. ADJUSTED MEANS ARE ADJUSTED FOR CENTRE
2. BASELINE = VISIT 2/2A, WEEK 13 = VISIT 7/7A, ENDPOINT = VISIT 7 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

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SB 207499

TABLE 14A.10B

DESCRIPTIVE STATISTICS FOR SPUTUM TOTAL CELL COUNTS (10^6/ML) BY TREATMENT GROUP - ITT
PROTOCOL 181

		BASELINE			WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	46	.	.	11.70	20.19	3.78	0.08	111.44	.	.	.	.	.
	SB 207499	44	.	.	8.38	13.21	3.80	0.20	78.38	.	.	.	.	.
WEEK 13	PLACEBO	46	11.70	20.19	6.27	6.36	4.07	0.16	29.88	-5.43	16.45	-0.55	-81.56	11.40
	SB 207499	44	8.38	13.21	4.24	4.42	3.39	0.23	19.61	-4.14	13.01	-1.00	-77.30	15.46
ENDPOINT	PLACEBO	46	11.70	20.19	6.27	6.36	4.07	0.16	29.88	-5.43	16.45	-0.55	-81.56	11.40
	SB 207499	44	8.38	13.21	4.24	4.42	3.39	0.23	19.61	-4.14	13.01	-1.00	-77.30	15.46

1. MEAN VALUES ARE THE SAMPLE MEAN
2. BASELINE = VISIT 2/2A, WEEK 13 = VISIT 7/7A, ENDPOINT = VISIT 7 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

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SB 207499

TABLE 14A.11A

SUMMARY OF CHANGE FROM BASELINE IN SPUTUM MACROPHAGES AS A PERCENTAGE OF TOTAL CELLS BY TREATMENT GROUP - ITT
PROTOCOL 181

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	ADJ MEAN	SEM	ADJ MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	37	42.80	3.81	.	.	.	.	.	.	.	.
	SB 207499	34	42.81	3.79	.	.	.	.	.	.	.	.
WEEK 13	PLACEBO	37	40.39	3.41	-2.41	5.11	-12.72	7.89	.	.	.	.
	SB 207499	34	47.64	3.40	4.83	5.10	-5.44	15.10	7.24	-6.43	20.91	0.292
ENDPOINT	PLACEBO	37	40.39	3.41	-2.41	5.11	-12.72	7.89	.	.	.	.
	SB 207499	34	47.64	3.40	4.83	5.10	-5.44	15.10	7.24	-6.43	20.91	0.292

1. ADJUSTED MEANS ARE ADJUSTED FOR CENTRE
2. BASELINE = VISIT 2/2A, WEEK 13 = VISIT 7/7A, ENDPOINT = VISIT 7 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

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SB 207499

TABLE 14A.11B

DESCRIPTIVE STATISTICS FOR SPUTUM MACROPHAGES AS A PERCENTAGE OF TOTAL CELLS BY TREATMENT GROUP - ITT
PROTOCOL 181

		BASELINE			WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	37	.	.	41.92	20.59	41.25	0.00	91.50	.	.	.	.	.
	SB 207499	34	.	.	43.69	21.56	41.88	8.88	91.50	.	.	.	.	.
WEEK 13	PLACEBO	37	41.92	20.59	34.21	20.55	29.25	3.50	90.00	-7.71	26.93	-5.00	-62.50	73.50
	SB 207499	34	43.69	21.56	42.51	27.35	33.63	8.75	90.97	-1.17	29.88	-0.08	-79.50	71.38
ENDPOINT	PLACEBO	37	41.92	20.59	34.21	20.55	29.25	3.50	90.00	-7.71	26.93	-5.00	-62.50	73.50
	SB 207499	34	43.69	21.56	42.51	27.35	33.63	8.75	90.97	-1.17	29.88	-0.08	-79.50	71.38

1. MEAN VALUES ARE THE SAMPLE MEAN
2. BASELINE = VISIT 2/2A, WEEK 13 = VISIT 7/7A, ENDPOINT = VISIT 7 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

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SB 207499

TABLE 14A.12A

SUMMARY OF CHANGE FROM BASELINE IN SPUTUM NEUTROPHIL ELASTASE (NG/ML) BY TREATMENT GROUP - ITT
PROTOCOL 181

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	ADJ MEAN	SEM	ADJ MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	44	45383.05	30313.54	.	.	.	.	.	.	.	.
	SB 207499	42	59516.37	30209.36	.	.	.	.	.	.	.	.
WEEK 13	PLACEBO	44	39650.20	37056.21	-5732.85	33553.17	-72872.6	61406.90	.	.	.	.
	SB 207499	42	62313.93	36928.86	2797.57	33437.87	-64111.5	69706.59	8530.41	-81142.7	98203.51	0.850
ENDPOINT	PLACEBO	44	39650.20	37056.21	-5732.85	33553.17	-72872.6	61406.90	.	.	.	.
	SB 207499	42	62313.93	36928.86	2797.57	33437.87	-64111.5	69706.59	8530.41	-81142.7	98203.51	0.850

1. ADJUSTED MEANS ARE ADJUSTED FOR CENTRE
2. BASELINE = VISIT 2/2A, WEEK 13 = VISIT 7/7A, ENDPOINT = VISIT 7 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

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SB 207499

TABLE 14A.12B

DESCRIPTIVE STATISTICS FOR SPUTUM NEUTROPHIL ELASTASE (NG/ML) BY TREATMENT GROUP - ITT
PROTOCOL 181

		BASELINE			WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	44	.	.	48924.6	184245	175.50	7.80	1133138	.	.	.	.	.
	SB 207499	42	.	.	51359.2	155839	162.83	15.60	898650	.	.	.	.	.
WEEK 13	PLACEBO	44	48924.6	184245	48212.4	139651	1500.25	48.75	762000	-712.16	127915	22.42	-492676	483329
	SB 207499	42	51359.2	155839	67070.7	250713	467.47	42.90	1335938	15711.4	220686	2.92	-400462	1308890
ENDPOINT	PLACEBO	44	48924.6	184245	48212.4	139651	1500.25	48.75	762000	-712.16	127915	22.42	-492676	483329
	SB 207499	42	51359.2	155839	67070.7	250713	467.47	42.90	1335938	15711.4	220686	2.92	-400462	1308890

1. MEAN VALUES ARE THE SAMPLE MEAN
2. BASELINE = VISIT 2/2A, WEEK 13 = VISIT 7/7A, ENDPOINT = VISIT 7 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

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GM2004/00090/00
SB-207499/181

SB 207499

TABLE 14A.13A

SUMMARY OF CHANGE FROM BASELINE IN SPUTUM EOSINOPHILS (%) BY TREATMENT GROUP - ITT
PROTOCOL 181

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	ADJ MEAN	SEM	ADJ MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	37	3.29	2.28	.	.	.	.	.	.	.	.
	SB 207499	34	3.29	2.27	.	.	.	.	.	.	.	.
WEEK 13	PLACEBO	37	4.57	1.68	1.28	2.41	-3.59	6.15	.	.	.	.
	SB 207499	34	2.72	1.67	-0.56	2.41	-5.41	4.29	-1.84	-8.30	4.61	0.568
ENDPOINT	PLACEBO	37	4.57	1.68	1.28	2.41	-3.59	6.15	.	.	.	.
	SB 207499	34	2.72	1.67	-0.56	2.41	-5.41	4.29	-1.84	-8.30	4.61	0.568

1. ADJUSTED MEANS ARE ADJUSTED FOR CENTRE
2. BASELINE = VISIT 2/2A, WEEK 13 = VISIT 7/7A, ENDPOINT = VISIT 7 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

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SB 207499

TABLE 14A.13B

DESCRIPTIVE STATISTICS FOR SPUTUM EOSINOPHILS (%) BY TREATMENT GROUP - ITT
PROTOCOL 181

		BASELINE			WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	37	.	.	4.40	7.30	1.50	0.00	30.25	.	.	.	.	.
	SB 207499	34	.	.	4.35	13.50	0.94	0.00	78.25	.	.	.	.	.
WEEK 13	PLACEBO	37	4.40	7.30	4.93	8.35	2.00	0.25	35.00	0.54	8.15	0.46	-25.50	33.75
	SB 207499	34	4.35	13.50	3.33	8.37	1.25	0.00	48.00	-1.02	14.07	0.20	-66.00	44.75
ENDPOINT	PLACEBO	37	4.40	7.30	4.93	8.35	2.00	0.25	35.00	0.54	8.15	0.46	-25.50	33.75
	SB 207499	34	4.35	13.50	3.33	8.37	1.25	0.00	48.00	-1.02	14.07	0.20	-66.00	44.75

1. MEAN VALUES ARE THE SAMPLE MEAN
2. BASELINE = VISIT 2/2A, WEEK 13 = VISIT 7/7A, ENDPOINT = VISIT 7 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

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SB 207499

TABLE 14A.14A

SUMMARY OF CHANGE FROM BASELINE IN SPUTUM LYMPHOCYTES (%) BY TREATMENT GROUP - ITT
PROTOCOL 181

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	ADJ MEAN	SEM	ADJ MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	37	0.85	0.30	.	.	.	.	.	.	.	.
	SB 207499	34	0.57	0.29	.	.	.	.	.	.	.	.
WEEK 13	PLACEBO	37	0.85	0.19	-0.00	0.29	-0.59	0.59	.	.	.	.
	SB 207499	34	0.56	0.19	-0.01	0.29	-0.59	0.58	-0.01	-0.78	0.77	0.989
ENDPOINT	PLACEBO	37	0.85	0.19	-0.00	0.29	-0.59	0.59	.	.	.	.
	SB 207499	34	0.56	0.19	-0.01	0.29	-0.59	0.58	-0.01	-0.78	0.77	0.989

1. ADJUSTED MEANS ARE ADJUSTED FOR CENTRE
2. BASELINE = VISIT 2/2A, WEEK 13 = VISIT 7/7A, ENDPOINT = VISIT 7 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

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SB 207499

TABLE 14A.14B

DESCRIPTIVE STATISTICS FOR SPUTUM LYMPHOCYTES (%) BY TREATMENT GROUP - ITT
PROTOCOL 181

		BASELINE			WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	37	.	.	0.99	1.43	0.25	0.00	5.00	.	.	.	.	.
	SB 207499	34	.	.	0.76	1.21	0.38	0.00	6.25	.	.	.	.	.
WEEK 13	PLACEBO	37	0.99	1.43	0.79	0.98	0.50	0.00	3.79	-0.19	1.10	0.00	-4.38	1.25
	SB 207499	34	0.76	1.21	0.64	0.92	0.25	0.00	4.00	-0.12	1.54	0.00	-5.25	4.00
ENDPOINT	PLACEBO	37	0.99	1.43	0.79	0.98	0.50	0.00	3.79	-0.19	1.10	0.00	-4.38	1.25
	SB 207499	34	0.76	1.21	0.64	0.92	0.25	0.00	4.00	-0.12	1.54	0.00	-5.25	4.00

1. MEAN VALUES ARE THE SAMPLE MEAN
2. BASELINE = VISIT 2/2A, WEEK 13 = VISIT 7/7A, ENDPOINT = VISIT 7 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

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SB 207499

TABLE 14A.15A

SUMMARY OF CHANGE FROM BASELINE IN SPUTUM IL-8 (NG/ML) BY TREATMENT GROUP - ITT
PROTOCOL 181

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	ADJ MEAN	SEM	ADJ MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	44	72.09	8.13	.	.	.	.	.	.	.	.
	SB 207499	42	45.17	8.11	.	.	.	.	.	.	.	.
WEEK 13	PLACEBO	44	47.62	7.45	-24.47	9.17	-42.82	-6.11	.	.	.	.
	SB 207499	42	25.73	7.42	-19.44	9.14	-37.73	-1.15	5.03	-19.49	29.54	0.683
ENDPOINT	PLACEBO	44	47.62	7.45	-24.47	9.17	-42.82	-6.11	.	.	.	.
	SB 207499	42	25.73	7.42	-19.44	9.14	-37.73	-1.15	5.03	-19.49	29.54	0.683

1. ADJUSTED MEANS ARE ADJUSTED FOR CENTRE
2. BASELINE = VISIT 2/2A, WEEK 13 = VISIT 7/7A, ENDPOINT = VISIT 7 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SB 207499

TABLE 14A.15B

DESCRIPTIVE STATISTICS FOR SPUTUM IL-8 (NG/ML) BY TREATMENT GROUP - ITT
PROTOCOL 181

		BASELINE			WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	44	.	.	60.28	96.26	24.68	0.37	531.62	.	.	.	.	.
	SB 207499	42	.	.	22.88	26.46	10.72	0.13	142.37	.	.	.	.	.
WEEK 13	PLACEBO	44	60.28	96.26	52.52	63.08	33.89	0.13	343.39	-7.76	101.70	4.28	-500.01	269.10
	SB 207499	42	22.88	26.46	30.10	40.12	13.79	1.73	178.81	7.21	39.58	0.11	-81.70	147.19
ENDPOINT	PLACEBO	44	60.28	96.26	52.52	63.08	33.89	0.13	343.39	-7.76	101.70	4.28	-500.01	269.10
	SB 207499	42	22.88	26.46	30.10	40.12	13.79	1.73	178.81	7.21	39.58	0.11	-81.70	147.19

1. MEAN VALUES ARE THE SAMPLE MEAN
2. BASELINE = VISIT 2/2A, WEEK 13 = VISIT 7/7A, ENDPOINT = VISIT 7 AND EWA
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

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SB 207499

TABLE 14A.16A

SUMMARY OF CHANGE FROM BASELINE IN PULMONARY FUNCTION TEST SVC BY TREATMENT GROUP - ITT
PROTOCOL 181

			WEEKLY ASSESSMENT		CHANGE FROM BASELINE				COMPARISON WITH PLACEBO			
WEEK	TREATMENT GROUP	N	ADJ MEAN	SEM	ADJ MEAN	SEM	LOWER 95% CI	UPPER 95% CI	MEAN DIFFERENCE	LOWER 95% CI	UPPER 95% CI	P-VALUE
BASELINE	PLACEBO	61	3.13	0.12	.	.	.	.	.	.	.	.
	SB 207499	59	3.30	0.12	.	.	.	.	.	.	.	.
WEEK 4	PLACEBO	60	3.09	0.12	-0.04	0.06	-0.16	0.09	.	.	.	.
	SB 207499	59	3.42	0.11	0.12	0.06	0.00	0.24	0.16	0.00	0.32	0.050
WEEK 8	PLACEBO	59	3.09	0.11	-0.02	0.07	-0.15	0.11	.	.	.	.
	SB 207499	56	3.43	0.11	0.09	0.06	-0.04	0.21	0.10	-0.07	0.27	0.227
WEEK 12	PLACEBO	55	3.07	0.12	-0.01	0.07	-0.14	0.12	.	.	.	.
	SB 207499	55	3.26	0.11	-0.05	0.06	-0.17	0.07	-0.04	-0.20	0.13	0.672
WEEK 13	PLACEBO	53	3.16	0.12	0.01	0.06	-0.12	0.13	.	.	.	.
	SB 207499	54	3.31	0.11	0.05	0.06	-0.07	0.16	0.04	-0.12	0.20	0.625
ENDPOINT	PLACEBO	61	3.15	0.11	0.02	0.06	-0.11	0.15	.	.	.	.
	SB 207499	59	3.33	0.11	0.03	0.06	-0.09	0.16	0.02	-0.15	0.18	0.849

1. ADJUSTED MEANS ARE ADJUSTED FOR CENTRE
2. BASELINE = VISIT 3, WEEK 4 = VISIT 5, WEEK 12 = VISIT 6/6A, WEEK 13 = VISIT 7, ENDPOINT = LAST ON-THERAPY OBSERVATION CARRIED FORWARD
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

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GM2004/00090/00
SB-207499/181

SB 207499

TABLE 14A.16B

DESCRIPTIVE STATISTICS FOR PULMONARY FUNCTION TEST SVC BY TREATMENT GROUP - ITT
PROTOCOL 181

		BASELINE			WEEKLY ASSESSMENT					CHANGE FROM BASELINE				
WEEK	TREATMENT GROUP	N	MEAN	SD	MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
BASELINE	PLACEBO	61	.	.	3.12	0.83	3.09	1.58	5.21	.	.	.	.	.
	SB 207499	59	.	.	3.31	0.97	3.30	1.09	5.97	.	.	.	.	.
WEEK 4	PLACEBO	60	3.11	0.84	3.06	0.80	3.10	1.68	4.68	-0.05	0.49	-0.04	-1.81	2.00
	SB 207499	59	3.31	0.97	3.42	1.00	3.37	1.50	6.41	0.11	0.32	0.06	-0.63	1.09
WEEK 8	PLACEBO	59	3.10	0.84	3.07	0.82	3.11	1.20	4.73	-0.03	0.45	-0.04	-1.30	1.90
	SB 207499	56	3.36	0.96	3.43	0.92	3.33	1.57	6.04	0.07	0.43	0.02	-1.07	1.71
WEEK 12	PLACEBO	55	3.11	0.84	3.08	0.79	3.06	1.72	4.64	-0.03	0.44	-0.07	-0.73	2.22
	SB 207499	55	3.35	0.97	3.27	0.99	3.18	1.15	6.20	-0.08	0.42	-0.06	-1.26	0.74
WEEK 13	PLACEBO	53	3.16	0.81	3.14	0.79	3.08	1.70	5.01	-0.02	0.32	-0.04	-0.85	0.92
	SB 207499	54	3.33	0.96	3.38	0.98	3.37	1.34	6.04	0.05	0.45	0.01	-1.13	1.29
ENDPOINT	PLACEBO	61	3.12	0.83	3.11	0.80	3.09	1.68	5.01	-0.00	0.43	-0.04	-0.85	2.22
	SB 207499	59	3.31	0.97	3.35	0.98	3.37	1.34	6.04	0.04	0.43	0.01	-1.13	1.29

1. MEAN VALUES ARE THE SAMPLE MEAN
2. BASELINE = VISIT 3, WEEK 4 = VISIT 5, WEEK 12 = VISIT 6/6A, WEEK 13 = VISIT 7, ENDPOINT = LAST ON-THERAPY OBSERVATION CARRIED FORWARD
3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

CONFIDENTIAL

SAFETY DATA SOURCE TABLES

Page

TABLE 15.1A - SUMMARY OF STUDY MEDICATION EXPOSURE (DAYS) BY TREATMENT GROUP 302
TABLE 15.1B - DESCRIPTIVE STATISTICS FOR STUDY MEDICATION EXPOSURE (DAYS) BY TREATMENT GROUP 303
TABLE 15.2A - INCIDENCE OF ALL ON-THERAPY ADVERSE EXPERIENCES BY PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE - AND TREATMENT GROUP 304
TABLE 15.2B - INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY MEDDRA SYSTEM ORGAN CLASS, PREFERRED TERM AND TREATMENT GROUP 309
TABLE 15.3 - INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT, - MEDDRA SYSTEM ORGAN CLASS, PREFERRED TERM AND TREATMENT GROUP 313
TABLE 15.4a - INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY, - MEDDRA SYSTEM ORGAN CLASS, AND PREFERRED TERM - PLACEBO 319
TABLE 15.4b - INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY, - MEDDRA SYSTEM ORGAN CLASS, AND PREFERRED TERM - SB 207499 322
TABLE 15.5 - INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES (>= 2%) BY INITIAL TIME OF ONSET, MEDDRA SYSTEM ORGAN CLASS, - PREFERRED TERM AND TREATMENT GROUP 325
TABLE 15.6 - INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES THAT LED TO DOSE INTERRUPTION BY SYSTEM ORGAN CLASS, - PREFERRED TERM AND TREATMENT GROUP 328
TABLE 15.7 - INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES THAT REQUIRED CORRECTIVE THERAPY BY MEDDRA SYSTEM ORGAN CLASS, - PREFERRED TERM AND TREATMENT GROUP . . 329
TABLE 15.8A - INCIDENCE OF PRE-THERAPY SERIOUS ADVERSE EXPERIENCES BY MEDDRA SYSTEM ORGAN CLASS, PREFERRED TERM AND TREATMENT GROUP 330
TABLE 15.8B - INCIDENCE OF ON-THERAPY SERIOUS ADVERSE EXPERIENCES BY MEDDRA SYSTEM ORGAN CLASS, PREFERRED TERM AND TREATMENT GROUP 331

TABLE 15.8C - INCIDENCE OF POST-THERAPY SERIOUS ADVERSE EXPERIENCES BY MEDDRA SYSTEM ORGAN CLASS, PREFERRED TERM AND TREATMENT GROUP 332
TABLE 15.9A - INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES LEADING TO PATIENT WITHDRAWAL BY PREFERRED TERM, DESCENDING - FREQUENCY OF OCCURRENCE AND TREATMENT GROUP 333
TABLE 15.9B - INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES LEADING TO PATIENT WITHDRAWAL BY MEDDRA SYSTEM ORGAN CLASS, PREFERRED TERM AND - TREATMENT GROUP . . 334
TABLE 15.10 - ALL POST-THERAPY ADVERSE EXPERIENCES BY MEDDRA SYSTEM ORGAN CLASS, PREFERRED TERM AND TREATMENT GROUP 335
TABLE 15.11A - INCIDENCE OF GASTROINTESTINAL ADVERSE EXPERIENCES OF CONCERN BY MEDDRA PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE - AND TREATMENT GROUP 337
TABLE 15.11B - INCIDENCE OF GASTROINTESTINAL ADVERSE EXPERIENCES OF CONCERN THAT LED TO PATIENT WITHDRAWAL BY PREFERRED TERM, DESCENDING FREQUENCY - AND TREATMENT GROUP 338
TABLE 15.12A - NUMBER AND PERCENT OF PATIENTS WITH GASTROINTESTINAL ADVERSE EVENTS OF CONCERN AND ON-THERAPY - FECAL OCCULT BLOOD BY TREATMENT GROUP AND BASELINE RESULT 339
TABLE 15.12B - NUMBER AND PERCENT OF PATIENTS WITH ON-THERAPY FAECAL OCCULT BLOOD BY TREATMENT GROUP AND BASELINE RESULT 340
TABLE 15.14 - DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND TREATMENT GROUP 341
TABLE 15.16 - DESCRIPTIVE STATISTICS FOR STANDARD VITAL SIGNS BY VISIT/WEEK AND TREATMENT GROUP 349
TABLE 15.17 - TRANSITIONS FROM BASELINE IN SITTING VITAL SIGNS 350
TABLE 15.20 - SUMMARY OF COPD EXACERBATIONS DURING THE DOUBLE-BLIND PERIOD BY LEVEL - ALL RANDOMISED PATIENTS . 356

SB 207499

TABLE 15.1A

SUMMARY OF STUDY MEDICATION EXPOSURE (DAYS) BY TREATMENT GROUP

PROTOCOL 181

EXPOSURE	TREATMENT GROUP PLACEBO (N=62)		SB 207499 (N=65)	
<= 13 Days	1	(1.6%)	1	(1.5%)
14 - 27 Days	1	(1.6%)	3	(4.6%)
28 - 55 Days	1	(1.6%)	3	(4.6%)
56 - 83 Days	5	(8.1%)	3	(4.6%)
84 - 90 Days	28	(45.2%)	17	(26.2%)
> 91 Days	26	(41.9%)	38	(58.5%)

1. EXPOSURE=(DATE OF LAST DOUBLE BLIND STUDY MEDICATION - DATE OF FIRST DOUBLE BLIND STUDY MEDICATION)+1
2. NO ADJUSTMENTS ARE MADE FOR DOSE INTERRUPTIONS

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GM2004/00090/00
SB-207499/181

SB 207499

TABLE 15.1B

DESCRIPTIVE STATISTICS FOR STUDY MEDICATION EXPOSURE (DAYS) BY TREATMENT GROUP

PROTOCOL 181

Statistic	PLACEBO	SB 207499
N	62	65
MEAN	86.65	84.32
STD	15.90	22.20
MEDIAN	90	91
MIN	8	8
MAX	109	120

1. EXPOSURE=(DATE OF LAST DOUBLE BLIND STUDY MEDICATION - DATE OF FIRST DOUBLE BLIND STUDY MEDICATION)+1
2. NO ADJUSTMENTS ARE MADE FOR DOSE INTERRUPTIONS

CONFIDENTIAL
GM2004/00090/00
SB-207499/181

SB 207499

TABLE 15.2A

INCIDENCE OF ALL ON-THERAPY ADVERSE EXPERIENCES BY PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND TREATMENT GROUP
PROTOCOL 181

MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=62)		SB 207499 (N=65)	
TOTAL	36	(58.1%)	41	(63.1%)
HEADACHE	12	(19.4%)	9	(13.8%)
NASOPHARYNGITIS	8	(12.9%)	8	(12.3%)
NAUSEA	4	(6.5%)	6	(9.2%)
DIARRHOEA	2	(3.2%)	5	(7.7%)
PHARYNGOLARYNGEAL PAIN	2	(3.2%)	5	(7.7%)
VOMITING	1	(1.6%)	5	(7.7%)
COUGH	2	(3.2%)	3	(4.6%)
DYSPEPSIA	0	.	3	(4.6%)
ARTHRALGIA	0	.	2	(3.1%)
BACK PAIN	0	.	2	(3.1%)
CHEST PAIN	1	(1.6%)	2	(3.1%)
DIZZINESS	0	.	2	(3.1%)
FAECAL OCCULT BLOOD POSITIVE	2	(3.2%)	2	(3.1%)
FATIGUE	1	(1.6%)	2	(3.1%)
GASTRITIS	0	.	2	(3.1%)
INFLUENZA	1	(1.6%)	2	(3.1%)
LOOSE STOOLS	0	.	2	(3.1%)
RHINITIS	1	(1.6%)	2	(3.1%)
AGGRESSION	0	.	1	(1.5%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AT LEAST ONE ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED
4. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO SB 207499 TREATMENT GROUP

CONFIDENTIAL

SB 207499

TABLE 15.2A

INCIDENCE OF ALL ON-THERAPY ADVERSE EXPERIENCES BY PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND TREATMENT GROUP
PROTOCOL 181

MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=62)	SB 207499 (N=65)
ANOREXIA	0 .	1 (1.5%)
ANXIETY	0 .	1 (1.5%)
APHONIA	0 .	1 (1.5%)
ASTHENIA	0 .	1 (1.5%)
ATRIAL FLUTTER	0 .	1 (1.5%)
CONSTIPATION	0 .	1 (1.5%)
ENTERITIS	0 .	1 (1.5%)
FREQUENT BOWEL MOVEMENTS	0 .	1 (1.5%)
GASTROOESOPHAGEAL REFLUX DISEASE	0 .	1 (1.5%)
GLYCOSURIA	0 .	1 (1.5%)
HELICOBACTER GASTRITIS	0 .	1 (1.5%)
HYPOTENSION	0 .	1 (1.5%)
JOINT SPRAIN	0 .	1 (1.5%)
JOINT SWELLING	1 (1.6%)	1 (1.5%)
LOWER RESPIRATORY TRACT INFECTION	2 (3.2%)	1 (1.5%)
MIGRAINE	0 .	1 (1.5%)
MUSCLE STRAIN	0 .	1 (1.5%)
MUSCLE TIGHTNESS	0 .	1 (1.5%)
NASAL CONGESTION	2 (3.2%)	1 (1.5%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AT LEAST ONE ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED
4. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO SB 207499 TREATMENT GROUP

CONFIDENTIAL

SB 207499

TABLE 15.2A

INCIDENCE OF ALL ON-THERAPY ADVERSE EXPERIENCES BY PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND TREATMENT GROUP
PROTOCOL 181

MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=62)	SB 207499 (N=65)
NASAL DISCOMFORT	0 .	1 (1.5%)
NECK PAIN	0 .	1 (1.5%)
OCULAR DISCOMFORT	0 .	1 (1.5%)
PAIN IN EXTREMITY	1 (1.6%)	1 (1.5%)
PHLEBITIS	0 .	1 (1.5%)
PYREXIA	1 (1.6%)	1 (1.5%)
RETROGRADE AMNESIA	0 .	1 (1.5%)
SINUS CONGESTION	0 .	1 (1.5%)
SNEEZING	0 .	1 (1.5%)
SPONDYLOSIS	0 .	1 (1.5%)
STOMACH DISCOMFORT	0 .	1 (1.5%)
STRIDOR	0 .	1 (1.5%)
TOOTHACHE	1 (1.6%)	1 (1.5%)
UPPER RESPIRATORY TRACT INFECTION	2 (3.2%)	1 (1.5%)
VIRAL INFECTION	0 .	1 (1.5%)
ABDOMINAL DISCOMFORT	1 (1.6%)	0 .
ABDOMINAL PAIN	2 (3.2%)	0 .
BLOOD CREATININE INCREASED	1 (1.6%)	0 .
BLOOD GLUCOSE INCREASED	1 (1.6%)	0 .

1. EACH PATIENT COUNTED ONCE PER MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AT LEAST ONE ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED
4. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO SB 207499 TREATMENT GROUP

CONFIDENTIAL

SB 207499

TABLE 15.2A

INCIDENCE OF ALL ON-THERAPY ADVERSE EXPERIENCES BY PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND TREATMENT GROUP
PROTOCOL 181

MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=62)	SB 207499 (N=65)
BLOOD URIC ACID INCREASED	1 (1.6%)	0 .
BRONCHIAL POLYP	1 (1.6%)	0 .
CHRONIC OBSTRUCTIVE AIRWAYS DISEASE EXACERBATED	1 (1.6%)	0 .
CORONARY ARTERY DISEASE	1 (1.6%)	0 .
CYSTITIS	1 (1.6%)	0 .
ECZEMA	1 (1.6%)	0 .
FLATULENCE	1 (1.6%)	0 .
HAEMOPTYSIS	3 (4.8%)	0 .
HEPATITIS	1 (1.6%)	0 .
HYPERGLYCAEMIA	1 (1.6%)	0 .
HYPERHIDROSIS	1 (1.6%)	0 .
HYPERLIPIDAEMIA	1 (1.6%)	0 .
LUNG DISORDER	1 (1.6%)	0 .
MUSCLE CRAMP	1 (1.6%)	0 .
MUSCULOSKELETAL STIFFNESS	1 (1.6%)	0 .
PAIN	1 (1.6%)	0 .
PALPITATIONS	1 (1.6%)	0 .
PRODUCTIVE COUGH	1 (1.6%)	0 .

1. EACH PATIENT COUNTED ONCE PER MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AT LEAST ONE ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED
4. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO SB 207499 TREATMENT GROUP

CONFIDENTIAL

SB 207499

TABLE 15.2A

INCIDENCE OF ALL ON-THERAPY ADVERSE EXPERIENCES BY PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND TREATMENT GROUP
PROTOCOL 181

MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=62)	SB 207499 (N=65)
RECTAL HAEMORRHAGE	1 (1.6%)	0 .
RESPIRATORY TRACT INFECTION	1 (1.6%)	0 .
RESTLESSNESS	1 (1.6%)	0 .
TENDONITIS	1 (1.6%)	0 .
TOOTH DISORDER	1 (1.6%)	0 .
TREMOR	2 (3.2%)	0 .
URINARY RETENTION	1 (1.6%)	0 .
WHEEZING	1 (1.6%)	0 .

1. EACH PATIENT COUNTED ONCE PER MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AT LEAST ONE ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED
4. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO SB 207499 TREATMENT GROUP

CONFIDENTIAL

SB 207499

TABLE 15.2B

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY MEDDRA SYSTEM ORGAN CLASS, PREFERRED TERM AND TREATMENT GROUP

PROTOCOL 181

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=62)		SB 207499 (N=65)	
TOTAL	TOTAL	36	(58.1%)	41	(63.1%)
CARDIAC DISORDERS	TOTAL	2	(3.2%)	1	(1.5%)
	ATRIAL FLUTTER	0	.	1	(1.5%)
	CORONARY ARTERY DISEASE	1	(1.6%)	0	.
	PALPITATIONS	1	(1.6%)	0	.
EYE DISORDERS	TOTAL	0	.	1	(1.5%)
	OCULAR DISCOMFORT	0	.	1	(1.5%)
GASTROINTESTINAL DISORDERS	TOTAL	10	(16.1%)	20	(30.8%)
	ABDOMINAL DISCOMFORT	1	(1.6%)	0	.
	ABDOMINAL PAIN	2	(3.2%)	0	.
	CONSTIPATION	0	.	1	(1.5%)
	DIARRHOEA	2	(3.2%)	5	(7.7%)
	DYSPEPSIA	0	.	3	(4.6%)
	ENTERITIS	0	.	1	(1.5%)
	FLATULENCE	1	(1.6%)	0	.
	FREQUENT BOWEL MOVEMENTS	0	.	1	(1.5%)
	GASTRITIS	0	.	2	(3.1%)
	GASTROOESOPHAGEAL REFLUX DISEASE	0	.	1	(1.5%)
	LOOSE STOOLS	0	.	2	(3.1%)
	NAUSEA	4	(6.5%)	6	(9.2%)
	RECTAL HAEMORRHAGE	1	(1.6%)	0	.
	STOMACH DISCOMFORT	0	.	1	(1.5%)
	TOOTH DISORDER	1	(1.6%)	0	.
	TOOTHACHE	1	(1.6%)	1	(1.5%)
	VOMITING	1	(1.6%)	5	(7.7%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	TOTAL	4	(6.5%)	5	(7.7%)
	ASTHENIA	0	.	1	(1.5%)
	CHEST PAIN	1	(1.6%)	2	(3.1%)
	FATIGUE	1	(1.6%)	2	(3.1%)
	PAIN	1	(1.6%)	0	.
	PYREXIA	1	(1.6%)	1	(1.5%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS/PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED

CONFIDENTIAL

SB 207499

TABLE 15.2B

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY MEDDRA SYSTEM ORGAN CLASS, PREFERRED TERM AND TREATMENT GROUP

PROTOCOL 181

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=62)	SB 207499 (N=65)
HEPATOBILIARY DISORDERS	TOTAL	1 (1.6%)	0 .
	HEPATITIS	1 (1.6%)	0 .
INFECTIONS AND INFESTATIONS	TOTAL	16 (25.8%)	15 (23.1%)
	CYSTITIS	1 (1.6%)	0 .
	HELICOBACTER GASTRITIS	0 .	1 (1.5%)
	INFLUENZA	1 (1.6%)	2 (3.1%)
	LOWER RESPIRATORY TRACT INFECTION	2 (3.2%)	1 (1.5%)
	NASOPHARYNGITIS	8 (12.9%)	8 (12.3%)
	RESPIRATORY TRACT INFECTION	1 (1.6%)	0 .
	RHINITIS	1 (1.6%)	2 (3.1%)
	UPPER RESPIRATORY TRACT INFECTION	2 (3.2%)	1 (1.5%)
	VIRAL INFECTION	0 .	1 (1.5%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	TOTAL	0 .	2 (3.1%)
	JOINT SPRAIN	0 .	1 (1.5%)
	MUSCLE STRAIN	0 .	1 (1.5%)
INVESTIGATIONS	TOTAL	4 (6.5%)	2 (3.1%)
	BLOOD CREATININE INCREASED	1 (1.6%)	0 .
	BLOOD GLUCOSE INCREASED	1 (1.6%)	0 .
	BLOOD URIC ACID INCREASED	1 (1.6%)	0 .
	FAECAL OCCULT BLOOD POSITIVE	2 (3.2%)	2 (3.1%)
METABOLISM AND NUTRITION DISORDERS	TOTAL	2 (3.2%)	1 (1.5%)
	ANOREXIA	0 .	1 (1.5%)
	HYPERGLYCAEMIA	1 (1.6%)	0 .
	HYPERLIPIDAEMIA	1 (1.6%)	0 .

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS/PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED

CONFIDENTIAL

GM2004/00090/00
SB-207499/181

SB 207499

TABLE 15.2B

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY MEDDRA SYSTEM ORGAN CLASS, PREFERRED TERM AND TREATMENT GROUP

PROTOCOL 181

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=62)	SB 207499 (N=65)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	TOTAL	5 (8.1%)	7 (10.8%)
	ARTHRALGIA	0 .	2 (3.1%)
	BACK PAIN	0 .	2 (3.1%)
	JOINT SWELLING	1 (1.6%)	1 (1.5%)
	MUSCLE CRAMP	1 (1.6%)	0 .
	MUSCLE TIGHTNESS	0 .	1 (1.5%)
	MUSCULOSKELETAL STIFFNESS	1 (1.6%)	0 .
	NECK PAIN	0 .	1 (1.5%)
	PAIN IN EXTREMITY	1 (1.6%)	1 (1.5%)
	SPONDYLOSIS	0 .	1 (1.5%)
	TENDONITIS	1 (1.6%)	0 .
NERVOUS SYSTEM DISORDERS	TOTAL	14 (22.6%)	10 (15.4%)
	APHONIA	0 .	1 (1.5%)
	DIZZINESS	0 .	2 (3.1%)
	HEADACHE	12 (19.4%)	9 (13.8%)
	MIGRAINE	0 .	1 (1.5%)
	RETROGRADE AMNESIA	0 .	1 (1.5%)
	TREMOR	2 (3.2%)	0 .
PSYCHIATRIC DISORDERS	TOTAL	1 (1.6%)	2 (3.1%)
	AGGRESSION	0 .	1 (1.5%)
	ANXIETY	0 .	1 (1.5%)
	RESTLESSNESS	1 (1.6%)	0 .
RENAL AND URINARY DISORDERS	TOTAL	1 (1.6%)	1 (1.5%)
	GLYCOSURIA	0 .	1 (1.5%)
	URINARY RETENTION	1 (1.6%)	0 .
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	TOTAL	11 (17.7%)	9 (13.8%)
	BRONCHIAL POLYP	1 (1.6%)	0 .

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS/PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED

CONFIDENTIAL

SB 207499

TABLE 15.2B

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY MEDDRA SYSTEM ORGAN CLASS, PREFERRED TERM AND TREATMENT GROUP

PROTOCOL 181

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=62)	SB 207499 (N=65)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE EXACERBATED	1 (1.6%)	0 .
	COUGH	2 (3.2%)	3 (4.6%)
	HAEMOPTYSIS	3 (4.8%)	0 .
	LUNG DISORDER	1 (1.6%)	0 .
	NASAL CONGESTION	2 (3.2%)	1 (1.5%)
	NASAL DISCOMFORT	0 .	1 (1.5%)
	PHARYNGOLARYNGEAL PAIN	2 (3.2%)	5 (7.7%)
	PRODUCTIVE COUGH	1 (1.6%)	0 .
	SINUS CONGESTION	0 .	1 (1.5%)
	SNEEZING	0 .	1 (1.5%)
	STRIDOR	0 .	1 (1.5%)
	WHEEZING	1 (1.6%)	0 .
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	TOTAL	2 (3.2%)	0 .
	ECZEMA	1 (1.6%)	0 .
	HYPERHIDROSIS	1 (1.6%)	0 .
VASCULAR DISORDERS	TOTAL	0 .	2 (3.1%)
	HYPOTENSION	0 .	1 (1.5%)
	PHLEBITIS	0 .	1 (1.5%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS/PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED

CONFIDENTIAL

SB 207499

TABLE 15.3

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT, MEDDRA SYSTEM ORGAN CLASS, PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 181

TREATMENT GROUP=PLACEBO(N=62)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	RELATIONSHIP MISSING	NOT RELATED	RELATED	Total
TOTAL	TOTAL	0 .	25 (40.3%)	11 (17.7%)	36 (58.1%)
CARDIAC DISORDERS	TOTAL	0 .	1 (1.6%)	1 (1.6%)	2 (3.2%)
	CORONARY ARTERY DISEASE	0 .	1 (1.6%)	0 .	1 (1.6%)
	PALPITATIONS	0 .	0 .	1 (1.6%)	1 (1.6%)
GASTROINTESTINAL DISORDERS	TOTAL	0 .	4 (6.5%)	6 (9.7%)	10 (16.1%)
	ABDOMINAL DISCOMFORT	0 .	0 .	1 (1.6%)	1 (1.6%)
	ABDOMINAL PAIN	0 .	0 .	2 (3.2%)	2 (3.2%)
	DIARRHOEA	0 .	2 (3.2%)	0 .	2 (3.2%)
	FLATULENCE	0 .	0 .	1 (1.6%)	1 (1.6%)
	NAUSEA	0 .	2 (3.2%)	2 (3.2%)	4 (6.5%)
	RECTAL HAEMORRHAGE	0 .	0 .	1 (1.6%)	1 (1.6%)
	TOOTH DISORDER	0 .	1 (1.6%)	0 .	1 (1.6%)
	TOOTHACHE	0 .	1 (1.6%)	0 .	1 (1.6%)
	VOMITING	0 .	0 .	1 (1.6%)	1 (1.6%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	TOTAL	0 .	4 (6.5%)	0 .	4 (6.5%)
	CHEST PAIN	0 .	1 (1.6%)	0 .	1 (1.6%)
	FATIGUE	0 .	1 (1.6%)	0 .	1 (1.6%)
	PAIN	0 .	1 (1.6%)	0 .	1 (1.6%)
	PYREXIA	0 .	1 (1.6%)	0 .	1 (1.6%)
HEPATOBILIARY DISORDERS	TOTAL	0 .	0 .	1 (1.6%)	1 (1.6%)
	HEPATITIS	0 .	0 .	1 (1.6%)	1 (1.6%)
INFECTIONS AND INFESTATIONS	TOTAL	0 .	16 (25.8%)	0 .	16 (25.8%)
	CYSTITIS	0 .	1 (1.6%)	0 .	1 (1.6%)
	INFLUENZA	0 .	1 (1.6%)	0 .	1 (1.6%)
	LOWER RESPIRATORY TRACT INFECTION	0 .	2 (3.2%)	0 .	2 (3.2%)
	NASOPHARYNGITIS	0 .	8 (12.9%)	0 .	8 (12.9%)
	RESPIRATORY TRACT INFECTION	0 .	1 (1.6%)	0 .	1 (1.6%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND RELATIONSHIP
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED
3. WORST-CASE RELATIONSHIP IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL

SB 207499

TABLE 15.3

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT, MEDDRA SYSTEM ORGAN CLASS, PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 181

TREATMENT GROUP=PLACEBO(N=62)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	RELATIONSHIP MISSING	NOT RELATED	RELATED	Total
INFECTIONS AND INFESTATIONS	RHINITIS	0 .	1 (1.6%)	0 .	1 (1.6%)
	UPPER RESPIRATORY TRACT INFECTION	0 .	2 (3.2%)	0 .	2 (3.2%)
INVESTIGATIONS	TOTAL	0 .	1 (1.6%)	3 (4.8%)	4 (6.5%)
	BLOOD CREATININE INCREASED	0 .	0 .	1 (1.6%)	1 (1.6%)
	BLOOD GLUCOSE INCREASED	0 .	1 (1.6%)	0 .	1 (1.6%)
	BLOOD URIC ACID INCREASED	0 .	0 .	1 (1.6%)	1 (1.6%)
	FAECAL OCCULT BLOOD POSITIVE	0 .	0 .	2 (3.2%)	2 (3.2%)
METABOLISM AND NUTRITION DISORDERS	TOTAL	0 .	1 (1.6%)	1 (1.6%)	2 (3.2%)
	HYPERGLYCAEMIA	0 .	1 (1.6%)	0 .	1 (1.6%)
	HYPERLIPIDAEMIA	0 .	0 .	1 (1.6%)	1 (1.6%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	TOTAL	0 .	5 (8.1%)	0 .	5 (8.1%)
	JOINT SWELLING	0 .	1 (1.6%)	0 .	1 (1.6%)
	MUSCLE CRAMP	0 .	1 (1.6%)	0 .	1 (1.6%)
	MUSCULOSKELETAL STIFFNESS	0 .	1 (1.6%)	0 .	1 (1.6%)
	PAIN IN EXTREMITY	0 .	1 (1.6%)	0 .	1 (1.6%)
	TENDONITIS	0 .	1 (1.6%)	0 .	1 (1.6%)
NERVOUS SYSTEM DISORDERS	TOTAL	0 .	12 (19.4%)	2 (3.2%)	14 (22.6%)
	HEADACHE	0 .	10 (16.1%)	2 (3.2%)	12 (19.4%)
	TREMOR	0 .	2 (3.2%)	0 .	2 (3.2%)
PSYCHIATRIC DISORDERS	TOTAL	0 .	1 (1.6%)	0 .	1 (1.6%)
	RESTLESSNESS	0 .	1 (1.6%)	0 .	1 (1.6%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND RELATIONSHIP
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED
3. WORST-CASE RELATIONSHIP IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL
GM2004/00090/00
SB-207499/181

SB 207499

TABLE 15.3

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT,
MEDDRA SYSTEM ORGAN CLASS, PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 181

TREATMENT GROUP=PLACEBO(N=62)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	RELATIONSHIP MISSING	NOT RELATED	RELATED	Total
RENAL AND URINARY DISORDERS	TOTAL	0 .	1 (1.6%)	0 .	1 (1.6%)
	URINARY RETENTION	0 .	1 (1.6%)	0 .	1 (1.6%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	TOTAL	0 .	11 (17.7%)	0 .	11 (17.7%)
	BRONCHIAL POLYP	0 .	1 (1.6%)	0 .	1 (1.6%)
	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE EXACERBATED	0 .	1 (1.6%)	0 .	1 (1.6%)
	COUGH	0 .	2 (3.2%)	0 .	2 (3.2%)
	HAEMOPTYSIS	0 .	3 (4.8%)	0 .	3 (4.8%)
	LUNG DISORDER	0 .	1 (1.6%)	0 .	1 (1.6%)
	NASAL CONGESTION	0 .	2 (3.2%)	0 .	2 (3.2%)
	PHARYNGOLARYNGEAL PAIN	0 .	2 (3.2%)	0 .	2 (3.2%)
	PRODUCTIVE COUGH	0 .	1 (1.6%)	0 .	1 (1.6%)
	WHEEZING	0 .	1 (1.6%)	0 .	1 (1.6%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	TOTAL	0 .	1 (1.6%)	1 (1.6%)	2 (3.2%)
	ECZEMA	0 .	0 .	1 (1.6%)	1 (1.6%)
	HYPERHIDROSIS	0 .	1 (1.6%)	0 .	1 (1.6%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND RELATIONSHIP
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED
3. WORST-CASE RELATIONSHIP IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL
GM2004/00090/00
SB-207499/181

SB 207499

TABLE 15.3

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT, MEDDRA SYSTEM ORGAN CLASS, PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 181

TREATMENT GROUP=SB 207499(N=65)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	RELATIONSHIP MISSING	NOT RELATED	RELATED	Total
TOTAL	TOTAL	0 .	28 (43.1%)	13 (20.0%)	41 (63.1%)
CARDIAC DISORDERS	TOTAL	0 .	1 (1.5%)	0 .	1 (1.5%)
	ATRIAL FLUTTER	0 .	1 (1.5%)	0 .	1 (1.5%)
EYE DISORDERS	TOTAL	0 .	1 (1.5%)	0 .	1 (1.5%)
	OCULAR DISCOMFORT	0 .	1 (1.5%)	0 .	1 (1.5%)
GASTROINTESTINAL DISORDERS	TOTAL	0 .	8 (12.3%)	12 (18.5%)	20 (30.8%)
	CONSTIPATION	0 .	1 (1.5%)	0 .	1 (1.5%)
	DIARRHOEA	0 .	2 (3.1%)	3 (4.6%)	5 (7.7%)
	DYSPEPSIA	0 .	0 .	3 (4.6%)	3 (4.6%)
	ENTERITIS	0 .	0 .	1 (1.5%)	1 (1.5%)
	FREQUENT BOWEL MOVEMENTS	0 .	0 .	1 (1.5%)	1 (1.5%)
	GASTRITIS	0 .	0 .	2 (3.1%)	2 (3.1%)
	GASTROOESOPHAGEAL REFLUX DISEASE	0 .	0 .	1 (1.5%)	1 (1.5%)
	LOOSE STOOLS	0 .	0 .	2 (3.1%)	2 (3.1%)
	NAUSEA	0 .	4 (6.2%)	2 (3.1%)	6 (9.2%)
	STOMACH DISCOMFORT	0 .	1 (1.5%)	0 .	1 (1.5%)
	TOOTHACHE	0 .	1 (1.5%)	0 .	1 (1.5%)
	VOMITING	0 .	2 (3.1%)	3 (4.6%)	5 (7.7%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	TOTAL	0 .	5 (7.7%)	0 .	5 (7.7%)
	ASTHENIA	0 .	1 (1.5%)	0 .	1 (1.5%)
	CHEST PAIN	0 .	2 (3.1%)	0 .	2 (3.1%)
	FATIGUE	0 .	2 (3.1%)	0 .	2 (3.1%)
	PYREXIA	0 .	1 (1.5%)	0 .	1 (1.5%)
INFECTIONS AND INFESTATIONS	TOTAL	0 .	15 (23.1%)	0 .	15 (23.1%)
	HELICOBACTER GASTRITIS	0 .	1 (1.5%)	0 .	1 (1.5%)
	INFLUENZA	0 .	2 (3.1%)	0 .	2 (3.1%)
	LOWER RESPIRATORY TRACT INFECTION	0 .	1 (1.5%)	0 .	1 (1.5%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND RELATIONSHIP
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED
3. WORST-CASE RELATIONSHIP IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL

SB 207499

TABLE 15.3

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT, MEDDRA SYSTEM ORGAN CLASS, PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 181

TREATMENT GROUP=SB 207499(N=65)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	RELATIONSHIP MISSING	NOT RELATED	RELATED	Total
INFECTIONS AND INFESTATIONS	NASOPHARYNGITIS	0 .	8 (12.3%)	0 .	8 (12.3%)
	RHINITIS	0 .	2 (3.1%)	0 .	2 (3.1%)
	UPPER RESPIRATORY TRACT INFECTION	0 .	1 (1.5%)	0 .	1 (1.5%)
	VIRAL INFECTION	0 .	1 (1.5%)	0 .	1 (1.5%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	TOTAL	0 .	2 (3.1%)	0 .	2 (3.1%)
	JOINT SPRAIN	0 .	1 (1.5%)	0 .	1 (1.5%)
	MUSCLE STRAIN	0 .	1 (1.5%)	0 .	1 (1.5%)
INVESTIGATIONS	TOTAL	0 .	0 .	2 (3.1%)	2 (3.1%)
	FAECAL OCCULT BLOOD POSITIVE	0 .	0 .	2 (3.1%)	2 (3.1%)
METABOLISM AND NUTRITION DISORDERS	TOTAL	0 .	1 (1.5%)	0 .	1 (1.5%)
	ANOREXIA	0 .	1 (1.5%)	0 .	1 (1.5%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	TOTAL	0 .	7 (10.8%)	0 .	7 (10.8%)
	ARTHRALGIA	0 .	2 (3.1%)	0 .	2 (3.1%)
	BACK PAIN	0 .	2 (3.1%)	0 .	2 (3.1%)
	JOINT SWELLING	0 .	1 (1.5%)	0 .	1 (1.5%)
	MUSCLE TIGHTNESS	0 .	1 (1.5%)	0 .	1 (1.5%)
	NECK PAIN	0 .	1 (1.5%)	0 .	1 (1.5%)
	PAIN IN EXTREMITY	0 .	1 (1.5%)	0 .	1 (1.5%)
	SPONDYLOSIS	0 .	1 (1.5%)	0 .	1 (1.5%)
NERVOUS SYSTEM DISORDERS	TOTAL	0 .	10 (15.4%)	0 .	10 (15.4%)
	APHONIA	0 .	1 (1.5%)	0 .	1 (1.5%)
	DIZZINESS	0 .	2 (3.1%)	0 .	2 (3.1%)
	HEADACHE	0 .	9 (13.8%)	0 .	9 (13.8%)
	MIGRAINE	0 .	1 (1.5%)	0 .	1 (1.5%)
	RETROGRADE AMNESIA	0 .	1 (1.5%)	0 .	1 (1.5%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND RELATIONSHIP
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED
3. WORST-CASE RELATIONSHIP IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL

SB 207499

TABLE 15.3

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT,
MEDDRA SYSTEM ORGAN CLASS, PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 181

TREATMENT GROUP=SB 207499(N=65)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	RELATIONSHIP MISSING	NOT RELATED	RELATED	Total
PSYCHIATRIC DISORDERS	TOTAL	0 .	1 (1.5%)	1 (1.5%)	2 (3.1%)
	AGGRESSION	0 .	0 .	1 (1.5%)	1 (1.5%)
	ANXIETY	0 .	1 (1.5%)	0 .	1 (1.5%)
RENAL AND URINARY DISORDERS	TOTAL	0 .	1 (1.5%)	0 .	1 (1.5%)
	GLYCOSURIA	0 .	1 (1.5%)	0 .	1 (1.5%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	TOTAL	0 .	9 (13.8%)	0 .	9 (13.8%)
	COUGH	0 .	3 (4.6%)	0 .	3 (4.6%)
	NASAL CONGESTION	0 .	1 (1.5%)	0 .	1 (1.5%)
	NASAL DISCOMFORT	0 .	1 (1.5%)	0 .	1 (1.5%)
	PHARYNGOLARYNGEAL PAIN	0 .	5 (7.7%)	0 .	5 (7.7%)
	SINUS CONGESTION	0 .	1 (1.5%)	0 .	1 (1.5%)
	SNEEZING	0 .	1 (1.5%)	0 .	1 (1.5%)
	STRIDOR	0 .	1 (1.5%)	0 .	1 (1.5%)
VASCULAR DISORDERS	TOTAL	0 .	2 (3.1%)	0 .	2 (3.1%)
	HYPOTENSION	0 .	1 (1.5%)	0 .	1 (1.5%)
	PHLEBITIS	0 .	1 (1.5%)	0 .	1 (1.5%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS, MEDDRA PREFERRED TERM AND RELATIONSHIP
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED
3. WORST-CASE RELATIONSHIP IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN MEDDRA SYSTEM ORGAN CLASS

CONFIDENTIAL

SB 207499

TABLE 15.4a

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY, MEDDRA SYSTEM ORGAN CLASS, AND PREFERRED TERM - PLACEBO
PROTOCOL 181

TREATMENT GROUP=PLACEBO (N=62)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	Intensity Mild	Moderate	Not appl	Severe	Total
TOTAL	TOTAL	17 (27.4%)	15 (24.2%)	1 (1.6%)	3 (4.8%)	36 (58.1%)
CARDIAC DISORDERS	TOTAL	0 .	2 (3.2%)	0 .	0 .	2 (3.2%)
	CORONARY ARTERY DISEASE	0 .	1 (1.6%)	0 .	0 .	1 (1.6%)
	PALPITATIONS	0 .	1 (1.6%)	0 .	0 .	1 (1.6%)
GASTROINTESTINAL DISORDERS	TOTAL	7 (11.3%)	2 (3.2%)	0 .	1 (1.6%)	10 (16.1%)
	ABDOMINAL DISCOMFORT	1 (1.6%)	0 .	0 .	0 .	1 (1.6%)
	ABDOMINAL PAIN	0 .	2 (3.2%)	0 .	0 .	2 (3.2%)
	DIARRHOEA	1 (1.6%)	0 .	0 .	1 (1.6%)	2 (3.2%)
	FLATULENCE	1 (1.6%)	0 .	0 .	0 .	1 (1.6%)
	NAUSEA	4 (6.5%)	0 .	0 .	0 .	4 (6.5%)
	RECTAL HAEMORRHAGE	1 (1.6%)	0 .	0 .	0 .	1 (1.6%)
	TOOTH DISORDER	1 (1.6%)	0 .	0 .	0 .	1 (1.6%)
	TOOTHACHE	1 (1.6%)	0 .	0 .	0 .	1 (1.6%)
	VOMITING	1 (1.6%)	0 .	0 .	0 .	1 (1.6%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	TOTAL	2 (3.2%)	2 (3.2%)	0 .	0 .	4 (6.5%)
	CHEST PAIN	0 .	1 (1.6%)	0 .	0 .	1 (1.6%)
	FATIGUE	0 .	1 (1.6%)	0 .	0 .	1 (1.6%)
	PAIN	1 (1.6%)	0 .	0 .	0 .	1 (1.6%)
	PYREXIA	1 (1.6%)	0 .	0 .	0 .	1 (1.6%)
HEPATOBILIARY DISORDERS	TOTAL	0 .	1 (1.6%)	0 .	0 .	1 (1.6%)
	HEPATITIS	0 .	1 (1.6%)	0 .	0 .	1 (1.6%)
INFECTIONS AND INFESTATIONS	TOTAL	8 (12.9%)	8 (12.9%)	0 .	0 .	16 (25.8%)
	CYSTITIS	1 (1.6%)	0 .	0 .	0 .	1 (1.6%)
	INFLUENZA	0 .	1 (1.6%)	0 .	0 .	1 (1.6%)
	LOWER RESPIRATORY TRACT INFECTION	1 (1.6%)	1 (1.6%)	0 .	0 .	2 (3.2%)
	NASOPHARYNGITIS	4 (6.5%)	4 (6.5%)	0 .	0 .	8 (12.9%)
	RESPIRATORY TRACT INFECTION	1 (1.6%)	0 .	0 .	0 .	1 (1.6%)

1. EACH PATIENT COUNTED ONCE PER SYSTEM ORGAN CLASS, PREFERRED TERM AND INTENSITY
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED
3. MAXIMUM INTENSITY IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN THE SYSTEM ORGAN CLASS

CONFIDENTIAL
GM2004/00090/00
SB-207499/181

SB 207499

TABLE 15.4a

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY,
MEDDRA SYSTEM ORGAN CLASS, AND PREFERRED TERM - PLACEBO
PROTOCOL 181

TREATMENT GROUP=PLACEBO (N=62)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	Intensity Mild	Moderate	Not appl	Severe	Total
INFECTIONS AND INFESTATIONS	RHINITIS	1 (1.6%)	0 .	0 .	0 .	1 (1.6%)
	UPPER RESPIRATORY TRACT INFECTION	0 .	2 (3.2%)	0 .	0 .	2 (3.2%)
INVESTIGATIONS	TOTAL	4 (6.5%)	0 .	0 .	0 .	4 (6.5%)
	BLOOD CREATININE INCREASED	1 (1.6%)	0 .	0 .	0 .	1 (1.6%)
	BLOOD GLUCOSE INCREASED	1 (1.6%)	0 .	0 .	0 .	1 (1.6%)
	BLOOD URIC ACID INCREASED	1 (1.6%)	0 .	0 .	0 .	1 (1.6%)
	FAECAL OCCULT BLOOD POSITIVE	2 (3.2%)	0 .	0 .	0 .	2 (3.2%)
METABOLISM AND NUTRITION DISORDERS	TOTAL	2 (3.2%)	0 .	0 .	0 .	2 (3.2%)
	HYPERGLYCAEMIA	1 (1.6%)	0 .	0 .	0 .	1 (1.6%)
	HYPERLIPIDAEMIA	1 (1.6%)	0 .	0 .	0 .	1 (1.6%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	TOTAL	2 (3.2%)	3 (4.8%)	0 .	0 .	5 (8.1%)
	JOINT SWELLING	1 (1.6%)	0 .	0 .	0 .	1 (1.6%)
	MUSCLE CRAMP	1 (1.6%)	0 .	0 .	0 .	1 (1.6%)
	MUSCULOSKELETAL STIFFNESS	0 .	1 (1.6%)	0 .	0 .	1 (1.6%)
	PAIN IN EXTREMITY	0 .	1 (1.6%)	0 .	0 .	1 (1.6%)
	TENDONITIS	0 .	1 (1.6%)	0 .	0 .	1 (1.6%)
NERVOUS SYSTEM DISORDERS	TOTAL	11 (17.7%)	3 (4.8%)	0 .	0 .	14 (22.6%)
	HEADACHE	10 (16.1%)	2 (3.2%)	0 .	0 .	12 (19.4%)
	TREMOR	1 (1.6%)	1 (1.6%)	0 .	0 .	2 (3.2%)
PSYCHIATRIC DISORDERS	TOTAL	1 (1.6%)	0 .	0 .	0 .	1 (1.6%)
	RESTLESSNESS	1 (1.6%)	0 .	0 .	0 .	1 (1.6%)

1. EACH PATIENT COUNTED ONCE PER SYSTEM ORGAN CLASS, PREFERRED TERM AND INTENSITY
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED
3. MAXIMUM INTENSITY IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN THE SYSTEM ORGAN CLASS

CONFIDENTIAL
GM2004/00090/00
SB-207499/181

SB 207499

TABLE 15.4a

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY,
MEDDRA SYSTEM ORGAN CLASS, AND PREFERRED TERM - PLACEBO
PROTOCOL 181

TREATMENT GROUP=PLACEBO (N=62)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	Intensity Mild	Moderate	Not appl	Severe	Total
RENAL AND URINARY DISORDERS	TOTAL	0 .	0 .	0 .	1 (1.6%)	1 (1.6%)
	URINARY RETENTION	0 .	0 .	0 .	1 (1.6%)	1 (1.6%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	TOTAL	7 (11.3%)	2 (3.2%)	1 (1.6%)	1 (1.6%)	11 (17.7%)
	BRONCHIAL POLYP	0 .	0 .	0 .	1 (1.6%)	1 (1.6%)
	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE EXACERBATED	0 .	1 (1.6%)	0 .	0 .	1 (1.6%)
	COUGH	2 (3.2%)	0 .	0 .	0 .	2 (3.2%)
	HAEMOPTYSIS	3 (4.8%)	0 .	0 .	0 .	3 (4.8%)
	LUNG DISORDER	0 .	0 .	1 (1.6%)	0 .	1 (1.6%)
	NASAL CONGESTION	2 (3.2%)	0 .	0 .	0 .	2 (3.2%)
	PHARYNGOLARYNGEAL PAIN	1 (1.6%)	1 (1.6%)	0 .	0 .	2 (3.2%)
	PRODUCTIVE COUGH	1 (1.6%)	0 .	0 .	0 .	1 (1.6%)
	WHEEZING	1 (1.6%)	0 .	0 .	0 .	1 (1.6%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	TOTAL	0 .	2 (3.2%)	0 .	0 .	2 (3.2%)
	ECZEMA	0 .	1 (1.6%)	0 .	0 .	1 (1.6%)
	HYPERHIDROSIS	0 .	1 (1.6%)	0 .	0 .	1 (1.6%)

1. EACH PATIENT COUNTED ONCE PER SYSTEM ORGAN CLASS, PREFERRED TERM AND INTENSITY
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED
3. MAXIMUM INTENSITY IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN THE SYSTEM ORGAN CLASS

CONFIDENTIAL
GM2004/00090/00
SB-207499/181

SB 207499

TABLE 15.4b

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY, MEDDRA SYSTEM ORGAN CLASS, AND PREFERRED TERM - SB 207499
PROTOCOL 181

TREATMENT GROUP=SB 207499 (N=65)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	Intensity Mild	Moderate	Severe	Total
TOTAL	TOTAL	18 (27.7%)	18 (27.7%)	5 (7.7%)	41 (63.1%)
CARDIAC DISORDERS	TOTAL	0 .	1 (1.5%)	0 .	1 (1.5%)
	ATRIAL FLUTTER	0 .	1 (1.5%)	0 .	1 (1.5%)
EYE DISORDERS	TOTAL	1 (1.5%)	0 .	0 .	1 (1.5%)
	OCULAR DISCOMFORT	1 (1.5%)	0 .	0 .	1 (1.5%)
GASTROINTESTINAL DISORDERS	TOTAL	9 (13.8%)	8 (12.3%)	3 (4.6%)	20 (30.8%)
	CONSTIPATION	0 .	1 (1.5%)	0 .	1 (1.5%)
	DIARRHOEA	1 (1.5%)	4 (6.2%)	0 .	5 (7.7%)
	DYSPEPSIA	3 (4.6%)	0 .	0 .	3 (4.6%)
	ENTERITIS	0 .	0 .	1 (1.5%)	1 (1.5%)
	FREQUENT BOWEL MOVEMENTS	1 (1.5%)	0 .	0 .	1 (1.5%)
	GASTRITIS	1 (1.5%)	1 (1.5%)	0 .	2 (3.1%)
	GASTROOESOPHAGEAL REFLUX DISEASE	0 .	1 (1.5%)	0 .	1 (1.5%)
	LOOSE STOOLS	2 (3.1%)	0 .	0 .	2 (3.1%)
	NAUSEA	4 (6.2%)	0 .	2 (3.1%)	6 (9.2%)
	STOMACH DISCOMFORT	1 (1.5%)	0 .	0 .	1 (1.5%)
	TOOTHACHE	0 .	1 (1.5%)	0 .	1 (1.5%)
	VOMITING	1 (1.5%)	4 (6.2%)	0 .	5 (7.7%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	TOTAL	3 (4.6%)	2 (3.1%)	0 .	5 (7.7%)
	ASTHENIA	1 (1.5%)	0 .	0 .	1 (1.5%)
	CHEST PAIN	0 .	2 (3.1%)	0 .	2 (3.1%)
	FATIGUE	2 (3.1%)	0 .	0 .	2 (3.1%)
	PYREXIA	1 (1.5%)	0 .	0 .	1 (1.5%)
INFECTIONS AND INFESTATIONS	TOTAL	9 (13.8%)	5 (7.7%)	1 (1.5%)	15 (23.1%)
	HELICOBACTER GASTRITIS	0 .	1 (1.5%)	0 .	1 (1.5%)
	INFLUENZA	0 .	1 (1.5%)	1 (1.5%)	2 (3.1%)
	LOWER RESPIRATORY TRACT INFECTION	1 (1.5%)	0 .	0 .	1 (1.5%)

1. EACH PATIENT COUNTED ONCE PER SYSTEM ORGAN CLASS, PREFERRED TERM AND INTENSITY
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED
3. MAXIMUM INTENSITY IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN THE SYSTEM ORGAN CLASS

CONFIDENTIAL

SB 207499

TABLE 15.4b

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY, MEDDRA SYSTEM ORGAN CLASS, AND PREFERRED TERM - SB 207499
PROTOCOL 181

TREATMENT GROUP=SB 207499 (N=65)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	Intensity Mild	Moderate	Severe	Total
INFECTIONS AND INFESTATIONS	NASOPHARYNGITIS	6 (9.2%)	2 (3.1%)	0 .	8 (12.3%)
	RHINITIS	2 (3.1%)	0 .	0 .	2 (3.1%)
	UPPER RESPIRATORY TRACT INFECTION	0 .	1 (1.5%)	0 .	1 (1.5%)
	VIRAL INFECTION	0 .	1 (1.5%)	0 .	1 (1.5%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	TOTAL	1 (1.5%)	1 (1.5%)	0 .	2 (3.1%)
	JOINT SPRAIN	0 .	1 (1.5%)	0 .	1 (1.5%)
	MUSCLE STRAIN	1 (1.5%)	0 .	0 .	1 (1.5%)
INVESTIGATIONS	TOTAL	2 (3.1%)	0 .	0 .	2 (3.1%)
	FAECAL OCCULT BLOOD POSITIVE	2 (3.1%)	0 .	0 .	2 (3.1%)
METABOLISM AND NUTRITION DISORDERS	TOTAL	1 (1.5%)	0 .	0 .	1 (1.5%)
	ANOREXIA	1 (1.5%)	0 .	0 .	1 (1.5%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	TOTAL	5 (7.7%)	2 (3.1%)	0 .	7 (10.8%)
	ARTHRALGIA	1 (1.5%)	1 (1.5%)	0 .	2 (3.1%)
	BACK PAIN	2 (3.1%)	0 .	0 .	2 (3.1%)
	JOINT SWELLING	1 (1.5%)	0 .	0 .	1 (1.5%)
	MUSCLE TIGHTNESS	1 (1.5%)	0 .	0 .	1 (1.5%)
	NECK PAIN	0 .	1 (1.5%)	0 .	1 (1.5%)
	PAIN IN EXTREMITY	0 .	1 (1.5%)	0 .	1 (1.5%)
	SPONDYLOSIS	0 .	1 (1.5%)	0 .	1 (1.5%)
NERVOUS SYSTEM DISORDERS	TOTAL	7 (10.8%)	2 (3.1%)	1 (1.5%)	10 (15.4%)
	APHONIA	1 (1.5%)	0 .	0 .	1 (1.5%)
	DIZZINESS	2 (3.1%)	0 .	0 .	2 (3.1%)
	HEADACHE	6 (9.2%)	2 (3.1%)	1 (1.5%)	9 (13.8%)
	MIGRAINE	1 (1.5%)	0 .	0 .	1 (1.5%)
	RETROGRADE AMNESIA	1 (1.5%)	0 .	0 .	1 (1.5%)

1. EACH PATIENT COUNTED ONCE PER SYSTEM ORGAN CLASS, PREFERRED TERM AND INTENSITY
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED
3. MAXIMUM INTENSITY IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN THE SYSTEM ORGAN CLASS

CONFIDENTIAL
GM2004/00090/00
SB-207499/181

SB 207499

TABLE 15.4b

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY, MEDDRA SYSTEM ORGAN CLASS, AND PREFERRED TERM - SB 207499
PROTOCOL 181

TREATMENT GROUP=SB 207499 (N=65)

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	Intensity Mild	Moderate	Severe	Total
PSYCHIATRIC DISORDERS	TOTAL	1 (1.5%)	1 (1.5%)	0 .	2 (3.1%)
	AGGRESSION	0 .	1 (1.5%)	0 .	1 (1.5%)
	ANXIETY	1 (1.5%)	0 .	0 .	1 (1.5%)
RENAL AND URINARY DISORDERS	TOTAL	0 .	1 (1.5%)	0 .	1 (1.5%)
	GLYCOSURIA	0 .	1 (1.5%)	0 .	1 (1.5%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	TOTAL	7 (10.8%)	2 (3.1%)	0 .	9 (13.8%)
	COUGH	1 (1.5%)	2 (3.1%)	0 .	3 (4.6%)
	NASAL CONGESTION	0 .	1 (1.5%)	0 .	1 (1.5%)
	NASAL DISCOMFORT	1 (1.5%)	0 .	0 .	1 (1.5%)
	PHARYNGOLARYNGEAL PAIN	4 (6.2%)	1 (1.5%)	0 .	5 (7.7%)
	SINUS CONGESTION	1 (1.5%)	0 .	0 .	1 (1.5%)
	SNEEZING	1 (1.5%)	0 .	0 .	1 (1.5%)
	STRIDOR	1 (1.5%)	0 .	0 .	1 (1.5%)
VASCULAR DISORDERS	TOTAL	1 (1.5%)	1 (1.5%)	0 .	2 (3.1%)
	HYPOTENSION	0 .	1 (1.5%)	0 .	1 (1.5%)
	PHLEBITIS	1 (1.5%)	0 .	0 .	1 (1.5%)

1. EACH PATIENT COUNTED ONCE PER SYSTEM ORGAN CLASS, PREFERRED TERM AND INTENSITY
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED
3. MAXIMUM INTENSITY IS USED FOR EACH ADVERSE ENVENT FOR EACH PATIENT
4. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN THE SYSTEM ORGAN CLASS

CONFIDENTIAL
GM2004/00090/00
SB-207499/181

SB 207499

TABLE 15.5

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES (>= 2%) BY INITIAL TIME OF ONSET, MEDDRA SYSTEM ORGAN CLASS, PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 181

TREATMENT GROUP: PLACEBO

DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	1 (N= 62)		2-7 (N= 62)		8-14 (N= 62)		15-28 (N= 61)		29-42 (N= 60)		43-56 (N= 59)		57-70 (N= 59)		>70 (N= 59)		TOTAL (N= 62)	
		n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
TOTAL PATIENTS WITH ADVERSE EXPERIENCES	TOTAL	1	2%	5	8%	5	8%	10	16%	8	13%	7	12%	6	10%	20	34%	36	58%
GASTROINTESTINAL DISORDERS	TOTAL	0	.	1	2%	1	2%	0	.	1	2%	1	2%	0	.	1	2%	5	8%
	DIARRHOEA	0	.	0	.	0	.	0	.	1	2%	1	2%	0	.	0	.	2	3%
	NAUSEA	0	.	1	2%	1	2%	0	.	1	2%	0	.	0	.	1	2%	4	6%
	VOMITING	0	.	0	.	0	.	0	.	0	.	0	.	0	.	1	2%	1	2%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	TOTAL	0	.	0	.	0	.	0	.	0	.	1	2%	0	.	1	2%	2	3%
	CHEST PAIN	0	.	0	.	0	.	0	.	0	.	1	2%	0	.	0	.	1	2%
	FATIGUE	0	.	0	.	0	.	0	.	0	.	0	.	0	.	1	2%	1	2%
INFECTIONS AND INFESTATIONS	TOTAL	0	.	0	.	1	2%	2	3%	1	2%	1	2%	1	2%	4	7%	10	16%
	INFLUENZA	0	.	0	.	0	.	0	.	0	.	1	2%	0	.	0	.	1	2%
	NASOPHARYNGITIS	0	.	0	.	1	2%	2	4%	1	2%	0	.	1	2%	3	6%	8	13%
	RHINITIS	0	.	0	.	0	.	0	.	0	.	0	.	0	.	1	2%	1	2%
INVESTIGATIONS	TOTAL	0	.	0	.	0	.	0	.	0	.	0	.	0	.	2	3%	2	3%
	FAECAL OCCULT BLOO	0	.	0	.	0	.	0	.	0	.	0	.	0	.	2	4%	2	3%
NERVOUS SYSTEM DISORDERS	TOTAL	0	.	1	2%	2	3%	2	3%	3	5%	0	.	2	3%	2	3%	12	19%
	HEADACHE	0	.	1	2%	2	4%	2	4%	3	6%	0	.	2	4%	2	4%	12	19%
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	TOTAL	0	.	0	.	1	2%	1	2%	0	.	0	.	0	.	2	3%	4	6%
	COUGH	0	.	0	.	0	.	1	2%	0	.	0	.	0	.	1	2%	2	3%
	PHARYNGOLARYNGEAL	0	.	0	.	1	2%	0	.	0	.	0	.	0	.	1	2%	2	3%

1. EACH PATIENT COUNTED ONCE PER SYSTEM ORGAN CLASS, PREFERRED TERM AND ONSET
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS EXPOSED TO STUDY MEDICATION WITHIN EACH TIME INTERVAL
4. EVENTS OCCURRING IN AT LEAST 2% OF PATIENTS IN THE SB 207499 GROUP ARE INCLUDED
5. EVENTS FOR WHICH THE ONSET IS UNDETERMINED ARE ASSUMED TO HAVE OCCURRED AT DAY 1

CONFIDENTIAL
GM2004/00090/00
SB-207499/181

SB 207499

TABLE 15.5

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES (>= 2%) BY INITIAL TIME OF ONSET, MEDDRA SYSTEM ORGAN CLASS, PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 181

TREATMENT GROUP: SB 207499

DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	1 (N= 65)		2-7 (N= 65)		8-14 (N= 65)		15-28 (N= 63)		29-42 (N= 61)		43-56 (N= 59)		57-70 (N= 58)		>70 (N= 58)		TOTAL (N= 65)	
		n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
TOTAL PATIENTS WITH ADVERSE EXPERIENCES	TOTAL	3	5%	13	20%	3	5%	11	17%	12	20%	9	15%	5	9%	17	29%	41	63%
GASTROINTESTINAL DISORDERS	TOTAL	1	2%	5	8%	0	.	3	5%	6	10%	3	5%	0	.	1	2%	16	25%
	DIARRHOEA	0	.	1	2%	0	.	1	2%	1	2%	1	2%	0	.	1	2%	5	8%
	DYSPEPSIA	0	.	1	2%	0	.	0	.	1	2%	1	2%	0	.	0	.	3	5%
	GASTRITIS	0	.	1	2%	0	.	0	.	1	2%	0	.	0	.	0	.	2	3%
	LOOSE STOOLS	0	.	1	2%	0	.	0	.	1	2%	0	.	0	.	0	.	2	3%
	NAUSEA	1	2%	0	.	0	.	2	4%	2	4%	1	2%	0	.	0	.	6	9%
	VOMITING	0	.	3	6%	0	.	0	.	1	2%	1	2%	0	.	0	.	5	8%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	TOTAL	0	.	2	3%	0	.	0	.	0	.	2	3%	0	.	0	.	4	6%
	CHEST PAIN	0	.	1	2%	0	.	0	.	0	.	1	2%	0	.	0	.	2	3%
	FATIGUE	0	.	1	2%	0	.	0	.	0	.	1	2%	0	.	0	.	2	3%
INFECTIONS AND INFESTATIONS	TOTAL	1	2%	1	2%	0	.	3	5%	1	2%	2	3%	3	5%	1	2%	11	17%
	INFLUENZA	0	.	1	2%	0	.	0	.	1	2%	0	.	0	.	0	.	2	3%
	NASOPHARYNGITIS	1	2%	0	.	0	.	3	6%	0	.	1	2%	3	6%	0	.	8	12%
	RHINITIS	0	.	0	.	0	.	0	.	0	.	1	2%	0	.	1	2%	2	3%
INVESTIGATIONS	TOTAL	0	.	0	.	0	.	0	.	0	.	0	.	0	.	2	3%	2	3%
	FAECAL OCCULT BLOO	0	.	0	.	0	.	0	.	0	.	0	.	0	.	2	4%	2	3%
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	TOTAL	0	.	0	.	0	.	3	5%	0	.	0	.	0	.	1	2%	4	6%
	ARTHRALGIA	0	.	0	.	0	.	2	4%	0	.	0	.	0	.	0	.	2	3%
	BACK PAIN	0	.	0	.	0	.	1	2%	0	.	0	.	0	.	1	2%	2	3%

1. EACH PATIENT COUNTED ONCE PER SYSTEM ORGAN CLASS, PREFERRED TERM AND ONSET
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS EXPOSED TO STUDY MEDICATION WITHIN EACH TIME INTERVAL
4. EVENTS OCCURRING IN AT LEAST 2% OF PATIENTS IN THE SB 207499 GROUP ARE INCLUDED
5. EVENTS FOR WHICH THE ONSET IS UNDETERMINED ARE ASSUMED TO HAVE OCCURRED AT DAY 1

CONFIDENTIAL

SB 207499

TABLE 15.5

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES (>= 2%) BY INITIAL TIME OF ONSET, MEDDRA SYSTEM ORGAN CLASS, PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 181

TREATMENT GROUP: SB 207499

DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	1 (N= 65)		2-7 (N= 65)		8-14 (N= 65)		15-28 (N= 63)		29-42 (N= 61)		43-56 (N= 59)		57-70 (N= 58)		>70 (N= 58)		TOTAL (N= 65)	
		n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
NERVOUS SYSTEM DISORDERS	TOTAL	1	2%	2	3%	1	2%	0	.	4	7%	1	2%	0	.	1	2%	10	15%
	DIZZINESS	0	.	0	.	0	.	0	.	1	2%	0	.	0	.	1	2%	2	3%
	HEADACHE	1	2%	2	4%	1	2%	0	.	4	8%	1	2%	0	.	0	.	9	14%
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	TOTAL	0	.	1	2%	1	2%	0	.	1	2%	1	2%	1	2%	3	5%	7	11%
	COUGH	0	.	1	2%	0	.	0	.	0	.	1	2%	0	.	1	2%	3	5%
	PHARYNGOLARYNGEAL	0	.	0	.	1	2%	0	.	1	2%	0	.	1	2%	2	4%	5	8%

1. EACH PATIENT COUNTED ONCE PER SYSTEM ORGAN CLASS, PREFERRED TERM AND ONSET
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS EXPOSED TO STUDY MEDICATION WITHIN EACH TIME INTERVAL
4. EVENTS OCCURRING IN AT LEAST 2% OF PATIENTS IN THE SB 207499 GROUP ARE INCLUDED
5. EVENTS FOR WHICH THE ONSET IS UNDETERMINED ARE ASSUMED TO HAVE OCCURRED AT DAY 1

CONFIDENTIAL
GM2004/00090/00
SB-207499/181

SB 207499

TABLE 15.6

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES THAT LED TO DOSE INTERRUPTION BY SYSTEM ORGAN CLASS, PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 181

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=62)	SB 207499 (N=65)	Total (N=127)
TOTAL	TOTAL	0 .	3 (4.6%)	3 (2.4%)
GASTROINTESTINAL DISORDERS	TOTAL	0 .	1 (1.5%)	1 (0.8%)
	NAUSEA	0 .	1 (1.5%)	1 (0.8%)
PSYCHIATRIC DISORDERS	TOTAL	0 .	1 (1.5%)	1 (0.8%)
	ANXIETY	0 .	1 (1.5%)	1 (0.8%)
VASCULAR DISORDERS	TOTAL	0 .	1 (1.5%)	1 (0.8%)
	PHLEBITIS	0 .	1 (1.5%)	1 (0.8%)

1. EACH PATIENT COUNTED ONCE PER SYSTEM ORGAN CLASS/PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN THE SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED

CONFIDENTIAL

SB 207499

TABLE 15.7

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES THAT REQUIRED CORRECTIVE THERAPY BY MEDDRA SYSTEM ORGAN CLASS, PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 181

NO DATA AVAILABLE FOR THIS REPORT

1. EACH PATIENT COUNTED ONCE PER SYSTEM ORGAN CLASS/PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN THE SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED

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SB 207499

TABLE 15.8A

INCIDENCE OF PRE-THERAPY SERIOUS ADVERSE EXPERIENCES BY MEDDRA SYSTEM ORGAN CLASS, PREFERRED TERM AND TREATMENT GROUP

PROTOCOL 181

MEDDRA SYSTEM ORGAN CLASS	PREFERRED TERM	TREATMENT GROUP PLACEBO (N=64)	SB 207499 (N=66)	NON-RAND. (N=30)	Total (N=160)
TOTAL	TOTAL	2 (3.1%)	0 .	2 (6.7%)	4 (2.5%)
INFECTIONS AND INFESTATIONS	TOTAL	0 .	0 .	1 (3.3%)	1 (0.6%)
	PNEUMONIA	0 .	0 .	1 (3.3%)	1 (0.6%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	TOTAL	1 (1.6%)	0 .	0 .	1 (0.6%)
	RADIUS FRACTURE	1 (1.6%)	0 .	0 .	1 (0.6%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	TOTAL	1 (1.6%)	0 .	0 .	1 (0.6%)
	SMALL CELL LUNG CANCER STAGE UNSPECIFIED	1 (1.6%)	0 .	0 .	1 (0.6%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	TOTAL	0 .	0 .	1 (3.3%)	1 (0.6%)
	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE EXACERBATED	0 .	0 .	1 (3.3%)	1 (0.6%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS/PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN THE SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED

CONFIDENTIAL

SB 207499

TABLE 15.8B

INCIDENCE OF ON-THERAPY SERIOUS ADVERSE EXPERIENCES BY MEDDRA SYSTEM ORGAN CLASS, PREFERRED TERM AND TREATMENT GROUP

PROTOCOL 181

MEDDRA SYSTEM ORGAN CLASS	PREFERRED TERM	TREATMENT GROUP PLACEBO (N=62)	SB 207499 (N=65)
TOTAL	TOTAL	1 (1.6%)	2 (3.1%)
CARDIAC DISORDERS	TOTAL	0 .	1 (1.5%)
	ATRIAL FLUTTER	0 .	1 (1.5%)
PSYCHIATRIC DISORDERS	TOTAL	0 .	1 (1.5%)
	ANXIETY	0 .	1 (1.5%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	TOTAL	1 (1.6%)	0 .
	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE EXACERBATED	1 (1.6%)	0 .

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS/PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN THE SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED

CONFIDENTIAL

SB 207499

TABLE 15.8C

INCIDENCE OF POST-THERAPY SERIOUS ADVERSE EXPERIENCES BY MEDDRA SYSTEM ORGAN CLASS, PREFERRED TERM AND TREATMENT GROUP

PROTOCOL 181

MEDDRA SYSTEM ORGAN CLASS	PREFERRED TERM	TREATMENT GROUP PLACEBO (N=62)	SB 207499 (N=65)
TOTAL	TOTAL	1 (1.6%)	0 .
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	TOTAL	1 (1.6%)	0 .
	LUNG ADENOCARCINOMA	1 (1.6%)	0 .

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS/PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN THE SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED

CONFIDENTIAL

SB 207499

TABLE 15.9A

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES LEADING TO PATIENT WITHDRAWAL BY PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND TREATMENT GROUP
PROTOCOL 181

	TREATMENT GROUP		
	PLACEBO (N=62)	SB 207499 (N=65)	Total (N=127)
PREFERRED TERM			
TOTAL	1 (1.6%)	4 (6.2%)	5 (3.9%)
ATRIAL FLUTTER	0 .	1 (1.5%)	1 (0.8%)
CHRONIC OBSTRUCTIVE AIRWAYS DISEASE EXACERBATED	1 (1.6%)	0 .	1 (0.8%)
ENTERITIS	0 .	1 (1.5%)	1 (0.8%)
GASTRITIS	0 .	1 (1.5%)	1 (0.8%)
GASTROOESOPHAGEAL REFLUX DISEASE	0 .	1 (1.5%)	1 (0.8%)
NAUSEA	0 .	1 (1.5%)	1 (0.8%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AT LEAST ONE ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED
4. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO SB 207499 TREATMENT GROUP

CONFIDENTIAL

SB 207499

TABLE 15.9B

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES LEADING TO PATIENT WITHDRAWAL BY MEDDRA SYSTEM ORGAN CLASS, PREFERRED TERM AND TREATMENT GROUP
PROTOCOL 181

MEDDRA SYSTEM ORGAN CLASS	PREFERRED TERM	TREATMENT GROUP PLACEBO (N=62)	SB 207499 (N=65)
TOTAL	TOTAL	1 (1.6%)	4 (6.2%)
CARDIAC DISORDERS	TOTAL	0 .	1 (1.5%)
	ATRIAL FLUTTER	0 .	1 (1.5%)
GASTROINTESTINAL DISORDERS	TOTAL	0 .	3 (4.6%)
	ENTERITIS	0 .	1 (1.5%)
	GASTRITIS	0 .	1 (1.5%)
	GASTROOESOPHAGEAL REFLUX DISEASE	0 .	1 (1.5%)
	NAUSEA	0 .	1 (1.5%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	TOTAL	1 (1.6%)	0 .
	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE EXACERBATED	1 (1.6%)	0 .

1. EACH PATIENT COUNTED ONCE PER SYSTEM ORGAN CLASS/PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN THE SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED

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SB 207499

TABLE 15.10

ALL POST-THERAPY ADVERSE EXPERIENCES BY MEDDRA SYSTEM ORGAN CLASS, PREFERRED TERM AND TREATMENT GROUP

PROTOCOL 181

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=62)	SB 207499 (N=65)	Total (N=127)
TOTAL	TOTAL	8 (12.9%)	11 (16.9%)	19 (15.0%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	TOTAL	0 .	2 (3.1%)	2 (1.6%)
	ANAEMIA	0 .	2 (3.1%)	2 (1.6%)
GASTROINTESTINAL DISORDERS	TOTAL	2 (3.2%)	1 (1.5%)	3 (2.4%)
	COLONIC POLYP	1 (1.6%)	0 .	1 (0.8%)
	DIARRHOEA	1 (1.6%)	1 (1.5%)	2 (1.6%)
	NAUSEA	0 .	1 (1.5%)	1 (0.8%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	TOTAL	1 (1.6%)	0 .	1 (0.8%)
	CHEST PAIN	1 (1.6%)	0 .	1 (0.8%)
INFECTIONS AND INFESTATIONS	TOTAL	2 (3.2%)	3 (4.6%)	5 (3.9%)
	NASOPHARYNGITIS	0 .	2 (3.1%)	2 (1.6%)
	RHINITIS	1 (1.6%)	0 .	1 (0.8%)
	SINUSITIS	0 .	1 (1.5%)	1 (0.8%)
	UPPER RESPIRATORY TRACT INFECTION	1 (1.6%)	0 .	1 (0.8%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	TOTAL	0 .	2 (3.1%)	2 (1.6%)
	FACE INJURY	0 .	1 (1.5%)	1 (0.8%)
	JOINT DISLOCATION	0 .	1 (1.5%)	1 (0.8%)
INVESTIGATIONS	TOTAL	1 (1.6%)	1 (1.5%)	2 (1.6%)
	ALANINE AMINOTRANSFERASE INCREASED	0 .	1 (1.5%)	1 (0.8%)
	BLOOD BILIRUBIN INCREASED	0 .	1 (1.5%)	1 (0.8%)
	CARDIAC MURMUR	1 (1.6%)	0 .	1 (0.8%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	TOTAL	0 .	1 (1.5%)	1 (0.8%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS/PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN THE SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED

CONFIDENTIAL

SB 207499

TABLE 15.10

ALL POST-THERAPY ADVERSE EXPERIENCES BY MEDDRA SYSTEM ORGAN CLASS, PREFERRED TERM AND TREATMENT GROUP

PROTOCOL 181

MEDDRA SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=62)	SB 207499 (N=65)	Total (N=127)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	GOUTY ARTHRITIS	0 .	1 (1.5%)	1 (0.8%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	TOTAL	1 (1.6%)	0 .	1 (0.8%)
	LUNG ADENOCARCINOMA	1 (1.6%)	0 .	1 (0.8%)
NERVOUS SYSTEM DISORDERS	TOTAL	1 (1.6%)	0 .	1 (0.8%)
	HEADACHE	1 (1.6%)	0 .	1 (0.8%)
RENAL AND URINARY DISORDERS	TOTAL	1 (1.6%)	0 .	1 (0.8%)
	URINARY RETENTION	1 (1.6%)	0 .	1 (0.8%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	TOTAL	1 (1.6%)	1 (1.5%)	2 (1.6%)
	NASAL CONGESTION	1 (1.6%)	0 .	1 (0.8%)
	PRODUCTIVE COUGH	0 .	1 (1.5%)	1 (0.8%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	TOTAL	0 .	1 (1.5%)	1 (0.8%)
	RASH PAPULAR	0 .	1 (1.5%)	1 (0.8%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA SYSTEM ORGAN CLASS/PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/ AT LEAST ONE AE WITHIN THE SYSTEM ORGAN CLASS
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED

CONFIDENTIAL

SB 207499

TABLE 15.11A

INCIDENCE OF GASTROINTESTINAL ADVERSE EXPERIENCES OF CONCERN BY MEDDRA PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND TREATMENT GROUP
PROTOCOL 181

MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=62)	SB 207499 (N=65)
TOTAL	1 (1.6%)	2 (3.1%)
ENTERITIS	0 .	1 (1.5%)
NAUSEA	1 (1.6%)	1 (1.5%)
ABDOMINAL PAIN	1 (1.6%)	0 .

1. EACH PATIENT COUNTED ONCE PER MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AT LEAST ONE ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED
4. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO SB 207499 TREATMENT GROUP

CONFIDENTIAL

SB 207499

TABLE 15.11B

INCIDENCE OF GASTROINTESTINAL ADVERSE EXPERIENCES OF CONCERN THAT LED TO PATIENT WITHDRAWAL BY PREFERRED TERM, DESCENDING FREQUENCY AND TREATMENT GROUP
PROTOCOL 181

MEDDRA PREFERRED TERM	TREATMENT GROUP PLACEBO (N=62)	SB 207499 (N=65)
TOTAL	0 (0.0%)	1 (1.5%)
ENTERITIS	0 .	1 (1.5%)

1. EACH PATIENT COUNTED ONCE PER MEDDRA PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AT LEAST ONE ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED
4. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO SB 207499 TREATMENT GROUP

CONFIDENTIAL

SB 207499

TABLE 15.12A

NUMBER AND PERCENT OF PATIENTS WITH GASTROINTESTINAL ADVERSE EVENTS OF CONCERN AND ON-THERAPY
FECAL OCCULT BLOOD BY TREATMENT GROUP AND BASELINE RESULT
PROTOCOL 181

		------DOUBLE BLIND PHASE------ NEGATIVE		POSITIVE	
TREATMENT GROUP	BASELINE				TOTAL
PLACEBO	NEGATIVE	1	(100.0%)	0	1
	POSITIVE	0		0	0
	TOTAL	1	(100.0%)	0	1
SB 207499	NEGATIVE	1	(100.0%)	0	1
	POSITIVE	0		0	0
	TOTAL	1	(100.0%)	0	1

1. ONLY PATIENTS WITH GASTROINTESTINAL ADVERSE EXPERIENCES OF CONCERN ARE INCLUDED IN THE SUMMARY

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SB 207499

TABLE 15.12B

NUMBER AND PERCENT OF PATIENTS WITH ON-THERAPY FAECAL OCCULT BLOOD BY TREATMENT GROUP AND BASELINE RESULT

PROTOCOL 181

		------DOUBLE BLIND PHASE------ NEGATIVE		POSITIVE		TOTAL
PLACEBO	NEGATIVE	35	(92.1%)	3	(7.9%)	38
	POSITIVE	0		2	(100.0%)	2
	MISSING	0		0		0
	TOTAL	35	(87.5%)	5	(12.5%)	40
SB 207499	NEGATIVE	37	(94.9%)	2	(5.1%)	39
	POSITIVE	0		1	(100.0%)	1
	MISSING	1	(100.0%)	0		1
	TOTAL	38	(92.7%)	3	(7.3%)	41

CONFIDENTIAL

SB 207499

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND TREATMENT GROUP

PROTOCOL 181

PARAMETER	VISIT/WEEK	TREATMENT GROUP	RESULT N	RESULT MEAN	RESULT STD	RESULT MIN	RESULT MAX	CHANGE FROM BASELINE N	CHANGE FROM BASELINE MEAN	CHANGE FROM BASELINE STD	CHANGE FROM BASELINE MIN	CHANGE FROM BASELINE MAX
Alanine Aminotransferase (IU/L)	VISIT 1/SCREENING	PLACEBO	61	21.52	12.57	5.0	75.0	0	.	.	.	.
		SB 207499	63	21.21	10.69	8.0	61.0	0	.	.	.	.
	VISIT 7/WEEK 13	PLACEBO	53	19.26	9.34	3.0	41.0	53	-2.43	8.31	-25.0	22.0
		SB 207499	53	20.62	10.80	6.0	54.0	52	-0.50	4.53	-11.0	10.0
	FOLLOW-UP	PLACEBO	5	36.00	22.49	10.0	72.0	5	12.20	28.28	-11.0	59.0
		SB 207499	8	23.75	13.52	12.0	52.0	8	-0.50	5.68	-10.0	7.0
	EARLY WITHDRAWAL	PLACEBO	4	24.00	8.04	18.0	35.0	4	3.25	8.92	-7.0	14.0
		SB 207499	2	20.00	4.24	17.0	23.0	2	-2.00	2.83	-4.0	0.0
Albumin (G/L)	VISIT 1/SCREENING	PLACEBO	61	44.46	3.15	35.0	52.0	0	.	.	.	.
		SB 207499	63	44.56	2.67	39.0	51.0	0	.	.	.	.
	VISIT 7/WEEK 13	PLACEBO	53	43.66	3.93	26.0	50.0	53	-0.94	2.74	-10.0	3.0
		SB 207499	53	44.11	2.88	38.0	51.0	52	-0.52	2.21	-5.0	6.0
	FOLLOW-UP	PLACEBO	5	43.00	1.87	41.0	45.0	5	-2.00	1.58	-4.0	0.0
		SB 207499	8	44.38	2.62	42.0	48.0	8	-0.13	2.59	-4.0	3.0
	EARLY WITHDRAWAL	PLACEBO	4	42.25	11.00	26.0	49.0	4	-1.50	5.26	-9.0	3.0
		SB 207499	2	43.50	0.71	43.0	44.0	2	-0.50	0.71	-1.0	0.0
Alkaline Phosphatase (IU/L)	VISIT 1/SCREENING	PLACEBO	61	71.82	19.36	39.0	116.0	0	.	.	.	.
		SB 207499	63	75.17	17.58	36.0	114.0	0	.	.	.	.
	VISIT 7/WEEK 13	PLACEBO	53	71.64	21.66	39.0	141.0	53	1.64	15.81	-21.0	81.0
		SB 207499	53	72.53	17.73	35.0	109.0	52	-0.48	8.92	-19.0	18.0
	FOLLOW-UP	PLACEBO	5	71.60	35.00	42.0	121.0	5	3.40	18.23	-11.0	35.0
		SB 207499	8	66.75	17.29	35.0	90.0	8	-2.50	11.35	-21.0	18.0
	EARLY WITHDRAWAL	PLACEBO	4	76.50	15.59	61.0	94.0	4	-6.75	11.67	-17.0	9.0
		SB 207499	2	92.50	14.85	82.0	103.0	2	-2.00	9.90	-9.0	5.0
Amylase (IU/L)	VISIT 1/SCREENING	PLACEBO	62	79.82	29.11	26.0	169.0	0	.	.	.	.
		SB 207499	64	82.14	56.34	27.0	462.0	0	.	.	.	.
	VISIT 7/WEEK 13	PLACEBO	51	74.53	27.49	30.0	161.0	51	-4.20	18.90	-69.0	33.0
		SB 207499	53	89.55	56.33	22.0	398.0	52	3.10	23.85	-64.0	105.0

1. BASELINE VALUE IS VALUE AT VISIT 1
2. IF A SUBJECT HAS MULTIPLE SCREENING VISITS THEN LAB VALUES FOR THE LATEST VISIT WERE UTILIZED

CONFIDENTIAL
GM2004/00090/00
SB-207499/181

SB 207499

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND TREATMENT GROUP

PROTOCOL 181

PARAMETER	VISIT/WEEK	TREATMENT GROUP	RESULT N	RESULT MEAN	RESULT STD	RESULT MIN	RESULT MAX	CHANGE FROM BASELINE N	CHANGE FROM BASELINE MEAN	CHANGE FROM BASELINE STD	CHANGE FROM BASELINE MIN	CHANGE FROM BASELINE MAX
Amylase (IU/L)	FOLLOW-UP	PLACEBO	5	71.40	33.50	35.0	116.0	5	-9.60	25.66	-53.0	14.0
		SB 207499	7	88.29	25.41	57.0	123.0	7	8.29	21.72	-20.0	46.0
	EARLY WITHDRAWAL	PLACEBO	4	69.50	13.30	59.0	89.0	4	-4.50	8.96	-17.0	4.0
		SB 207499	2	55.50	7.78	50.0	61.0	2	4.50	9.19	-2.0	11.0
Aspartate Aminotransferase (IU/L)	VISIT 1/SCREENING	PLACEBO	61	22.90	9.77	10.0	63.0	0	.	.	.	.
		SB 207499	64	23.80	13.18	11.0	115.0	0	.	.	.	.
	VISIT 7/WEEK 13	PLACEBO	52	21.46	8.47	12.0	54.0	52	-1.75	5.78	-20.0	16.0
		SB 207499	53	22.32	8.60	10.0	52.0	52	-1.92	11.75	-76.0	22.0
	FOLLOW-UP	PLACEBO	5	53.80	69.10	16.0	177.0	5	26.40	63.14	-7.0	139.0
		SB 207499	8	20.38	6.00	15.0	34.0	8	-0.13	3.68	-6.0	4.0
	EARLY WITHDRAWAL	PLACEBO	4	25.00	2.16	23.0	28.0	4	5.25	6.60	-4.0	10.0
		SB 207499	2	22.00	2.83	20.0	24.0	2	-2.50	0.71	-3.0	-2.0
Basophils absolute (10^9/L)	VISIT 1/SCREENING	PLACEBO	61	0.02	0.02	0.0	0.1	0	.	.	.	.
		SB 207499	62	0.03	0.03	0.0	0.1	0	.	.	.	.
	VISIT 7/WEEK 13	PLACEBO	50	0.03	0.02	0.0	0.1	50	0.00	0.02	-0.0	0.1
		SB 207499	48	0.03	0.03	0.0	0.1	46	0.00	0.03	-0.1	0.1
	FOLLOW-UP	PLACEBO	5	0.04	0.03	0.0	0.1	5	-0.01	0.01	-0.0	0.0
		SB 207499	9	0.02	0.01	0.0	0.0	9	-0.01	0.01	-0.0	0.0
	EARLY WITHDRAWAL	PLACEBO	4	0.02	0.01	0.0	0.0	4	0.00	0.01	0.0	0.0
		SB 207499	2	0.06	0.06	0.0	0.1	2	0.01	0.01	0.0	0.0
Blood Urea Nitrogen (MMOL/L)	VISIT 1/SCREENING	PLACEBO	61	5.59	1.74	2.5	10.9	0	.	.	.	.
		SB 207499	63	5.66	1.54	2.1	9.0	0	.	.	.	.
	VISIT 7/WEEK 13	PLACEBO	53	6.13	6.78	1.6	53.0	53	0.62	6.85	-3.7	48.7
		SB 207499	53	5.43	1.61	2.3	9.6	52	-0.17	1.23	-3.0	2.5
	FOLLOW-UP	PLACEBO	5	5.84	2.26	3.6	9.1	5	-0.44	2.80	-3.6	4.0
		SB 207499	8	5.91	1.54	4.5	9.0	8	0.27	1.31	-1.0	3.0
	EARLY WITHDRAWAL	PLACEBO	4	5.10	1.52	3.6	7.2	4	-0.08	2.26	-2.4	3.0
		SB 207499	2	4.95	0.35	4.7	5.2	2	-0.20	1.70	-1.4	1.0

1. BASELINE VALUE IS VALUE AT VISIT 1
2. IF A SUBJECT HAS MULTIPLE SCREENING VISITS THEN LAB VALUES FOR THE LATEST VISIT WERE UTILIZED

CONFIDENTIAL

SB 207499

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND TREATMENT GROUP

PROTOCOL 181

PARAMETER	VISIT/WEEK	TREATMENT GROUP	RESULT N	RESULT MEAN	RESULT STD	RESULT MIN	RESULT MAX	CHANGE FROM BASELINE N	CHANGE FROM BASELINE MEAN	CHANGE FROM BASELINE STD	CHANGE FROM BASELINE MIN	CHANGE FROM BASELINE MAX
Chloride (MMOL/L)	VISIT 1/SCREENING	PLACEBO	61	103.70	2.53	97.0	109.0	0	.	.	.	.
		SB 207499	63	104.30	2.87	97.0	110.0	0	.	.	.	.
	VISIT 7/WEEK 13	PLACEBO	53	102.98	3.15	95.0	107.0	53	-0.68	2.61	-9.0	4.0
		SB 207499	53	104.79	2.88	99.0	110.0	52	0.56	2.87	-6.0	9.0
	FOLLOW-UP	PLACEBO	5	100.80	3.11	96.0	104.0	5	-0.20	2.39	-3.0	3.0
		SB 207499	8	103.38	1.41	102.0	106.0	8	-1.50	2.20	-5.0	2.0
	EARLY WITHDRAWAL	PLACEBO	4	102.00	6.06	93.0	106.0	4	-0.50	2.38	-4.0	1.0
		SB 207499	2	102.50	2.12	101.0	104.0	2	0.00	0.00	0.0	0.0
Creatinine (UMOL/L)	VISIT 1/SCREENING	PLACEBO	61	85.13	14.94	53.0	126.0	0	.	.	.	.
		SB 207499	63	85.14	20.07	44.0	180.0	0	.	.	.	.
	VISIT 7/WEEK 13	PLACEBO	53	121.57	280.3	45.0	2120.0	53	35.87	278.2	-19.0	2022
		SB 207499	53	88.62	22.38	49.0	182.0	52	2.17	9.61	-15.0	35.0
	FOLLOW-UP	PLACEBO	5	82.60	18.28	61.0	105.0	5	-0.80	4.44	-6.0	6.0
		SB 207499	8	84.88	12.84	67.0	106.0	8	3.00	12.64	-16.0	26.0
	EARLY WITHDRAWAL	PLACEBO	4	80.75	20.58	54.0	103.0	4	1.00	7.83	-7.0	11.0
		SB 207499	2	77.50	2.12	76.0	79.0	2	-1.50	4.95	-5.0	2.0
Eosinophils absolute (10^9/L)	VISIT 1/SCREENING	PLACEBO	61	0.22	0.15	0.0	0.7	0	.	.	.	.
		SB 207499	62	0.18	0.12	0.0	0.6	0	.	.	.	.
	VISIT 7/WEEK 13	PLACEBO	50	0.23	0.20	0.0	1.2	50	0.01	0.15	-0.5	0.5
		SB 207499	48	0.19	0.11	0.0	0.7	46	0.00	0.09	-0.2	0.2
	FOLLOW-UP	PLACEBO	5	0.27	0.30	0.0	0.8	5	-0.00	0.10	-0.2	0.1
		SB 207499	9	0.24	0.16	0.1	0.5	9	-0.04	0.14	-0.3	0.2
	EARLY WITHDRAWAL	PLACEBO	4	0.21	0.11	0.1	0.4	4	0.02	0.14	-0.2	0.2
		SB 207499	2	0.15	0.08	0.1	0.2	2	0.08	0.03	0.1	0.1
Gamma Glutamyl Transferase (IU/L)	VISIT 1/SCREENING	PLACEBO	61	41.67	55.96	8.0	435.0	0	.	.	.	.
		SB 207499	63	31.75	18.46	8.0	99.0	0	.	.	.	.
	VISIT 7/WEEK 13	PLACEBO	53	49.70	123.2	10.0	919.0	53	6.75	67.75	-51.0	484.0
		SB 207499	53	29.43	18.92	8.0	116.0	52	-1.10	12.78	-30.0	68.0

1. BASELINE VALUE IS VALUE AT VISIT 1
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CONFIDENTIAL

SB 207499

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND TREATMENT GROUP

PROTOCOL 181

PARAMETER	VISIT/WEEK	TREATMENT GROUP	RESULT N	RESULT MEAN	RESULT STD	RESULT MIN	RESULT MAX	CHANGE FROM BASELINE N	CHANGE FROM BASELINE MEAN	CHANGE FROM BASELINE STD	CHANGE FROM BASELINE MIN	CHANGE FROM BASELINE MAX
Gamma Glutamyl Transferase (IU/L)	FOLLOW-UP	PLACEBO	5	328.20	543.3	18.0	1280.0	5	197.40	367.2	-3.0	845.0
		SB 207499	8	30.63	11.78	16.0	48.0	8	-4.88	11.78	-22.0	11.0
	EARLY WITHDRAWAL	PLACEBO	4	52.25	14.03	41.0	71.0	4	-10.00	40.47	-67.0	28.0
		SB 207499	2	35.50	14.85	25.0	46.0	2	1.50	3.54	-1.0	4.0
Glucose - Random (MMOL/L)	VISIT 1/SCREENING	PLACEBO	61	6.10	1.62	4.3	11.6	0	.	.	.	.
		SB 207499	63	5.67	1.02	4.3	10.1	0	.	.	.	.
	VISIT 7/WEEK 13	PLACEBO	53	6.34	2.74	2.9	21.2	53	0.17	2.03	-4.2	9.6
		SB 207499	53	5.86	1.92	4.0	13.7	52	0.21	1.82	-3.3	7.3
	FOLLOW-UP	PLACEBO	5	6.12	1.89	4.1	9.2	5	-0.00	0.82	-1.3	0.9
		SB 207499	8	6.34	1.63	4.7	9.9	8	0.31	0.65	-0.5	1.5
	EARLY WITHDRAWAL	PLACEBO	4	6.33	1.26	5.3	8.1	4	0.80	1.44	-0.3	2.9
		SB 207499	2	5.35	0.21	5.2	5.5	2	0.10	0.57	-0.3	0.5
Hematocrit (%)	VISIT 1/SCREENING	PLACEBO	61	43.17	3.56	35.7	57.9	0	.	.	.	.
		SB 207499	62	43.11	3.68	31.6	51.3	0	.	.	.	.
	VISIT 7/WEEK 13	PLACEBO	50	42.82	3.59	32.8	51.5	50	-0.46	2.62	-8.4	5.0
		SB 207499	50	42.70	3.86	34.2	49.7	48	-0.32	2.19	-5.4	6.9
	FOLLOW-UP	PLACEBO	5	39.84	1.38	38.0	41.6	5	-1.96	2.19	-5.6	0.1
		SB 207499	10	40.96	3.88	33.9	45.9	10	-1.48	2.13	-5.6	1.2
	EARLY WITHDRAWAL	PLACEBO	4	40.30	6.78	31.1	47.3	4	-1.25	3.40	-4.6	3.5
		SB 207499	2	43.10	1.56	42.0	44.2	2	-1.85	1.77	-3.1	-0.6
Hemoglobin (G/L)	VISIT 1/SCREENING	PLACEBO	61	144.18	12.34	109.0	186.0	0	.	.	.	.
		SB 207499	62	143.95	12.10	103.0	167.0	0	.	.	.	.
	VISIT 7/WEEK 13	PLACEBO	50	144.24	11.67	116.0	173.0	50	-0.74	7.31	-20.0	16.0
		SB 207499	50	143.10	12.71	110.0	169.0	48	-0.81	7.33	-15.0	26.0
	FOLLOW-UP	PLACEBO	5	136.40	4.28	129.0	140.0	5	-3.60	5.03	-12.0	1.0
		SB 207499	10	137.90	12.51	115.0	152.0	10	-3.30	6.52	-14.0	5.0
	EARLY WITHDRAWAL	PLACEBO	4	136.00	23.83	104.0	160.0	4	-0.75	8.10	-7.0	11.0
		SB 207499	2	144.00	2.83	142.0	146.0	2	-5.00	4.24	-8.0	-2.0

1. BASELINE VALUE IS VALUE AT VISIT 1
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CONFIDENTIAL

SB 207499

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND TREATMENT GROUP

PROTOCOL 181

PARAMETER	VISIT/WEEK	TREATMENT GROUP	RESULT N	RESULT MEAN	RESULT STD	RESULT MIN	RESULT MAX	CHANGE FROM BASELINE N	CHANGE FROM BASELINE MEAN	CHANGE FROM BASELINE STD	CHANGE FROM BASELINE MIN	CHANGE FROM BASELINE MAX
Lymphocytes absolute (10^9/L)	VISIT 1/SCREENING	PLACEBO	61	2.16	0.59	1.2	4.0	0	.	.	.	.
		SB 207499	62	2.21	0.75	0.7	3.9	0	.	.	.	.
	VISIT 7/WEEK 13	PLACEBO	50	2.11	0.55	1.3	3.6	50	-0.02	0.51	-1.7	1.1
		SB 207499	48	2.27	0.80	0.6	4.2	46	0.06	0.49	-0.9	1.3
	FOLLOW-UP	PLACEBO	5	1.99	0.36	1.4	2.4	5	-0.09	0.44	-0.7	0.4
		SB 207499	9	2.03	0.37	1.2	2.5	9	-0.18	0.40	-0.9	0.4
	EARLY WITHDRAWAL	PLACEBO	4	1.44	0.15	1.3	1.6	4	-0.46	0.41	-0.9	0.1
		SB 207499	2	2.45	0.08	2.4	2.5	2	0.39	0.27	0.2	0.6
Monocytes absolute (10^9/L)	VISIT 1/SCREENING	PLACEBO	61	0.52	0.19	0.2	1.0	0	.	.	.	.
		SB 207499	62	0.46	0.18	0.1	0.9	0	.	.	.	.
	VISIT 7/WEEK 13	PLACEBO	50	0.52	0.14	0.1	0.8	50	0.01	0.14	-0.3	0.4
		SB 207499	48	0.52	0.17	0.2	1.0	46	0.03	0.16	-0.3	0.4
	FOLLOW-UP	PLACEBO	5	0.61	0.19	0.4	0.8	5	0.02	0.11	-0.1	0.1
		SB 207499	9	0.58	0.27	0.2	1.0	9	0.10	0.30	-0.4	0.5
	EARLY WITHDRAWAL	PLACEBO	4	0.48	0.21	0.2	0.7	4	-0.13	0.35	-0.6	0.1
		SB 207499	2	0.39	0.12	0.3	0.5	2	0.03	0.04	0.0	0.1
Neutrophils absolute (10^9/L)	VISIT 1/SCREENING	PLACEBO	61	4.86	1.77	2.8	13.2	0	.	.	.	.
		SB 207499	62	4.53	1.45	1.9	10.2	0	.	.	.	.
	VISIT 7/WEEK 13	PLACEBO	50	4.54	1.60	2.3	12.3	50	-0.18	1.39	-4.2	2.8
		SB 207499	48	4.73	1.87	2.0	10.5	46	0.06	1.26	-2.8	4.9
	FOLLOW-UP	PLACEBO	5	6.08	1.68	4.1	8.0	5	1.30	1.19	0.3	3.1
		SB 207499	9	5.42	1.36	3.4	7.4	9	0.36	0.94	-1.1	1.9
	EARLY WITHDRAWAL	PLACEBO	4	5.99	4.42	3.3	12.6	4	-0.38	0.51	-1.0	0.1
		SB 207499	2	4.12	0.59	3.7	4.5	2	-0.05	0.63	-0.5	0.4
Occult Blood Feces ()	FOLLOW-UP	PLACEBO	0	.	.	.	.	0	.	.	.	.
		SB 207499	0	.	.	.	.	0	.	.	.	.
Platelets (10^9/L)	VISIT 1/SCREENING	PLACEBO	60	263.17	61.84	133.0	461.0	0	.	.	.	.

1. BASELINE VALUE IS VALUE AT VISIT 1
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CONFIDENTIAL
GM2004/00090/00
SB-207499/181

SB 207499

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND TREATMENT GROUP

PROTOCOL 181

PARAMETER	VISIT/WEEK	TREATMENT GROUP	RESULT N	RESULT MEAN	RESULT STD	RESULT MIN	RESULT MAX	CHANGE FROM BASELINE N	CHANGE FROM BASELINE MEAN	CHANGE FROM BASELINE STD	CHANGE FROM BASELINE MIN	CHANGE FROM BASELINE MAX
Platelets (10^9/L)	VISIT 1/SCREENING	SB 207499	62	262.15	55.05	90.0	443.0	0	.	.	.	.
	VISIT 7/WEEK 13	PLACEBO	50	271.02	77.21	156.0	663.0	50	5.14	47.98	-86.0	202.0
		SB 207499	49	257.53	52.14	163.0	358.0	47	-1.19	42.15	-146.0	109.0
	FOLLOW-UP	PLACEBO	5	283.40	54.27	211.0	363.0	5	-8.60	43.78	-63.0	46.0
		SB 207499	10	277.10	73.11	189.0	428.0	10	11.40	51.11	-30.0	147.0
	EARLY WITHDRAWAL	PLACEBO	3	238.33	41.02	208.0	285.0	3	-51.33	38.99	-95.0	-20.0
		SB 207499	2	261.50	20.51	247.0	276.0	2	-7.50	33.23	-31.0	16.0
Potassium (MMOL/L)	VISIT 1/SCREENING	PLACEBO	61	4.47	0.32	3.8	5.1	0	.	.	.	.
		SB 207499	64	4.38	0.35	3.8	5.3	0	.	.	.	.
	VISIT 7/WEEK 13	PLACEBO	51	4.46	0.39	3.6	5.6	51	-0.00	0.44	-1.0	0.8
		SB 207499	53	4.40	0.39	3.6	5.7	52	0.02	0.45	-1.1	1.3
	FOLLOW-UP	PLACEBO	5	4.74	0.54	4.1	5.5	5	0.46	0.59	-0.4	1.2
		SB 207499	8	4.35	0.23	3.9	4.6	8	-0.04	0.21	-0.3	0.4
	EARLY WITHDRAWAL	PLACEBO	4	4.43	0.30	4.1	4.8	4	-0.10	0.52	-0.7	0.5
		SB 207499	2	3.90	0.14	3.8	4.0	2	-0.05	0.07	-0.1	0.0
Red Blood Cell Count (10^12/L)	VISIT 1/SCREENING	PLACEBO	61	4.60	0.36	3.6	5.5	0	.	.	.	.
		SB 207499	62	4.63	0.43	3.5	5.5	0	.	.	.	.
	VISIT 7/WEEK 13	PLACEBO	50	4.58	0.41	3.1	5.3	50	-0.02	0.28	-0.8	0.6
		SB 207499	50	4.62	0.47	3.3	5.7	48	0.00	0.23	-0.6	0.7
	FOLLOW-UP	PLACEBO	5	4.32	0.43	3.8	5.0	5	-0.14	0.20	-0.5	0.0
		SB 207499	10	4.37	0.53	3.2	4.9	10	-0.07	0.20	-0.4	0.2
	EARLY WITHDRAWAL	PLACEBO	4	4.35	0.89	3.2	5.3	4	-0.08	0.39	-0.4	0.5
		SB 207499	2	4.76	0.36	4.5	5.0	2	-0.22	0.03	-0.2	-0.2
Sodium (MMOL/L)	VISIT 1/SCREENING	PLACEBO	61	141.00	2.66	134.0	148.0	0	.	.	.	.
		SB 207499	63	141.17	2.18	131.0	145.0	0	.	.	.	.
	VISIT 7/WEEK 13	PLACEBO	53	139.81	3.43	128.0	146.0	53	-1.38	3.00	-13.0	5.0
		SB 207499	53	140.79	2.91	133.0	149.0	52	-0.40	2.55	-6.0	8.0

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CONFIDENTIAL

SB 207499

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND TREATMENT GROUP

PROTOCOL 181

PARAMETER	VISIT/WEEK	TREATMENT GROUP	RESULT N	RESULT MEAN	RESULT STD	RESULT MIN	RESULT MAX	CHANGE FROM BASELINE N	CHANGE FROM BASELINE MEAN	CHANGE FROM BASELINE STD	CHANGE FROM BASELINE MIN	CHANGE FROM BASELINE MAX
Sodium (MMOL/L)	FOLLOW-UP	PLACEBO	5	136.00	4.47	129.0	141.0	5	-1.40	3.05	-5.0	3.0
		SB 207499	8	140.38	1.06	139.0	142.0	8	-1.25	1.28	-3.0	1.0
	EARLY WITHDRAWAL	PLACEBO	4	139.50	6.56	130.0	145.0	4	0.25	2.87	-4.0	2.0
		SB 207499	2	139.50	0.71	139.0	140.0	2	-1.00	1.41	-2.0	0.0
Total Bilirubin (UMOL/L)	VISIT 1/SCREENING	PLACEBO	61	9.13	2.87	4.0	20.0	0	.	.	.	.
		SB 207499	63	9.90	3.90	4.0	23.0	0	.	.	.	.
	VISIT 7/WEEK 13	PLACEBO	53	8.98	2.62	4.0	15.0	53	-0.11	3.07	-8.0	7.0
		SB 207499	53	9.38	3.32	3.0	22.0	52	-0.52	3.50	-12.0	8.0
	FOLLOW-UP	PLACEBO	5	9.40	2.19	8.0	13.0	5	0.60	2.30	-2.0	3.0
		SB 207499	8	10.50	6.76	6.0	24.0	8	1.50	2.56	-2.0	6.0
	EARLY WITHDRAWAL	PLACEBO	4	12.50	1.00	12.0	14.0	4	3.50	1.29	2.0	5.0
		SB 207499	2	6.00	1.41	5.0	7.0	2	-2.00	0.00	-2.0	-2.0
Total Protein (G/L)	VISIT 1/SCREENING	PLACEBO	61	73.41	4.65	59.0	87.0	0	.	.	.	.
		SB 207499	63	74.13	4.89	63.0	84.0	0	.	.	.	.
	VISIT 7/WEEK 13	PLACEBO	53	72.00	5.34	53.0	83.0	53	-1.62	4.11	-9.0	9.0
		SB 207499	53	72.47	4.94	64.0	87.0	52	-1.54	3.96	-11.0	7.0
	FOLLOW-UP	PLACEBO	5	72.80	5.26	69.0	82.0	5	-1.20	4.27	-5.0	6.0
		SB 207499	8	69.63	4.81	62.0	78.0	8	-0.38	5.04	-10.0	6.0
	EARLY WITHDRAWAL	PLACEBO	4	73.75	2.99	71.0	78.0	4	0.00	4.83	-7.0	4.0
		SB 207499	2	73.50	2.12	72.0	75.0	2	0.00	0.00	0.0	0.0
Uric Acid (UMOL/L)	VISIT 1/SCREENING	PLACEBO	61	326.89	84.11	162.0	639.0	0	.	.	.	.
		SB 207499	63	327.86	90.82	151.0	586.0	0	.	.	.	.
	VISIT 7/WEEK 13	PLACEBO	53	334.66	124.2	180.0	1023.0	53	2.92	104.9	-223.0	635.0
		SB 207499	53	322.42	91.22	173.0	600.0	52	3.46	50.38	-129.0	96.0
	FOLLOW-UP	PLACEBO	5	292.00	111.3	161.0	457.0	5	-6.60	24.58	-43.0	25.0
		SB 207499	8	352.88	128.8	227.0	640.0	8	4.13	58.59	-64.0	130.0
	EARLY WITHDRAWAL	PLACEBO	4	432.75	147.1	344.0	651.0	4	84.75	162.1	-25.0	325.0
		SB 207499	2	336.50	85.56	276.0	397.0	2	-52.00	45.25	-84.0	-20.0

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CONFIDENTIAL
GM2004/00090/00
SB-207499/181

SB 207499

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND TREATMENT GROUP

PROTOCOL 181

PARAMETER	VISIT/WEEK	TREATMENT GROUP	RESULT N	RESULT MEAN	RESULT STD	RESULT MIN	RESULT MAX	CHANGE FROM BASELINE N	CHANGE FROM BASELINE MEAN	CHANGE FROM BASELINE STD	CHANGE FROM BASELINE MIN	CHANGE FROM BASELINE MAX
Urine Glucose - Dipstick ()	FOLLOW-UP	PLACEBO	0	.	.	.	.	0	.	.	.	.
		SB 207499	0	.	.	.	.	0	.	.	.	.
Urine Ketones - Dipstick ()	FOLLOW-UP	PLACEBO	0	.	.	.	.	0	.	.	.	.
		SB 207499	0	.	.	.	.	0	.	.	.	.
Urine Protein - Dipstick ()	FOLLOW-UP	PLACEBO	0	.	.	.	.	0	.	.	.	.
		SB 207499	0	.	.	.	.	0	.	.	.	.
White Blood Cell Count (10^9/L)	VISIT 1/SCREENING	PLACEBO	61	7.78	2.06	4.9	16.3	0	.	.	.	.
		SB 207499	62	7.40	1.75	4.0	13.9	0	.	.	.	.
	VISIT 7/WEEK 13	PLACEBO	50	7.42	1.76	4.8	16.1	50	-0.19	1.39	-4.3	2.0
		SB 207499	48	7.73	2.30	4.0	14.9	46	0.15	1.37	-2.9	6.0
	FOLLOW-UP	PLACEBO	5	8.96	2.20	6.0	11.2	5	1.20	1.52	-0.6	3.5
		SB 207499	9	8.29	1.50	6.1	10.5	9	0.24	1.32	-1.8	2.1
	EARLY WITHDRAWAL	PLACEBO	4	8.13	4.08	5.7	14.2	4	-0.95	0.79	-2.1	-0.4
		SB 207499	2	7.10	0.57	6.7	7.5	2	0.40	0.99	-0.3	1.1

1. BASELINE VALUE IS VALUE AT VISIT 1
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CONFIDENTIAL
GM2004/00090/00
SB-207499/181

SB 207499

TABLE 15.16

DESCRIPTIVE STATISTICS FOR STANDARD VITAL SIGNS BY VISIT/WEEK AND TREATMENT GROUP

PROTOCOL 181

PARAMETER	VISIT/WEEK	TREATMENT GROUP	RESULT N	RESULT MEAN	RESULT STD	RESULT MIN	RESULT MAX	CHANGE FROM BASELINE N	CHANGE FROM BASELINE MEAN	CHANGE FROM BASELINE STD	CHANGE FROM BASELINE MIN	CHANGE FROM BASELINE MAX
SYSTOLIC BP (MM HG)	BASELINE	PLACEBO	62	131.9	17.2	93	180	62	0.0	0.0	0	0
		SB 207499	65	133.5	19.6	90	180	65	0.0	0.0	0	0
	VISIT 6	PLACEBO	54	133.1	13.7	108	176	54	1.4	15.2	-40	35
		SB 207499	56	133.3	18.6	96	179	56	-0.8	19.1	-34	65
	VISIT 7	PLACEBO	53	129.5	14.2	98	165	53	-1.9	13.4	-30	28
		SB 207499	56	132.3	18.8	94	189	56	-1.8	16.5	-44	48
DIASTOLIC BP (MM HG)	BASELINE	PLACEBO	62	77.1	9.8	60	100	62	0.0	0.0	0	0
		SB 207499	65	78.2	11.5	50	107	65	0.0	0.0	0	0
	VISIT 6	PLACEBO	54	79.7	8.3	60	94	54	2.0	9.2	-18	26
		SB 207499	56	79.5	11.4	60	106	56	1.6	11.8	-26	30
	VISIT 7	PLACEBO	53	76.9	7.9	58	92	53	-0.6	10.4	-20	23
		SB 207499	56	76.7	11.7	45	115	56	-1.3	11.7	-45	25
HEART RATE (BPM)	BASELINE	PLACEBO	62	75.7	9.2	53	103	62	0.0	0.0	0	0
		SB 207499	65	74.3	12.2	52	118	65	0.0	0.0	0	0
	VISIT 6	PLACEBO	54	76.3	10.6	55	103	54	0.5	10.0	-20	24
		SB 207499	56	73.9	11.5	52	106	56	-1.0	11.2	-28	24
	VISIT 7	PLACEBO	53	78.9	12.4	60	116	53	3.0	11.7	-23	46
		SB 207499	56	75.1	10.1	54	100	56	0.2	9.1	-25	20

1. BASELINE VALUE IS VALUE AT VISIT 1

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GM2004/00090/00
SB-207499/181

SB 207499

TABLE 15.17

TRANSITIONS FROM BASELINE IN SITTING VITAL SIGNS

PROTOCOL 181

PARAMETER: SYSTOLIC BP TIME POINT: TOTAL ON-THERAPY

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<75 MM HG)	0	0	0	0	0	0
	LOW (75-89 MM HG)	0	0	0	0	0	0
	NORMAL (90-139 MM HG)	37	0	0	27 (73.0%)	10 (27.0%)	0
	HIGH (140-180 MM HG)	21	0	0	5 (23.8%)	16 (76.2%)	0
	HIGH CONCERN (>180 MM HG)	0	0	0	0	0	0
	TOTAL	58	0	0	32 (55.2%)	26 (44.8%)	0
SB 207499	LOW CONCERN (<75 MM HG)	0	0	0	0	0	0
	LOW (75-89 MM HG)	0	0	0	0	0	0
	NORMAL (90-139 MM HG)	32	0	0	26 (81.3%)	6 (18.8%)	0
	HIGH (140-180 MM HG)	27	0	0	8 (29.6%)	18 (66.7%)	1 (3.7%)
	HIGH CONCERN (>180 MM HG)	0	0	0	0	0	0
	TOTAL	59	0	0	34 (57.6%)	24 (40.7%)	1 (1.7%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY; OTHER PARAMETERS TO BE APPLIED: DIASTOLIC BP, HEART RATE; OTHER INTERVALS TO BE APPLIED: ENDPOINT

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SB 207499

TABLE 15.17

TRANSITIONS FROM BASELINE IN SITTING VITAL SIGNS

PROTOCOL 181

PARAMETER: SYSTOLIC BP TIME POINT: ENDPOINT

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: LOW CONCERN	LOW	NORMAL		HIGH		HIGH CONCERN	
PLACEBO	LOW CONCERN (<75 MM HG)	0	0	0	0		0		0	
	LOW (75-89 MM HG)	0	0	0	0		0		0	
	NORMAL (90-139 MM HG)	37	0	0	33	(89.2%)	4	(10.8%)	0	
	HIGH (140-180 MM HG)	21	0	0	7	(33.3%)	14	(66.7%)	0	
	HIGH CONCERN (>180 MM HG)	0	0	0	0		0		0	
	TOTAL	58	0	0	40	(69.0%)	18	(31.0%)	0	
SB 207499	LOW CONCERN (<75 MM HG)	0	0	0	0		0		0	
	LOW (75-89 MM HG)	0	0	0	0		0		0	
	NORMAL (90-139 MM HG)	32	0	0	28	(87.5%)	4	(12.5%)	0	
	HIGH (140-180 MM HG)	27	0	0	10	(37.0%)	16	(59.3%)	1	(3.7%)
	HIGH CONCERN (>180 MM HG)	0	0	0	0		0		0	
	TOTAL	59	0	0	38	(64.4%)	20	(33.9%)	1	(1.7%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY; OTHER PARAMETERS TO BE APPLIED: DIASTOLIC BP, HEART RATE; OTHER INTERVALS TO BE APPLIED: ENDPOINT

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SB 207499

TABLE 15.17

TRANSITIONS FROM BASELINE IN SITTING VITAL SIGNS

PROTOCOL 181

PARAMETER: DIASTOLIC BP TIME POINT: TOTAL ON-THERAPY

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<50 MM HG)	0	0	0	0	0	0
	LOW (50-59 MM HG)	0	0	0	0	0	0
	NORMAL (60-89 MM HG)	48	0	1 (2.1%)	39 (81.3%)	8 (16.7%)	0
	HIGH (90-110 MM HG)	10	0	0	6 (60.0%)	4 (40.0%)	0
	HIGH CONCERN (>110 MM HG)	0	0	0	0	0	0
	TOTAL	58	0	1 (1.7%)	45 (77.6%)	12 (20.7%)	0
SB 207499	LOW CONCERN (<50 MM HG)	0	0	0	0	0	0
	LOW (50-59 MM HG)	1	0	0	1 (100.0%)	0	0
	NORMAL (60-89 MM HG)	43	0	1 (2.3%)	37 (86.0%)	5 (11.6%)	0
	HIGH (90-110 MM HG)	15	1 (6.7%)	0	5 (33.3%)	8 (53.3%)	1 (6.7%)
	HIGH CONCERN (>110 MM HG)	0	0	0	0	0	0
	TOTAL	59	1 (1.7%)	1 (1.7%)	43 (72.9%)	13 (22.0%)	1 (1.7%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY; OTHER PARAMETERS TO BE APPLIED: DIASTOLIC BP, HEART RATE; OTHER INTERVALS TO BE APPLIED: ENDPOINT

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GM2004/00090/00
SB-207499/181

SB 207499

TABLE 15.17

TRANSITIONS FROM BASELINE IN SITTING VITAL SIGNS

PROTOCOL 181

PARAMETER: DIASTOLIC BP TIME POINT: ENDPOINT

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<50 MM HG)	0	0	0	0	0	0
	LOW (50-59 MM HG)	0	0	0	0	0	0
	NORMAL (60-89 MM HG)	48	0	1 (2.1%)	44 (91.7%)	3 (6.3%)	0
	HIGH (90-110 MM HG)	10	0	0	9 (90.0%)	1 (10.0%)	0
	HIGH CONCERN (>110 MM HG)	0	0	0	0	0	0
	TOTAL	58	0	1 (1.7%)	53 (91.4%)	4 (6.9%)	0
SB 207499	LOW CONCERN (<50 MM HG)	0	0	0	0	0	0
	LOW (50-59 MM HG)	1	0	0	1 (100.0%)	0	0
	NORMAL (60-89 MM HG)	43	0	1 (2.3%)	39 (90.7%)	3 (7.0%)	0
	HIGH (90-110 MM HG)	15	1 (6.7%)	0	9 (60.0%)	4 (26.7%)	1 (6.7%)
	HIGH CONCERN (>110 MM HG)	0	0	0	0	0	0
	TOTAL	59	1 (1.7%)	1 (1.7%)	49 (83.1%)	7 (11.9%)	1 (1.7%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY; OTHER PARAMETERS TO BE APPLIED: DIASTOLIC BP, HEART RATE; OTHER INTERVALS TO BE APPLIED: ENDPOINT

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TABLE 15.17

TRANSITIONS FROM BASELINE IN SITTING VITAL SIGNS

PROTOCOL 181

PARAMETER: HEART RATE TIME POINT: TOTAL ON-THERAPY

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<50 BPM)	0	0	0	0	0	0
	LOW (50-59 BPM)	1	0	1 (100.0%)	0	0	0
	NORMAL (60-99 BPM)	56	0	1 (1.8%)	51 (91.1%)	4 (7.1%)	0
	HIGH (100-120 BPM)	1	0	0	1 (100.0%)	0	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0
	TOTAL	58	0	2 (3.4%)	52 (89.7%)	4 (6.9%)	0
SB 207499	LOW CONCERN (<50 BPM)	0	0	0	0	0	0
	LOW (50-59 BPM)	4	0	1 (25.0%)	3 (75.0%)	0	0
	NORMAL (60-99 BPM)	53	0	6 (11.3%)	44 (83.0%)	2 (3.8%)	1 (1.9%)
	HIGH (100-120 BPM)	2	0	0	2 (100.0%)	0	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0
	TOTAL	59	0	7 (11.9%)	49 (83.1%)	2 (3.4%)	1 (1.7%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY; OTHER PARAMETERS TO BE APPLIED: DIASTOLIC BP, HEART RATE; OTHER INTERVALS TO BE APPLIED: ENDPOINT

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SB 207499

TABLE 15.17

TRANSITIONS FROM BASELINE IN SITTING VITAL SIGNS

PROTOCOL 181

PARAMETER: HEART RATE TIME POINT: ENDPOINT

TREATMENT GROUP	BASELINE	NUMBER OF PATIENTS TESTED	DOUBLE BLIND PHASE: LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<50 BPM)	0	0	0	0	0	0
	LOW (50-59 BPM)	1	0	0	1 (100.0%)	0	0
	NORMAL (60-99 BPM)	56	0	0	52 (92.9%)	4 (7.1%)	0
	HIGH (100-120 BPM)	1	0	0	1 (100.0%)	0	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0
	TOTAL	58	0	0	54 (93.1%)	4 (6.9%)	0
SB 207499	LOW CONCERN (<50 BPM)	0	0	0	0	0	0
	LOW (50-59 BPM)	4	0	1 (25.0%)	3 (75.0%)	0	0
	NORMAL (60-99 BPM)	53	0	3 (5.7%)	48 (90.6%)	1 (1.9%)	1 (1.9%)
	HIGH (100-120 BPM)	2	0	0	2 (100.0%)	0	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0
	TOTAL	59	0	4 (6.8%)	53 (89.8%)	1 (1.7%)	1 (1.7%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
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GM2004/00090/00
SB-207499/181

SB 207499

TABLE 15.20

SUMMARY OF COPD EXACERBATIONS DURING THE DOUBLE-BLIND PERIOD BY LEVEL - ALL RANDOMISED PATIENTS

PROTOCOL 181

Treatment Group	Level	Number of Patients	Number of Exacerbations
PLACEBO (N=62)	Mild	3	3
	Moderate	8	8
	Severe	0	0
	Total	11	11
SB 207499 (N=65)	Mild	5	5
	Moderate	4	4
	Severe	1	1
	Total	10	10

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Title:

A 13-week randomised, double-blind, parallel group, multicentre study to compare the bronchial anti-inflammatory activity of oral cilomilast (15 mg bd) with placebo twice daily in subjects with Chronic Obstructive Pulmonary Disease (COPD)

Document Number: GM2002/00252/02
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GM2002/00252/02	25 November 2003	Amendment No, 2: To clarify discrepancies and inconsistencies in the original protocol and in Amendment 1

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Sponsor Signatory: [redacted]
Vice President,
Respiratory, Clinical
Development and Medical
Affairs

Signature: [redacted]

Date: 25/11/07

SPONSOR INFORMATION PAGE

Title: A 13-week randomised, double-blind, parallel group, multicentre study to compare the bronchial anti-inflammatory activity of oral cilomilast (15 mg bd) with placebo twice daily in subjects with Chronic Obstructive Pulmonary Disease (COPD)

Study Identifier: SB207499/181

GlaxoSmithKline Companies participating in this study:

GlaxoSmithKline Australia

GlaxoSmithKline Canada

GlaxoSmithKline Finland

GlaxoSmithKline Ireland

GlaxoSmithKline Lithuania

GlaxoSmithKline Norway

GlaxoSmithKline Romania

GlaxoSmithKline Slovakia

GlaxoSmithKline Slovenia

GlaxoSmithKline South Africa

GlaxoSmithKline Sweden

GlaxoSmithKline UK

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4. [redacted] Respiratory, Clinical Development and Medical Affairs
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6. [redacted] Biomedical Data Sciences, Statistics
7. [redacted] Biomedical Data Sciences, Statistics
8. [redacted] Biomedical Data Sciences, Data Management
9. [redacted] Biomedical Data Sciences, Data Management
10. [redacted] European Regulatory Affairs
11. [redacted] Clinical Trials Supplies-Packaging (Europe)

12. [redacted] Clinical Trials Supplies-Packaging (North America)
13. [redacted] Global Clinical Safety and Pharmacovigilance
14. [redacted] Worldwide Clinical Compliance
15. [redacted] European Medical Operations, Clinical Development and Medical Affairs
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INVESTIGATOR AGREEMENT PAGE

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with this protocol amendment and with any other study conduct procedures provided by GlaxoSmithKline (GSK).
- Not to implement this protocol amendment without agreement from the sponsor and prior submission to and written approval from (where required) the Institutional Review Board (IRB) or Independent Ethics Committee (IEC), except when necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- Note to implement any other changes to the protocol without agreement from the sponsor and prior review and written approval from the IRB or IEC, except where necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- That I am thoroughly familiar with the appropriate use of the investigational product(s), as described herein, and any other information provided by the sponsor including, but not limited to, the following: the current Investigator's Brochure (IB) or equivalent document, IB supplement (if applicable), and approved product label (if the product is marketed in this country and the label is not already provided as an equivalent to an IB).
- That I am aware of, and will comply with, "good clinical practices" (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the GSK investigational product(s) and of their study-related duties and functions as described herein.
- That I have been informed that certain regulatory authorities require the Sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the Sponsor or the investigational product, and more generally about his/her financial ties with the Sponsor. GSK will use and disclose the information solely for the purpose of complying with regulatory requirements.

  Hence I:

  - Agree to supply GSK with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children);
  - Agree to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study; and
  - Agree that GSK may disclose any information it has about such ownership interests and financial ties to regulatory authorities.

Investigator Name: _____

_____ _____
Investigator Signature Date

The following co-signature is required only when the investigator is not a insert the appropriate text such as “physician” or “dentist”

Physician Name: _____

_____ _____
Physician Signature Date

Table of Contents

Page

ABBREVIATIONS 17
RATIONALE 18
OBJECTIVE(S) 19
PRIMARY OBJECTIVES 19
SECONDARY OBJECTIVES 19
ENDPOINT(S) 19
PRIMARY 19
SECONDARY EFFICACY ENDPOINTS 20
SAFETY ENDPOINTS 20
STUDY DESIGN 21
STUDY POPULATION 22
STUDY ASSESSMENTS AND PROCEDURES 22
INVESTIGATIONAL PRODUCT(S) 23
1. INTRODUCTION 24
1.1. Background 24
COPD 24
1.2. Rationale 26
2. OBJECTIVE(S) 28
2.1. Primary 28
2.2. Secondary 28
3. ENDPOINT(S) 28
3.1. Primary 28
3.2. Secondary 28
3.3. Tertiary 29
4. STUDY DESIGN 29
OUTLINE OF PROCEDURES: 30
VISIT TIMINGS: 30
5. STUDY POPULATION 30
5.1. Number of Subjects 31
5.2. Eligibility Criteria 31
5.2.1. Inclusion Criteria 31
INCLUSION CRITERIA (SCREENING VISIT 1): 31
5.2.2. Exclusion Criteria 32
EXCLUSION CRITERIA (SCREENING VISIT 1): 32

5.2.3. Randomisation Criteria at visit 3: 33
EXCLUSION CRITERIA AT RANDOMISATION VISIT (VISIT 3) 33
5.2.4. Other Eligibility Criteria Considerations 33
6. STUDY ASSESSMENTS AND PROCEDURES 33
6.1. Demographic and Baseline Assessments 35
6.1.1. History of COPD 35
6.1.2. Chest X-ray 36
6.1.3. Smoking History 36
6.2. Safety 36
6.2.1. Pregnancy 37
6.2.2. Adverse Events, COPD Exacerbation and Concurrent illness and Medications 37
6.2.3. Physical Examination 38
6.2.4. Vital Signs and Temperature 39
6.2.5. Resting SaO2 39
6.2.6. Clinical Laboratory tests [including Pre-Biopsy Blood Test for blood clotting analysis Prior to Visits 2/2A and 6/6A and. 39
6.3. Efficacy 40
6.3.1. Primary 40
6.3.2. Secondary 41
6.3.3. Tertiary Efficacy Endpoints 41
6.3.4. Bronchial Biopsy 41
6.3.5. Sputum Induction 43
6.3.6. Blinding Issues 44
6.3.7. Pulmonary Function Tests (PFTs) 44
6.4. Outline of Study Procedures at Each Visit 46
6.4.1. Visit 1: Screening and Start of the 4-Week Run-In Period 46
6.4.2. Visit 2 (Week -1): Continuation of the 4-Week Run„In Period . 48
6.4.3. Visit 2A (Only if Biopsy Has Been Rescheduled) 50
6.4.4. Visit 3 (Week 0): Start of the Double-Blind Treatment 50
SUBJECTS WHO DO NOT MEET THE RANDOMISATION CRITERIA MUST BE WITHDRAWN FROM THE STUDY. 51
6.4.5. Visit 4: (Week 4 of the Double-Blind Treatment Period) 52
6.4.6. Visit 5: (Week 8 of the Double-Blind Treatment Period) 53
6.4.7. Visit 6: (Week 12 of the Double-Blind Treatment Period) 54
6.4.8. Visit 6A (Only if Biopsy Has Been Rescheduled) 56
6.4.9. Visit 7: (Week 13 - End of the Double-Blind Treatment Period) 57
6.4.10. Visit 8: Safety Follow-Up Visit 58
6.4.11. Early Withdrawal Visit 59
7. INVESTIGATIONAL PRODUCT(S) 60
7.1. Description of Investigational Product 60
7.1.1. Rescue Medication 60
7.2. Dosage and Administration 60
7.3. Dose Rationale 60

7.4. Blinding 61
7.5. Treatment Assignment 62
7.6. Packaging 63
7.7. Labeling and Preparation 63
7.8. Handling and Storage 64
7.9. Product Accountability 64
7.10. Assessment of Compliance 64
7.11. Treatment of Investigational Product Overdose 65
7.12. Occupational Safety 65

8. CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES 65
8.1. Permitted Medications 65
8.2. Prohibited Medications 66
8.3. Medical Devices 66
8.4. Non-Drug Therapies 66

9. SUBJECT COMPLETION AND WITHDRAWAL 66
9.1. Subject Completion 66
9.2. Subject Withdrawal 66
9.2.1. Subject Withdrawal from Study 67
9.2.2. Subject Withdrawal from Investigational Product 67
9.3. Screen and Baseline Failures 68
9.4. Early Withdrawal Assessments in the Treatment Period 68

10. ADVERSE EVENTS (AE) AND SERIOUS ADVERSE EVENTS (SAE) . . 69
10.1. Definition of an AE 69
10.2. Definition of a SAE 70
10.3. Lack of Efficacy 71
10.4. Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs and SAEs 71
10.5. Time Period, Frequency, and Method of Detecting AEs and SAEs . 72
10.6. Recording of AEs and SAEs 72
10.7. Evaluating AEs and SAEs 72
10.7.1. Assessment of Intensity 72
10.7.2. Assessment of Causality 73
10.8. Follow-Up of AEs and SAEs 73
10.9. Prompt Reporting of SAEs to GSK 74
10.9.1. Timeframes for Submitting SAE Reports to GSK 74
10.9.2. Completion and Transmission of the SAE Reports 74
10.10. Regulatory Reporting Requirements For SAEs 75
10.11. Post-study AEs and SAEs 75
10.12. SAEs Related to Study Participation 75

11. MEDICAL DEVICES INCIDENTS AND NEAR„INCIDENTS (INCLUDING MALFUNCTIONS) 76
11.1. Definitions of a Medical Device, Incident, Near-Incident, Malfunction, and Remedial Action 76

11.2. Time Period for Detecting Medical Device Incidents and Near-Incidents . . . 77
11.3. Documenting Medical Device Incidents and Near-Incidents . . . 77
11.4. Follow-up of Medical Device Incidents and Near-Incidents . . . 77
11.5. Prompt Reporting of Medical Device Incidents and Near„Incidents to GSK . . . 78
11.5.1. Timeframes for Submitting Medical Device Incident and Near„Incident Reports to GSK . . . 78
11.5.2. Transmission of Medical Device Incident and Near-Incident Reports . . . 78
11.6. Regulatory Reporting Requirements For Medical Devices . . . 78
11.7. Post-Study Medical Device Incidents and Near-Incidents . . . 79
12. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS. . . . 79
12.1. Hypotheses . . . 79
12.2. Sample Size Considerations . . . 79
12.2.1. Target Sample Size . . . 79
12.2.2. Sample Size Sensitivity . . . 79
12.3. Method of Randomization . . . 80
12.4. Planned Efficacy Analysis . . . 80
12.4.1. Primary Efficacy Variables . . . 80
12.4.2. Secondary Efficacy Variables . . . 80
12.4.3. Derivation of Efficacy Variables for Analysis . . . 81
12.4.4. Comparisons of Interest . . . 81
12.4.5. Populations to be Evaluated . . . 81
12.4.6. Methods of Analysis . . . 81
12.5. Planned Safety Evaluation . . . 82
12.6. Interim Analysis . . . 82
13. STUDY ADMINISTRATION. . . . 82
13.1. Regulatory and Ethical Considerations . . . 82
13.1.1. Regulatory Authority Approval . . . 82
13.1.2. Ethical Conduct of the Study and Ethics Approval . . . 83
13.1.3. Informed Consent . . . 83
13.1.4. Investigator Reporting Requirements . . . 84
13.2. Study Monitoring . . . 84
13.3. Quality Assurance . . . 85
13.4. Study and Site Closure . . . 85
13.5. Records Retention . . . 86
13.6. Provision of Study Results and Information to Investigators . . . 86
13.7. Information Disclosure and Inventions . . . 86
OWNERSHIP: . . . 86
CONFIDENTIALITY: . . . 87
PUBLICATION: . . . 87
13.8. Data Management . . . 88

13.8.1. Data Collection 88
14. REFERENCES 89
15. APPENDICES 93
15.1. Appendix 1: Time and Events Table 93
15.2. Appendix 2: Protocol Amendment 1 95
ORIGINAL TEXT: 95
AMENDED TEXT: 95
SAFETY ENDPOINTS (SUMMARY AND SECTION 6.1) 95
ORIGINAL TEXT: 95
AMENDED TEXT: 95
STUDY PLAN (SUMMARY AND SECTION 4) 95
ORIGINAL TEXT: 95
AMENDED TEXT: 96
ORIGINAL TEXT: 96
AMENDED TEXT: 96
VISIT TIMINGS (SECTION 4) 96
ORIGINAL TEXT: 96
INCLUSION CRITERIA (SECTION 5.2.1) 96
ORIGINAL TEXT: 96
ORIGINAL TEXT: 97
ORIGINAL TEXT: 97
ORIGINAL TEXT: 97
ORIGINAL TEXT: 97
EXCLUSION CRITERIA AT RANDOMISATION VISIT (VISIT 3) 98
ORIGINAL TEXT: 98
ORIGINAL TEXT: 98
ORIGINAL TEXT: 98
ORIGINAL TEXT: 99
ORIGINAL TEXT: 99
ORIGINAL TEXT: 99
ORIGINAL TEXT: 99
6.2.1.1. PREGNANCY TESTING 99
6.2.1.2. TIME PERIOD FOR COLLECTING PREGNANCY INFORMATION . 100
6.2.1.1. PREGNANCY TESTING 100

6.2.1.2. TIME PERIOD FOR COLLECTING PREGNANCY INFORMATION . 100
ORIGINAL TEXT: 100
ORIGINAL TEXT: 102
ORIGINAL TEXT: 102
ORIGINAL TEXT: 102
ORIGINAL TEXT: 103
ORIGINAL TEXT: 103
ORIGINAL TEXT: 103
ORIGINAL TEXT: 104
TIME AND EVENTS TABLE (APPENDIX 1) 109
15.3. Appendix 3: Protocol Amendment 2 113
AMENDMENTS: 113
TIMING OF PRE-TREATMENT BIOPSY CLARIFICATION 113
PROTOCOL SUMMARY 113
STUDY DESIGN, 2ND PARAGRAPH, 1ST SENTENCE 113
ORIGINAL TEXT: 113
AMENDED TEXT: 113
CLARIFICATION OF SUBJECT WITHDRAWALS FOR BIOPSY AND SPUTUM 113
MAIN BODY OF PROTOCOL 113
SECTION 6, 2ND BULLET POINT 113
ORIGINAL TEXT 113
AMENDED TEXT. 113
3RD BULLET POINT, 1ST SENTENCE 113
ORIGINAL TEXT 113
AMENDED TEXT. 114
SPUTUM INDUCTION. 114
MAIN BODY OF PROTOCOL 114
SECTION 6.3.5.1, 1ST SENTENCE 114
ORIGINAL TEXT: 114
AMENDED TEXT. 114
TIMINGS OF PULMONARY FUNCTION TESTS 114
PROTOCOL SUMMARY 114
STUDY DESIGN, 3RD PARAGRAPH. 114

ORIGINAL TEXT: 114
AMENDED TEXT: 114
MAIN BODY OF PROTOCOL 115
ORIGINAL TEXT: 115
AMENDED TEXT: 115
FOOTNOTE AT THE BOTTOM OF THE STUDY PLAN. 115
ORIGINAL TEXT: 115
AMENDED TEXT: 115
LAST PARAGRAPH AFTER LAST BULLET POINT. 115
ORIGINAL TEXT: 115
AMENDED TEXT: 116
SECTION 6.1 DEMOGRAPHIC AND BASELINE ASSESSMENTS, ... 116
BULLET POINT NUMBER 10 116
ORIGINAL TEXT: 116
AMENDED TEXT: 116
SECTION 6.3.7.1 PULMONARY FUNCTION TEST AND REVERSIBILITY. . 116
VISIT 1, 1ST PARAGRAPH. 116
ADDITION OF BULLET POINT AFTER THE FORMULA: 116
SECTION 6.3.7.3 PULMONARY FUNCTION TESTS. 116
ALL OTHER VISITS (EXCEPT VISIT 1) 116
ORIGINAL TEXT: 116
AMENDED TEXT: ADDITION OF 2 FURTHER BULLET POINTS AFTER LAST BULLET POINT :. 116
SECTION 6.4.1, VISIT 1, SCREENING AND START OF THE 4-WEEK RUN-IN PERIOD 117
11TH BULLET POINT 117
AMENDED TEXT: 117
SECTION 6.4.9 VISIT 7: (WEEK 13 ENDOF THE DOUBLE-BLIND TREATMENT PERIOD) 118
9TH BULLET POINT 118
AMENDED TEXT. 118
SECTION 6.4.11. EARLY WITHDRAWAL VISIT 118
4TH PARAGRAPH, 2ND SENTENCE 118
ORIGINAL TEXT 118

AMENDED TEXT. 118
SECTION 9.4 EARLY WITHDRAWAL ASSESSMENTS IN THE TREATMENT PERIOD 118
PHYSICAL EXAMINATION 119
SECTION 6.2.3 VISITS 1, 8 AND EWV, LAST SENTENCE. 119
ORIGINAL TEXT: 119
AMENDED TEXT: 119
BLINDING ISSUES 119
SECTION 6.3.6, 1ST SENTENCE. 119
ORIGINAL TEXT: 119
AMENDED TEXT: 119
TIMING OF TAKING CONSENT 119
SECTION 6.4.1 VISIT 1 SCREENING AND START OF THE 4-WEEK RUN-IN PERIOD 119
BULLET POINT NUMBER 1 119
ORIGINAL TEXT: 119
AMENDED TEXT: 119
PROVISION OF RESCUE MEDICATION 120
SECTION 5.2.3 EXCLUSION CRITERIA AT RANDOMISATION VISIT (VISIT 3) 120
ORIGINAL TEXT: 120
AMENDED TEXT: 120
SECTION 8.1 PERMITTED MEDICATIONS, BULLET POINT NUMBER 2. . 120
ORIGINAL TEXT: 120
AMENDED TEXT: 120
SECTION 8.1 PERMITTED MEDICATIONS, 4TH BULLET POINT 120
AMENDED TEXT. 120
SECTION 6.3.7.3 SECTION 7.1.1 121
AMENDED TEXT. 121
CONTAINER NUMBER 121
SECTION 6.4.4 VISIT 3 (WEEK 0) START OF THE DOUBLE-BLIND TREATMENT 121
RANDOMISATION CRITERIA. 121
BULLET POINTS NUMBER 2 AND 3 AND ADDITION OF BULLET POINT NUMBER 4 121

ORIGINAL TEXT: 121
AMENDED TEXT: 121
SECTION 7.5 TREATMENT ASSIGNMENT 121
BULLET POINTS NUMBER 2, 3 AND 5 (LAST SENTENCE) 121
ORIGINAL TEXT: 121
AMENDED TEXT: 122
STUDY MEDICATION TAKEN AT CLINIC VISITS 122
SECTION 6.4.4 VISIT 3 (WEEK 0): START OF THE DOUBLE-BLIND TREATMENT TO SECTION 6.4.7 (VISIT 6A (ONLY IF BIOPSY HAS BEEN RESCHED 122
1ST POINT AFTER BULLET POINT NUMBER 1 122
ORIGINAL TEXT: 122
AMENDED TEXT: 122
SECTION 7.2 DOSAGE AND ADMINISTRATION 122
ADDITIONAL SENTENCE AT THE END OF LAST SENTENCE 122
ORIGINAL TEXT: 122
AMENDED TEXT: 123
ECG 123
SECTION 10 ADVERSE EVENTS (AE) AND SERIOUS ADVERSE EVENTS 123
ADDITIONAL MONITORING FOR GASTROINTESTINAL ADVERSE EVENTS: 123
1ST AND LAST SENTENCES. 123
ORIGINAL TEXT: 123
AMENDED TEXT: 123
TIMING OF COLLECTING AES AND SAES. 124
PROTOCOL SUMMARY 124
STUDY ASSESSMENTS AND PROCEDURES 124
BULLET POINT NUMBER 6 124
ORIGINAL TEXT: 124
AMENDED TEXT: 124
SECTION 6.1 DEMOGRAPHIC AND BASELINE ASSESSMENTS 124
BULLET POINT NUMBER 6 124
ORIGINAL TEXT: 124
AMENDED TEXT: 124

SECTION 6.4.1 2ND BULLET POINT 124
ORIGINAL TEXT: 124
AMENDED TEXT: 124
SECTION 10.6 TIME PERIOD, FREQUENCY, AND METHOD OF DETECTING AES AND SAES 125
1ST SENTENCE 125
ORIGINAL TEXT: 125
AMENDED TEXT: 125
SECTION 15.1 APPENDIX 1: TIME AND EVENTS TABLE 125
LAST FOOTNOTE (*) AT THE BOTTOM OF THE TIME AND EVENTS TABLE 125
ORIGINAL TEXT 125
AMENDED TEXT. 125
TIMING OF CLINIC VISITS 125
SECTION 6.4 OUTLINE OF STUDY PROCEDURES AT EACH CLINIC VISIT 125
2ND PARAGRAPH, 2ND SENTENCE 125
ORIGINAL TEXT: 125
AMENDED TEXT: 125

ABBREVIATIONS

AE	Adverse Event
BBPD	Bronchial Biopsy Procedures Document
bd	Twice daily
BTPS	Body temperature and Pressure , saturated with water vapour (referring to conditions in the lung) All spirometric recordings should be corrected to BTPS conditions
CD 4, 8 and 45	Cluster of Differential molecules 4, 8 and 45
CIB	Clinical Investigator's Brochure
COPD	Chronic Obstructive Pulmonary Disease
CRF	Clinical Record Form
CV	*Curriculum vitae*
D-PBS	Dulbecco's-Phosphate buffered saline
DRC	Daily Record Card
DQ	Data Queries
ECCS	European Community for Coal and Steel
EISR	Expedited Investigator Safety Report
EWV	Early Withdrawal Visit
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilence
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GSK	GlaxoSmithKline
IEC	Independent Ethics Committee
IFNγ	Interferon gamma
IL-8	Interlukin -8
IRB	Institutional Review Board
ITT	Intent-To-Treat
IUD	Intrauterine Device
IVRS	Interactive Voice Response System
LTOT	Long Term Oxygen Therapy
MDI	Metered Dose Inhaler
NSAID (s)	Non-Steroidal Anti-Inflammatory Drug (s)
PFT	Pulmonary Function test
PP	Per Protocol
RAMOS	Registration and Medication Ordering System
SAE	Serious Adverse Event
SCA	Standard Clarification Agreement
SaO_2	Saturated Oxygen
SPD	Sputum Procedures Document
SVC	Slow Vital Capacity

PROTOCOL SUMMARY

Rationale

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of death worldwide, fourth or fifth highest in developed countries, with an increasing prevalence and mortality (Thom 1989; ATS, 1995) and is projected to be the third leading cause of death worldwide by 2020 (Murray and Lopez, 1997).

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

The distinctive nature of the inflammation underlying COPD has recently been established and differs from that of asthma in a number of respects, in particular in the predominance of CD8+ cells (Jeffery PK, 2000). A predominance of CD8+ T-lymphocytes and CD68+ macrophages has been demonstrated in the airway and alveolar tissues of smokers with COPD (O'Shaughnessy T et al., 1997). Furthermore, CD8+ cell numbers in all lung compartments have been shown to correlate inversely with FEV_1 percent of predicted normal (Saetta M et al., 2001). Increased numbers of neutrophils have been reported in bronchoalveolar lavage (BAL) and sputum (Thompson AB et al., 1989; Lacoste J-Y et al., 1993) and correlate with a decline in FEV_1 over a 15 year follow-up period (Stanescu D et al., 1996). The cytokines interleukin (IL) -8 and tumor necrosis factor (TNF) α are increased in induced sputum (Keatings VM et al., 1996) and play a role in the selective recruitment of the inflammatory cells into the airways in subjects with COPD (Pauwels RA et al., 2001).

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

Cilomilast is a potent and selective phosphodiesterase type 4 (PDE4) inhibitor currently under development for the treatment of COPD. The rationale for the use of PDE4 inhibitors in the treatment of COPD is based upon the role of cyclic adenosine monophosphate (cyclic AMP) as a second messenger that mediates a broad suppression of immune and inflammatory cell activities, along with the knowledge that PDE4 is the major cyclic AMP-hydrolysing isozyme in these cells (Torphy and Undem, 1991).

A previous, multicentre study (207499/076) of similar design evaluating the anti-inflammatory effects of cilomilast has been completed successfully. A total of 59 subjects, with a diagnosis of COPD, were randomised to receive cilomilast 15 mg bd or placebo for a period of 12 weeks. The study aimed to evaluate the anti-inflammatory effects of cilomilast by quantification of the key inflammatory cells in biopsies. Compared with placebo, analysis of change from baseline values demonstrated significant reductions in counts of bronchial biopsy CD8+ ($p=0.001$) and CD68+ ($p=0.04$) cells in the cilomilast group. Poisson regression analysis confirmed the reductions in the cilomilast group compared with the placebo group for CD8+ (48%, $p=0.004$), CD68+ (55%, $p<0.001$). Additionally there were reductions in subepithelial CD4+ cells (42%, $p=0.025$) and neutrophils (37%, $p=0.049$). There were no significant treatment related effects seen in the numbers of epithelial neutrophils, IL-8mRNA or TNFα mRNA+cells. Sputum neutrophil % did not change significantly from baseline in either group. There were no significant changes in sputum macrophage %, total cell counts, IL-8 or neutrophil elastase concentrations.

The purpose of this proposed clinical study is to further explore the potential for cilomilast to demonstrate anti-inflammatory effects in subjects with COPD.

Objective(s)

Primary Objectives

- To compare the numbers of inflammatory cell of distinct immuno and ultrastructural phenotype after treatment with cilomilast 15 mg twice daily (bd) and with placebo bd in subjects with COPD, using bronchial biopsy

Secondary Objectives

- To compare the relative numbers (i.e. percentage) of distinct inflammatory cells after treatment with cilomilast 15mg bd and with placebo bd in sputum induced from subjects with COPD

Endpoint(s)

Primary

- The numbers of sub-epithelial CD68+ (macrophages) per area of biopsy tissue
- The numbers of sub-epithelial CD8+ (cytotoxic T-lymphocytes) per area of biopsy tissue

Secondary Efficacy Endpoints

Secondary Efficacy Endpoints

In Biopsy

- To compare the number of the following sub-epithelial cells per area of biopsy tissue from subjects treated with cilomilast and from subjects treated with placebo:

- Neutrophil elastase positive cells (neutrophils)
- CD4+ lymphocytes
- IL-8 mRNA positive cells
- TNFα mRNA positive cells
- CD45 positive cells
- Mucin expression

In Sputum

- To compare the number of the following cells in sputum per unit volume from subjects treated with cilomilast and from subjects treated with placebo:

- Sputum total cell count and differential cell counts
- Macrophages as a percentage of total cells and as a total cell count per unit volume
- Eosinophils as a percentage of total cells and as a total cell count per unit volume
- Lymphocytes as a percentage of total cells and as a total cell count per unit volume
- Neutophil elastase
- IL-8

NB: *Additional secondary efficacy variables may be analysed before the study final statistical results, depending on sample availability and results of initial analysis*

Tertiary Efficacy Endpoints

- Slow vital capacity (SVC)

Safety Endpoints

- Incidence of adverse events
- Vital signs
- Clinical laboratory tests [Chemistry, Haematology, Urinalysis, Faecal Occult Blood test (FOB), and pregnancy testing for females of childbearing potential]

Study Design

This is a randomised, double-blind, placebo-controlled, parallel-group multicentre study in subjects with moderate to severe COPD. Subjects will complete a four-week single blind placebo Run-In period before randomisation to cilomilast 15mg bd or placebo bd for 13 weeks. This will be followed by a 1-week Follow-Up period.

Bronchial biopsies will be performed one week prior to randomisation for the baseline sample (i.e. at Week -1, Visit 2), at the end of 12 weeks' treatment at Visit 6, or 1 week after Early Withdrawal Visit (EWV). The baseline and end of treatment bronchial biopsies will only be performed, if the safety criteria listed in the Bronchial Biopsy Procedures Section are met, otherwise the biopsy procedure should be rescheduled within 1 to 7 days (Visit 2A and Visit 6A respectively). An induced sputum sample will be collected at Visit 3 at Week 0, at Visit 7 (at the end of 13 weeks' treatment), and at EWV if the biopsy was not done.

At visit 1 pulmonary function tests (FEV_1, FVC, and slow SVC) will be conducted before and after administration of salbutamol 400mcg via an MDI and a **VOLUMATIC**[*] spacer. At Visits, 2-8 and including the Early Withdrawal Visit (EWV), Slow Vital Capacity (SVC), (before and after the administration of salbutamol 400mcg via an MDI and a **VOLUMATIC** spacer) will be measured and recorded in the CRF.

In addition, at Visits 2/2A and 6/6A and at EWV (if applicable), before the biopsy procedures, FEV_1 (before and after the administration of salbutamol 400mcg via an MDI and a **VOLUMATIC** spacer) will be measured and the results recorded in the Biopsy Safety Form. FVC data generated while measuring the FEV_1 should be recorded in the subject's source notes.

At Visits 3 and 7, FEV_1 (before and after the administration of salbutamol 400mcg via an MDI and a **VOLUMATIC** spacer) will be measured as part of the sputum induction procedure. These results are not recorded in the CRF but are kept with the subject's source notes.

All other procedures are outlined in the Time and Events Schedule (see Appendix 1).

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[*] **VOLUMATIC** is a Trademark of the GlaxoSmithKline group of companies.

Study Plan:

	Run-In	TREATMENT PERIOD *Cilomilast 15mg bd* OR Placebo bd					Follow-up	
Visit	**V1**	**V2/2A**	**V3**	**V4**	**V5**	**V6/6A**	**V7**	**V8**	**EWVV**
Week	**-4**	**-1**	**0**	**4**	**8**	**12**	**13**	**14**	
Biopsy		**x**				**x**			**x**
Sputum			**x**				**x**		**x[1]**
PFTs	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**

PFT -Pulmonary Function Tests at V1 (and only SVC at all other visits) (see Section 6.3.7 for details)
EWV- Early Withdrawal Visit
1. if possible

Study Population

Male or female out-patients with documented history of COPD will be randomised to the study. Approximately 250 subjects from about 15 centres will be screened and 116 randomised in order to obtain 86 evaluable subjects. **Only specialist centres with the expertise in taking biopsies and induced sputum samples will be enlisted in this study.**

Study Assessments and Procedures

The following demographic information and procedures will be recorded for each subject during the 18-week period of the study:

- Gender, ethnic origin, date of birth, height and weight
- Physical examination
- Vital signs (blood pressure and heart rate) and temperature
- Smoking history (subjects will be stratified according to whether they are current smokers or ex-smokers. Ex-smokers are defined as those who have stopped smoking for at least 6 months prior to Visit 1)
- History of COPD, including details of any exacerbation in the 12 months prior to the Visit 1
- Any adverse events that the subject may experience following consent, when the subject is asked to withdraw any prohibited medication, till the Follow-Up period
- Current medical conditions and concurrent medications (both COPD and non-COPD)
- A full medical and surgical history, including history of myocardial infarctions

- Measurement of oxygen saturation (SaO_2%) using pulse oximetry
- Pulmonary Function Tests (PFTs) FEV_1 and FVC including reversibility after administration of 400mcg of salbutamol, and slow vital capacity (SVC)
- Chest X-ray (if one has not been taken recently i.e. not more than 9 weeks before Visit 1) to exclude the possibility of any abnormality that may mimic or co-exist with COPD (e.g. pneumothorax, bronchial carcinoma or active pulmonary TB)
- Clinical Laboratory test [Chemistry, Haematology, Urinalysis, Faecal Occult Blood test (FOB), and pregnancy testing for females of childbearing potential]
- Biopsy and sputum samples

Investigational Product(s)

GSK will supply the following investigational products for this study:

Cilomilast 15mg/dose bd (2 tablets/day)

Matching placebo bd (2 tablets/day)

1. INTRODUCTION

1.1. Background

COPD

Chronic Obstructive Pulmonary Disease (COPD) is a leading cause of morbidity and mortality worldwide and results in an economic and social burden for society. The disease is highly prevalent and can be severely disabling. The WHO/World Bank using the composite measure of the burden of each health problem, The Disability-Adjusted Life Year (DALY) lost has estimated COPD to be the 12th leading cause of mortality in 1990 and has predicted it to be the 5th leading cause of mortality in the year 2020 [Murray, 1996a], [Murray, 1996b]

The GOLD guidelines define COPD, as a disease state characterised by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particle or gases [GOLD, 2000].

The pathological hallmarks of COPD are inflammation of the peripheral airways and emphysema. The functional consequence of these abnormalities is expiratory airflow limitation, since both loss of elastic recoil and increase in airway resistance play an important role in the observed decrease in airflow.

Emphysema reduces elastic recoil through parenchymal destruction thus leading to loss of elastic recoil. Inflammation of the peripheral airways, on the other hand contribute to airway inflammation by increasing the thickness of the airway wall which together with fibrosis and smooth muscle hypertrophy, may cause airway narrowing [Saetta, 2001].

The role of chronic bronchitis in the development of chronic airflow limitation is controversial. Chronic sputum production has traditionally been considered to be irrelevant to the development of chronic airflow limitation [Peto, 1983]. However, a recent study has shown that chronic sputum production was significantly associated with both an excess of FEV_1 decline and an increased risk of subsequent hospitalisation related to COPD, suggesting a causal role for mucus hypersecretion in the development of chronic airflow limitation in smokers [Vestbo, 1996]. The main site of mucus hypersecretion is the central airways and there is increasing evidence that the central airway is inflamed in COPD.

It has been reported that some of the above changes can be seen in the lungs of smokers with normal lung function, indicating that smoking itself is able to damage the lungs even before airflow limitation occurs [Rutgers, 2000]. It is well accepted that the main risk factor for COPD is inhalation of cigarette smoke and that this can elicit an inflammatory reaction involving the entire tracheobronchial tree.

The airway inflammation is caused by an influx of inflammatory cells and release of mediators into tissue [Keatings, 1996]. A predominance of CD68+

(monocyte/macrophages) and CD8+ T-lymphocytes in the sub-epithelium, and increased neutrophils have been demonstrated in induced sputum and bronchoalveolar lavage fluid [Riise, 1995; Ronchi, 1996]. During exacerbations there are increases in eosinophils and neutrophils in sub-epithelial tissue and increased recovery of eosinophils from sputum [Riise, 1995; Ronchi, 1996].

Many studies have implicated the macrophage as the major inflammatory effector cell [Niewoehner, 1974; Merchant, 1992]. A direct relationship between lung destruction and the number of macrophages, in the alveolar parenchyma has been also been reported [Finkelstein, 1995]. There is also evidence that increased numbers of macrophages in bronchial biopsy correlates with airflow limitation [Di Stefano, 1996; Di Stefano, 1998].

Macrophages play an orchestrating role by releasing mediators such as tumour necrosis factor-α (TNF-α) and interlukin -8 (IL-8) which promote neutrophilic inflammation. TNF-α is present in high concentrations in sputum and is detectable in bronchial biopsies in subjects with COPD [Keatings, 1996]. IL-8 is also secreted by neutrophils and epithelial cells and is present at high concentrations in induced sputum and bronchoaleveolar fluid in subjects with COPD [Keatings, 1996; Pesci, 1998; Yamamoto, 1997].

Significant correlations with severity of airflow obstruction have also been observed for sub-epithelial CD8+ T-cells [O'Shaughnessy, 1997]. The role of CD8+ cells in COPD inflammation is not fully understood but one way that CD8+ cells may contribute to COPD is by releasing perforin, granzyme-B, and TNF-α which can cause the cytolysis and apoptosis of alveolar epithelial cells [Liu, 1999].

Neutrophils are scarce in the sub-epithelial area, but are present in the epithelium and in the bronchial glands [O'Shaughnessy, 1997] as well in the lumen. Neutrophils secrete several proteinases, including neutrophil elastase, neutrophil cathepsin G and neutrophil proteinase-3 that may contribute to parenchymal destruction and chronic mucus hypersecretion [Saetta, 2002]

The presence and role of eosinophils in COPD is uncertain [Saetta, 1994; Laciest, 1993]. Some studies have shown a rise in eosinophils in COPD subjects, while other studies have not. Some subjects with COPD have co-existing asthma which may explain the presence of eosinophils [O'Shaughnessy, 1997]. However, the levels of eosinophil cationic protein (ECP) and eosinophil peroxidase (EPO) in induced sputum are elevated in COPD, suggesting that eosinophils may be present but degranulated and is therefore not detectable by light microscopy [Keatings, 1997a].

Emphysema is an inflammatory condition of the alveoli associated with permanent destructive enlargement of air spaces distal to terminal bronchiole without obvious fibrosis. There are two types of emphysema: centriacinar emphysema and panacinar emphysema. Centriacinar emphysema is characterised by focal destruction restricted to respiratory bronchioli and the central portions of the acinus. Panacinar emphysema involves destruction of the walls in a uniform manner of all the air spaces beyond the terminal bronchioles. The early changes of emphysema include the subtle disruption to elastic fibres with accompanying loss of elastic recoil and subsequent bronchiolar and

alveolar distortion. The inflammatory cell profile associated with emphysema includes T-lymphocytes, neutrophils and alveolar macrophages which all release large amounts of elastase, which overwhelms the normal anti-protease protective screen.

COPD is a debilitating disease, which has a considerable impact on subjects' lives due to chronic progressive symptoms (breathlessness, wheezing, and cough and sputum production), disruption caused by exacerbations and limitations on normal activities. Exacerbations are a major cause of morbidity and mortality in COPD and are closely associated with symptomatic and physiological deterioration and their frequency is an important determinant of the subject's health status.

The single most effective means of improving the prognosis in subjects with COPD is smoking cessation. It is associated with a reduction in the accelerated rate of decline in FEV_1. None of the currently available pharmacological treatments have been shown to modify disease progression in COPD. The present goals of therapy are therefore symptomatic management of COPD, aimed at preventing and controlling the symptoms, reducing the frequency and severity of exacerbations and improving or at least maintaining pulmonary function and health status. The vast majority of subjects are treated with inhaled or oral short-acting bronchodilators, including short-acting β_2-agonists, anticholinergics and methyxanthines. These drugs are recommended in guidelines as first-line therapy and have become central to the symptomatic management of COPD. They treat the bronchospasm associated with COPD by relaxing the smooth muscle in the airways, thereby increasing airflow. However, short-acting bronchodilators have little or no effect on exacerbations or health status, or on the underlying inflammatory process.

Inhaled corticosteroids are frequently used in COPD, although there are conflicting opinions as to their benefit and their role in reducing inflammation and its sequelae [Barnes, 2000; Calverley, 2000]. Despite this controversy, the GOLD guidelines recommend regular treatment with inhaled corticosteroids for symptomatic subjects with moderate-to-severe COPD who have either a documented spirometric response to corticosteroids or repeated exacerbations [GOLD, 2001]. Oral corticosteroids and antibiotics are used intermittently to treat exacerbations of COPD.

Overall, regular treatment options are limited and few have shown a significant effect on clinically important parameters, such as exacerbations or health status, which have a substantial impact on subjects' lives. There remains a clear unmet medical need for more effective therapies for the symptomatic management of COPD [Barnes, 2000].

1.2. Rationale

The distinctive nature of the inflammation underlying COPD has recently been established and differs from that of asthma in a number of respects, in particular in the predominance of CD8+ cells (Jeffery PK, 2000). A predominance of CD8+ T-lymphocytes and CD68+ macrophages has been demonstrated in the airway and alveolar tissues of smokers with COPD (O'Shaughnessy T et al., 1997). Furthermore, CD8+ cell numbers in all lung compartments have been shown to correlate inversely with FEV_1 percent of predicted normal (Saetta M et al., 2001). Increased numbers of neutrophils

have been reported in bronchoalveolar lavage (BAL) and sputum (Thompson AB et al., 1989; Lacoste J-Y et al., 1993) and correlate with a decline in FEV_1 over a 15 year follow-up period (Stanescu D et al., 1996). The cytokines interleukin (IL) -8 and tumor necrosis factor (TNF) α are increased in induced sputum (Keatings VM et al., 1996) and play a role in the selective recruitment of the inflammatory cells into the airways in subjects with COPD (Pauwels RA et al., 2001).

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

Cilomilast is a potent and selective phosphodiesterase type 4 (PDE4) inhibitor currently under development for the treatment of COPD. The rationale for the use of PDE4 inhibitors in the treatment of COPD is based upon the role of cyclic adenosine monophosphate (cyclic AMP) as a second messenger that mediates a broad suppression of immune and inflammatory cell activities, along with the knowledge that PDE 4 is the major cyclic AMP-hydrolysing isozyme in these cells (Torphy and Undem, 1991).

A previous, multicentre study (207499/076) of similar design evaluating the anti-inflammatory effects of cilomilast has been completed successfully. A total of 59 subjects, with a diagnosis of COPD, were randomised to receive cilomilast 15 mg bd or placebo for a period of 12 weeks. The study aimed to evaluate the anti-inflammatory effects of cilomilast by quantification of the key inflammatory cells in biopsies. Compared with placebo, analysis of change from baseline values demonstrated significant reductions in counts of bronchial biopsy CD8+ ($p=0.001$) and CD68+ ($p=0.04$) cells in the cilomilast group. Poisson regression analysis confirmed the reductions in the cilomilast group compared with the placebo group for CD8+ (48%, $p=0.004$), CD68+ (55%, $p<0.001$). Additionally there were reductions in subepithelial CD4+ cells (42%, $p=0.025$) and neutrophils (37%, $p=0.049$). There were no significant treatment related effects seen in the numbers of epithelial neutrophils, IL-8mRNA or TNFα mRNA+cells. Sputum neutrophil % did not change significantly from baseline in either group. There were no significant changes in sputum macrophage %, total cell counts, IL-8 or neutrophil elastase concentrations.

The purpose of this proposed clinical study is to further explore the potential for cilomilast to demonstrate anti-inflammatory effects in subjects with COPD

2. OBJECTIVE(S)

2.1. Primary

- To compare the numbers of inflammatory cell of distinct immuno and ultrastructural phenotype after treatment with cilomilast 15 mg twice daily (bd) and with placebo bd in subjects with COPD, using bronchial biopsy

2.2. Secondary

- To compare the relative numbers (i.e. percentage) of distinct inflammatory cells after treatment with cilomilast 15mg bd and with placebo bd in sputum induced from subjects with COPD

3. ENDPOINT(S)

3.1. Primary

- The numbers of sub-epithelial CD68+ (macrophages) per area of biopsy tissue
- The numbers of sub-epithelial CD8+ (cytotoxic T-lymphocytes) per area of biopsy tissue

3.2. Secondary

Secondary Efficacy Endpoints

In Biopsy

To compare the number of the following sub-epithelial cells per area of biopsy tissue from subjects treated with cilomilast and from subjects treated with placebo:

- Neutrophil elastase positive cells (neutrophils)
- CD4+ lymphocytes
- IL-8 mRNA positive cells
- TNFα mRNA positive cells
- CD45 positive cells
- Mucin expression

In Sputum

To compare the number of the following cells in sputum per unit volume from subjects treated with cilomilast and from subjects treated with placebo:

- Sputum total cell count and differential cell counts

- Macrophages as a percentage of total cells and as a total cell count per unit volume
- Eosinophils as a percentage of total cells and as a total cell count per unit volume
- Lymphocytes as a percentage of total cells and as a total cell count per unit volume
- Neutophil elastase
- IL-8

NB: *Additional secondary efficacy variables may be analysed before the study final statistical results, depending on sample availability and results of initial analysis*

3.3. Tertiary

- Slow Vital Capacity (SVC)

4. STUDY DESIGN

This is a randomised, double-blind, placebo-controlled, parallel-group multicentre study in subjects with moderate to severe COPD. Subjects will complete a four-week single-blind placebo Run-In period before randomisation to cilomilast 15mg bd or placebo bd for 13 weeks. This will be followed by a 1-week Follow-Up period.

Bronchial biopsies will be performed one week prior to randomisation for the baseline sample (i.e. at Week -1, Visit 2), at the end of 12 weeks' treatment at Visit 6, or 1 week after EWV. The baseline and end of treatment bronchial biopsies will only be performed, if the safety criteria listed in the Bronchial Biopsy Procedures Section are met, otherwise the biopsy procedure should be rescheduled within 1 to 7 days (Visit 2A and Visit 6A respectively). An induced sputum sample will be collected at Visit 3 (Week 0), at Visit 7 (at the end of 13 weeks' treatment), and at EWV if the biopsy was not done.

At visit 1 pulmonary function tests (FEV_1, FVC, and slow SVC) will be conducted before and after administration of salbutamol 400mcg via an MDI and a **VOLUMATIC** spacer. At Visits, 2-8 and including the Early Withdrawal Visit (EWV), Slow Vital Capacity (SVC), (before and after the administration of salbutamol 400mcg via an MDI and a **VOLUMATIC** spacer) will be measured and recorded in the CRF.

In addition, at Visits 2/2A and 6/6A and at EWV (if applicable), before the biopsy procedures, FEV_1 (before and after the administration of salbutamol 400mcg via an MDI and a **VOLUMATIC** spacer) will be measured and the results recorded in the Biopsy Safety Form. FVC data generated while measuring the FEV_1 should be recorded in the subject's source notes.

At Visits 3 and 7, FEV_1 (before and after the administration of salbutamol 400mcg via an MDI and a **VOLUMATIC** spacer) will be measured as part of the sputum induction procedure. These results are not recorded in the CRF but are kept with the subject's source notes.

All other procedures are outlined in the Time and Events Schedule (see Appendix 1).

Study Plan:

			TREATMENT PERIOD						
			Cilomilast 15mg bd						
	Run-In		OR					Follow- up	
			Placebo bd						
Visit	**V1**	**V2/2A**	**V3**	**V4**	**V5**	**V6/6A**	**V7**	**V8**	**EWV**
Week	**-4**	**-1**	**0**	**4**	**8**	**12**	**13**	**14**	
Biopsy		**x**				**x**			**x**
Sputum			**x**				**x**		**x**[1]
PFTs	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**

PFT - Pulmonary Function Tests see Section 6.3.7 for details
EWV- Early Withdrawal Visit
1. if possible

OUTLINE OF PROCEDURES:

Each subject will plan to visit the clinic on 8 occasions over a 18-week period. Study procedures will be performed according to the schedule in Appendix 1.

Smoking must be avoided for at least 2 hours before the clinic visit. The use of salbutamol and anticholinergic agents must be avoided for at least 6 hours before the clinic visit.

VISIT TIMINGS:

Visits should be scheduled at the same time of day (± 2 hours) and should be conducted preferably in the morning.

Clinic visits should take place within +/- 3 days of the scheduled visit date.

5. STUDY POPULATION

Subjects who are out-patients with a documented history of moderate to severe COPD as defined by the GOLD guidelines [GOLD, 2001] who have given written informed consent to participate in the clinical study, have met all the criteria required for entry into the clinical study and who receives no other investigational product, may participate in this study.

Subject participation in this study is voluntary and refusal to participate will involve no penalty or loss of benefits to which the subject would otherwise be entitled.

No administration of investigational product beyond that detailed in the clinical protocol is associated with this study.

5.1. Number of Subjects

Male or female out-subjects with documented history of COPD will be randomised to the study. Approximately 250 subjects from about 15 centres will be screened to randomise 116 subjects in order to obtain 86 evaluable subjects. Each centre will recruit a minimum of 4 subjects.

5.2. Eligibility Criteria

5.2.1. Inclusion Criteria

INCLUSION CRITERIA (SCREENING VISIT 1):

Subjects who fulfil all of the following 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. Subjects with a clinical diagnosis of COPD, as defined by GOLD guidelines. *(A diagnosis of COPD should be considered in any subject who has symptoms of cough, sputum production, or dyspnea, and/or a history of exposure to risk factors for the disease. Post-bronchodilator FEV1/FVC should be ≤70% predicted at visit 1.*
3. Subjects with a smoking history (current or ex-smoker) of ≥ 10 pack years (1 pack year = 20 cigarettes smoked per day for 1 year or equivalent). *(Ex-smokers are defined as those who have stopped smoking for at least 6 months prior to Visit 1. Ex-smokers are eligible to enter the study provided they have at least 10 pack years smoking history).*
4. Subjects with a pre-bronchodilator FEV_1 to FVC ratio (FEV_1:FVC) ≤ 0.7 at Visit 1.
5. Subjects with poor reversibility of airway obstruction, defined by ≤10% increase in FEV_1 as % of predicted normal or ≤200 ml (or both) increase in FEV_1 after the administration of salbutamol 400 mcg via MDI at Visit 1 (Screening visit).

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† Norplant is a registered trademark for Levonorgestrel.

† Depo-Provera is a registered trademark for medroxyprogestrone acetate by Pharmacia.

6. Subjects with a post-salbutamol FEV_1 of ≥ 40 and ≤ 80% of predicted normal for height, age and gender at Visit 1. Subjects will be assessed 30 minutes after the administration of 400mcg salbutamol via MDI and spacer.

   (Predicted normal values will be taken from the report of the working party of the European Community for Coal and Steel, 1993).

7. Subjects without hypoxaemia (all subjects must have an O_2 saturation ≥88% on room air.
8. Subjects who give their signed and dated written informed consent to participate.

5.2.2. Exclusion Criteria

EXCLUSION CRITERIA (SCREENING VISIT 1):

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

1. Women who are pregnant or lactating.
2. Subjects with asthma and/or atopy as the main component of their obstructive airways disease.
3. Subjects with poorly controlled COPD, defined as the occurrence of any of the following in the 4 weeks prior to Visit 1 (Screening): acute worsening of COPD that is managed by the subject at home by self-treatment with corticosteroids or antibiotics, or that requires treatment prescribed by a physician, or for which the subject is hospitalised.
4. Subjects with known active tuberculosis, lung cancer, clinically overt bronchiectasis, or other known specific pulmonary disease, any other condition known to be associated with inflammation (sarcoidosis and arthritis).
5. Subjects with a chest X-ray indicating diagnosis other than COPD that might interfere with the study (chest X-ray to be taken at entry to the run-in period or in the 9 weeks prior to entry to the run-in period).
6. Subjects with clinically significant cardiovascular, neurological, renal, endocrine, or haematological abnormalities that are uncontrolled on permitted therapy.
7. Subjects with clinically significant gastrointestinal or hepatic abnormalities.
8. Subjects with a history of bleeding diathesis.
9. Subjects with a history of hypersensitivity to PDE4 inhibitors.
10. Subjects with a suspected abuse of alcohol or any other recreational substance.
11. Subjects receiving treatment with inhaled cromolyn sodium or nedocromil, inhaled long-acting $beta_2$-agonists, and/or oral $beta_2$-agonists, long acting anticolinergic (e.g. tiotropium bromide) xanthines, leukotriene modifiers, mucolytics, oral/inhaled corticosteroids, or NACs N-Acetyl Cysteine. **All COPD medications except short-acting anticholinergic medication (ipratropium bromide) and/or salbutamol or Combivent, should be withdrawn prior to or at Visit 1 (Screening). All**

oral/inhaled corticosteroids, long-acting anticolinergic (e.g. tiotropium bromide), xanthines must be withdrawn at least four weeks prior to Visit 1.

12. Subjects receiving treatment with long term oxygen therapy (LTOT) or those subjects who require supplemental oxygen more often than on an occasional (prn) basis.
13. Subjects who have received an investigational drug within 30 days of entry into this study (Visit 1), or within 5 drug half-lives of the investigational drug (whichever is longer).
14. Subjects who are unable or unwilling to comply with all protocol specified procedures.

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

5.2.3. Randomisation Criteria at visit 3:

Subjects who fulfil the Randomisation Criteria below at end of 4 weeks single blind placebo controlled run-in period (Visit 3) may enter the double-blind treatment phase of the study, and all subjects will be stratified before treatment, according to their smoking habit (i.e. current smokers or ex-smokers):

Exclusion Criteria at randomisation visit (visit 3)

1. Subjects who have had any changes to their COPD medication (other than salbutamol, ipratropium bromide or Combivent), received corticosteroids (oral or inhaled) for respiratory disease, or hospitalised for COPD/lower respiratory tract infections during the run-in period.
2. Subjects receiving any other medication during the run-in period which in the opinion of the investigator, is judged as likely to affect baseline assessments
3. Subjects unable to tolerate withdrawal of medications during the Run-In period
4. Subjects who are unable to tolerate or comply with the protocol procedures

5.2.4. Other Eligibility Criteria Considerations

To assess any potential impact on subject eligibility with regard to safety, the investigator must refer to the following document(s) for detailed information regarding warnings, precautions, contraindications, adverse events, and other significant data pertaining to the investigational product(s) being used in this study.

6. STUDY ASSESSMENTS AND PROCEDURES

The schedule of the measurements and evaluations to be performed at each clinic visit is given in the Time and Events Schedule as outlined in Appendix 1.

All subjects will start the study at Visit 1, and if they meet all the entry criteria, they will enter a 4-week single-blind placebo Run-In Period which includes a 3-week Screening Period and a 1-Week Baseline Period. This will be followed by a 13-week Treatment Period at Visit 3, when subjects will be randomised to one of two-treatment arms i.e.cilomilast 15mg bd or placebo bd. Following the Treatment Period, subjects will enter a one-week safety Follow-Up Period.

Each study visit for treatment will be calculated from Visit 3 (week 0). Visits will be scheduled for 4, 8, 12, 13 and 14 weeks from Visit 3. Visits may vary from these timelines by ±3days. The Follow-Up period (Week 14) will be 1 week in duration.

Bronchial biopsy samples will be collected at Visits 2, 6, or 1 week after EWV. The baseline and end of treatment bronchial biopsies will only be performed if the safety criteria listed in the Bronchial Biopsy Procedures document are met, otherwise the biopsy procedure should be rescheduled within 1 to 7 days (Visit 2A and Visit 6A respectively). Methodology for collection, fixing and storage of samples will be standardised throughout the study. Biopsy samples will be pre-processed at the investigator sites, using the agreed protocols supplied by the specialised central laboratory and then sent to Meakins-Christie Laboratories, Canada for assessment.

Induced sputum will be collected at Visits 3, 7, or EWV (if possible). Methodology for collection and storage of samples will be standardised throughout the study. Sputum samples will be pre-processed at the investigator sites, using the agreed protocols supplied by the specialised central laboratory, and then sent to John Hunter Hospital, Australia for assessment.

Randomised subjects who withdraw from the study at a scheduled visit should complete the assessments scheduled at that visit. A physical examination, respiratory examination, temperature assessment, vital signs, and biopsy procedure will be performed if not already included in the scheduled visit assessments.

Subjects who withdraw between clinic visits will be required to attend the clinic within 24 hours for an Early Withdrawal Visit (EWV).

- If a subject is withdrawing at the unscheduled visit a biopsy should be performed 1 week after the EWV. If possible, a sputum induction should be performed 7 days after the biopsy procedure.
- If for any reason, both baseline biopsy sample and the sputum sample are unobtainable, the subject should be withdrawn.
- If the baseline biopsy sample is unobtainable but the baseline sputum sample is obtainable, the post-treatment biopsy should not be taken, but the sputum sample should be induced at the visit scheduled for sputum induction.
- If the baseline sputum sample is unobtainable, no further sputum samples should be taken, but biopsy samples should be taken as scheduled.
- Methodology for bronchial biopsy and for sputum induction and the fixing and storage of samples will be standardised throughout the study. The procedures will be

outlined in the procedures documents called the Sputum Procedures document and Bronchial Biopsy Procedures document respectively. Bronchoscopy will be performed according to the BTS guidelines.

Pulmonary Function Tests (PFTs) will be conducted as outlined in Section 6.3.7 All other procedures are outlined in the Time and Events Schedule (see Appendix 1)

6.1. Demographic and Baseline Assessments

The following demographic information and procedures will be recorded for each subject during the 18-week period of the study:

- Gender, ethnic origin, date of birth, height and weight
- Physical examination
- Vital signs (blood pressure and heart rate) and temperature
- Smoking history (Ex-smokers are defined as those who have stopped smoking for at least 6 months prior to Visit 1)
- History of COPD, including details of any exacerbation in the 12 months prior to the Visit 1
- Any adverse events that the subject may experience following consent, when the subject is asked to withdraw any prohibited medication, till the Follow-Up period. AEs may include pre or post–treatment events that occur as a result of protocol mandated procedures (i.e. invasive procedures, modifications of the subject's previous therapeutic regimen)
- Current medical conditions and concurrent medications (both COPD and non-COPD)
- A full medical and surgical history, including history of myocardial infarctions
- Measurement of oxygen saturation (SaO_2%) using pulse oximetry for all subjects
- Pulmonary Function Tests (PFTs): FEV_1, FVC and SVC including reversibility after administration of 400mcg of salbutamol will be conducted at Visit 1.
- Chest X-ray (if one has not been taken recently i.e. not more than 9 weeks prior to Visit 1) to exclude the possibility of any abnormality that may mimic or co-exist with COPD (e.g. pneumothorax, bronchial carcinoma or active pulmonary TB)
- Clinical laboratory tests [Chemistry, Haematology, Urinalysis, Faecal Occult Blood test (FOB), and pregnancy testing for females of childbearing potential]
- Biopsy and sputum samples

6.1.1. History of COPD

The subject's history of COPD including duration of COPD, subject-reported number of COPD exacerbations in the previous 12 months that required oral corticosteroids, antibiotics and/or hospitalisation. Subjects with poorly controlled COPD in the 4 weeks before Visit 1 that required oral corticosteroids or antibiotics or any changes in COPD

medication (other than the use of required relief medication) will not be eligible to participate.

6.1.2. Chest X-ray

A postero-anterior (P-A) chest radiograph (X-ray) should have been performed within 9 weeks prior to Visit 1 and the results (including film) must be made available by Visit 2 prior to taking the biopsy. Abnormal findings not consistent with the diagnosis of COPD should be documented in the CRF and followed up as appropriate.

6.1.3. Smoking History

Smoking history should include both the number of cigarettes smoked (or equivalent if subject smoked cigars or a pipe) and for how long. From this the pack years will be calculated using the calculation below. One pack of 20 cigarettes smoked/day for one year = one pack year. One cigar is equivalent to 7 cigarettes and one gram of tobacco is equivalent to one cigarette.

$$\textbf{Total pack years} = \frac{\textbf{No. of cigarettes smoked/day}}{\textbf{20}} \times \textbf{No. of years smoked}$$

(*Ex-smokers are defined as those who have stopped smoking for at least 6 months prior to Visit 1. Ex-smokers are eligible to enter the study provided they have at least 10 pack years smoking history*)

Smoking history will also be taken at Visits 7 and at the EWV.

6.2. Safety

Safety will be assessed by:

- Clinical laboratory tests [Chemistry, Haematology, Urinalysis, Faecal Occult Blood test (FOB), and pregnancy testing for females of childbearing potential]
- Recording of all adverse events [see Section 6.2.1 and Section 10 Adverse Events (AE) and Serious Adverse Events (SAEs)]
- Physical examination
- Measurement of vital signs (blood pressure and heart rate) and temperature
- Measurement of oxygen saturation (SaO_2%) using pulse oximetry for all subjects
- Pre-biopsy blood testing (blood clotting tests)

6.2.1. Pregnancy

6.2.1.1. Pregnancy testing

A urine or serum pregnancy test will be conducted at Visits 1 and 7 in all women of childbearing potential. Subjects will be asked to provide approximately 20mls of urine sample for pregnancy testing. Subjects with a positive pregnancy test should be excluded from entry to the study. If a subject becomes aware that she is pregnant during the course of the study, she must be withdrawn.

6.2.1.2. Time period for collecting pregnancy information

The time period for collecting pregnancy information includes the period between Visit 1 and the end of treatment period (i.e. between Visit 1 and Visit 7). A pregnancy occurring during this period will be followed up for the times specified below.

6.2.1.3. Action to be taken if pregnancy occurs

The investigator, or his/her designee, will collect pregnancy information on any female subject, or both who becomes pregnant while participating in this study. The investigator, or his/her designee, will record pregnancy information on the appropriate form and submit it to GSK within 2 weeks of learning of a subject's pregnancy. The subject will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or a SAE, as described in Section 10.6, "Recording of AEs and SAEs" and will be followed as described in Section 10.8, "Follow-up of AEs and SAEs."

A spontaneous abortion is always considered to be a SAE and will be reported as described in Section 10, “Adverse Events (AE) and Serious Adverse Events (SAE).” Furthermore, any SAE occurring as a result of a post-study pregnancy **and** is considered reasonably related to the investigational product by the investigator, will be reported to GSK as described in Section 10.11, "Post-study AEs and SAEs." While the investigator is not obligated to actively seek this information in former study participants, he/she may learn of an SAE through spontaneous reporting.

6.2.2. Adverse Events, COPD Exacerbation and Concurrent illness and Medications

Each adverse event, COPD exacerbation or concurrent illness that occurs during the study must be documented in the CRF, as outlined in Section 10. If there has been a change in the subject's concurrent medication, this must be documented in the appropriate Concurrent Medication section of the CRF. The procedure for dealing with COPD exacerbations is described in Section 6.2.2.1.

6.2.2.1. COPD Exacerbation Definition

An exacerbation of COPD is defined as a worsening of COPD symptoms requiring changes to normal treatment, including antibiotic 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 the adverse event section of the CRF. COPD exacerbations are categorised as follows:

- Mild exacerbation: Acute worsening of COPD that is self-managed by the subject at home by increasing usual COPD bronchdilators medications, and should not be taking any antibiotics (i.e. the subject does not see a doctor for this episode)
- Moderate exacerbation: Acute worsening of COPD that requires additional treatment (e.g. a short course of oral steroids, antibiotics, etc) prescribed by primary care physician or as a result of a hospital out-patient visit (including a visit to the Emergency Room)
- Severe exacerbation: Acute worsening of COPD that requires the subject to be admitted to hospital for treatment.

Subjects who experience moderate or severe exacerbations during the Run-In period are not eligible to be randomised to the double-blind Treatment Period.

Subjects who experience a severe exacerbation during the Treatment period will be withdrawn from the study. Subjects who experience a moderate exacerbation requiring the use of oral corticosteroids will also be withdrawn from the study. However, if subjects experience **one** moderate exacerbation requiring the use of antibiotics, they would be allowed to continue. Subjects experiencing more than one moderate exacerbation requiring the use of antibiotics will be withdrawn from the study. If subjects are withdrawn from the study, the withdrawal procedures should be followed as described in Section 6.4.11.

Subjects will be provided with Daily Record Cards to record exacerbations that they may experience during the course of the study.

6.2.3. Physical Examination

Visits 1, 8 and the EWV

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 Visit 8 or upon early withdrawal, the Investigator will answer the following question "Has there been a clinically significant worsening since the last assessment in the subject's physical condition? Any changes should be documented as an Adverse Event at Visit 8, or the EWV

6.2.4. Vital Signs and Temperature

Visits 2/2A, 3, 6/6A, 7, 8 and EWV

Vital Signs (blood pressure and heart rate), and temperature will be recorded at Visits 2/2A, 3, 6/6A, 7, 8 and the EWV. Vital signs (blood pressure and heart rate) will be measured after the subject has been sitting for 5 minutes.

6.2.5. Resting SaO_2

Resting SaO_2 will be measured by pulse oximetry for all subjects at Visit 1.

Subjects with SaO_2 values < 88% in room air are not eligible to participate in the study.

6.2.6. Clinical Laboratory tests [including Pre-Biopsy Blood Test for blood clotting analysis Prior to Visits 2/2A and 6/6A and EWV (if appropriate)]

Approximately 20 ml of blood and a urine sample will be collected at visit 1, 7 and/or EWV for laboratory analyses. Patients who complete the study or withdraw will have blood and urine samples collected at the Safety Follow-up Visit, only if abnormalities were observed at V7 and/or EWV. Clotting parameters (prothrombin time, thrombin time and activated partial thromboplastin time), haemoglobin concentration and platelet counts will also be measured at the hospital's local laboratory (where possible) within 4 weeks of bronchial biopsy. The Investigator is responsible for arranging with the local laboratories for these tests to be made and reported.

The following parameters will be measured:

Haematology: Haemoglobin concentration, haematocrit, red cell count, white cell count with differential, platelet count.

Clinical chemistry: Blood urea, creatinine, aspartate transaminase (ASAT/SGOT), alanine transaminase (ALAT/SGPT), gamma glutamyl-transferase (GGT), alkaline phosphatase (ALP), total protein, albumin, total bilirubin, sodium, potassium, chloride, glucose, uric acid.

Amylase will be measured at Visit 1 (Screening), Visit 7 (End of treatment), and at early withdrawal (also for patients who report gastrointestinal symptoms which are of concern to them or interfere with daily activities).

Faeces: Faecal occult blood tests will be conducted at Visits 2 and 7, and if applicable at Visits 8 (Follow-Up), and Early Withdrawal Visit (EWV) (three tests collected on consecutive bowel movements). The tests are to be performed according to the instructions provided with the faecal occult blood kits. Faecal occult blood will also be tested in patients who report gastrointestinal symptoms which are of concern to them or interfere with daily activities. **Please note that the FOB test should be done at home, prior to the designated clinic visit.**

Urinalysis: Blood, glucose, protein, ketones.

Pregnancy: Urine/Serum beta-HCG for women of childbearing potential

Urinary beta-HCG for women of child bearing potential at the Safety Follow-up Visit.

Additional laboratory tests will be performed where indicated for patients who report gastrointestinal adverse experiences, which are of concern to them or interfere with their daily activities or sleep.

All clinically significant abnormal laboratory findings are to be repeated until the values return to normal. If such values do not return to normal within a period judged reasonable by the Investigator, the aetiology should be identified and the sponsor notified. Clinically significant worsenings in laboratory findings must be recorded in the Baseline Signs and Symptoms or Adverse Experiences section of the CRF. Values outside of the reference range, but of no clinical significance, should be marked "NCS" by the Investigator on the printed laboratory report sheet. If the faecal occult blood test is positive, 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.

6.3. Efficacy

Efficacy will be assessed by:

In Biopsy

- Analysis of markers of inflammation in the sub-epithelial bronchial biopsy tissue

6.3.1. Primary

To compare the following inflammatory cells in biopsy tissue obtained from subjects treated with Cilomilast 15mg bd and to compare these in biopsy tissue obtained from subjects treated with placebo bd.

- Sub-epithelial CD68+ (macrophages) per unit area of tissue
- Sub-epithelial CD8+ (cytotoxic T-lymphocytes) per unit area of tissue

6.3.2. Secondary

To compare the number of the following sub-epithelial cells, per area of biopsy tissue from subjects treated with Cilomilast and from subjects treated with placebo:

- Neutrophil elastase positive cells (neutrophils)
- CD4+ lymphocytes
- IL-8 mRNA positive cells
- TNFα mRNA positive cells
- CD45 positive cells
- Mucin expression

In Sputum

To compare the number of the following cells in sputum per unit volume from subjects treated with **Cilomilast** and from subjects treated with placebo:

- Sputum total cell count and differential cell counts
- Macrophages as a percentage of total cells and as a total cell count per unit volume
- Eosinophils as a percentage of total cells and as a total cell count per unit volume
- Lymphocytes as a percentage of total cells and as a total cell count per unit volume
- Neutophil elastase
- IL-8 positive cells

NB: *Additional secondary efficacy variables may be analysed before the study final statistical results, depending on sample availability and results of initial analysis*

6.3.3. Tertiary Efficacy Endpoints

- Slow vital capacity (SVC)

6.3.4. Bronchial Biopsy

Bronchial biopsies will be performed prior to randomisation (Visit 2/2A, week -1) and after 12 weeks of treatment (Visit 6/6A) or 7 days after early withdrawal from the study (if possible). The full procedure is described in the Bronchial Biopsy Procedures (BBP) document. It is essential that the methodology described in the BBP document be followed precisely. The following is intended only as a summary of the procedures and should only be used in conjunction with the full methodology.

6.3.4.1. Overview and Plan

The bronchial biopsy will be performed by a physician experienced with the use of this technique in subjects with COPD, and the procedure will be standardised across all

participating centres according to a detailed protocol. **Following consent approval from a subject at the site, the physician who will be conducting biopsies for this study must take the pilot sample biopsy.**

Prior to screening the first subject at each centre, the pilot biopsy samples will be sent to the central biopsy laboratory Meakins-Christie Laboratories, McGill University Canada to confirm biopsy size and logistics. Each site must await confirmation from the Meakins-Christie Laboratories that the sample quality is acceptable before commencing the study.

The pilot biopsy samples are to be obtained once written informed consent has been obtained from subjects already undergoing a bronchial biopsy, i.e. an extra biopsy is taken. **The Hospital's local consent should be used for this purpose.**

There will be central analysis of biopsy material at **Meakins-Christie Laboratory, McGill University** Specific safety criteria on the day of bronchoscopy must be met by each subject in order for the test to proceed. The procedure will be deferred if the subject is unsuitable for bronchoscopy on the scheduled day.

6.3.4.2. Eligibility/Safety Criteria

In addition to fulfilling inclusion/exclusion criteria for the study in general, subjects must also meet the following criteria on the scheduled day of the biopsy procedure.

- Pre-salbutamol FEV_1 40-80% predicted normal value
- No history of bleeding diathesis.
- Normal platelet count (see Section 6.2.6)
- Ability to be collected by a friend/relative at the end of the biopsy procedure

Note: A "Biopsy Safety Form" should be completed and stored in the subject's notes prior to performing the bronchoscopy

6.3.4.3. Biopsy Procedure

Please see the provided Biopsy Procedure Document.

6.3.4.4. Processing of Fixed Biopsies

Please see the provided Biopsy Procedure Document.

6.3.4.5. Biopsy Processing Worksheet

All data generated during biopsy processing should be recorded on the Biopsy Processing Worksheet. This worksheet will be provided on 2-part NCR paper. When completed for a sample, the top copy will be forwarded to the central laboratory when the slides prepared for that sample are dispatched to the central laboratory.

6.3.4.6. Dispatch of Biopsy Samples

All samples will be shipped in batches using DHL or World Courier to QUEST in Heston, UK. QUEST will then forward them on to Meakins-Christie Laboratory Laboratory at the McGill University, Montreal, Canada. The samples will be analysed using the appropriate immunohistological and in-situ hybridisation techniques as described in the BBP document.

6.3.5. Sputum Induction

6.3.5.1. Overview and Plan

Sputum induction will be conducted at Visit 3 (0 weeks), Visit 7 (+13 weeks), and if applicable at EWV, a week after taking the biopsy at EWV. If the sputum sample taken at Visit 3 is unsatisfactory, no further sputum samples should be taken for this subject, but the subject will continue in the study and biopsy procedures should be performed at the scheduled visits.

The sputum will be collected and processed as described in the Sputum Procedures (SP) document. It is essential that the methodology described in the SP document be followed precisely. An induced sputum sample should be taken, as a pilot sample at each centre, (fixed slides and frozen supernatants) which will be sent via QUEST Laboratories to John Hunter Hospital, Australia to confirm sputum sample quality and logistics. Each site must await confirmation from the John Hunter Hospital, Australia that the sample quality is acceptable prior to induction, and processing of any recruited subject sample.

It is essential that all sites adhere strictly to the standard procedure for sputum processing. Sputum samples should only be processed by appropriately qualified laboratory staff who have been trained in conducting the procedure.

The following is intended only as summary of the procedures and should only be used in conjunction with the full methodology as described in the SP document:

6.3.5.2. Procedure for Sputum Processing

Please see the provided Sputum Procedure Document.

6.3.5.3. Personnel

Sputum samples should only be processed by appropriately qualified laboratory trained staff with experience conducting the procedure. The CVs of all persons that will be processing the samples should be submitted to GSK for review prior to processing any samples obtained in the study.

6.3.5.4. Sputum Processing Worksheet

All data generated during sputum processing should be recorded on the Sputum Processing Worksheet. This worksheet will be provided on 2-part NCR paper. When

completed for a sample, the top copy will be forwarded to the central laboratory when the slides prepared for that sample are dispatched to the central laboratory.

6.3.5.5. Dispatch of Samples

Fixed slides and frozen samples of sputum supernatant will be shipped from sites in batches using the QUEST Laboratories designated courier (either DHL or World Courier) to QUEST Laboratories in Heston, UK. QUEST Laboratories will then forward the samples to the John Hunter Hospital, Australia. The exception to this is where the samples are produced in the same hospital to where they are analysed. The slides will be stained and counted at the John Hunter Hospital, Australia and the supernatants processed according to the methodology in the SP Document.

6.3.6. Blinding Issues

To prevent the potential for reader bias based on knowledge of visit number; the sputum slides produced for each subject visit will be assigned a random code number generated by GSK (a Slide Identification Number). The biopsy tissue blocks for each subject will be identified by a unique number, generated by the Meakins-Christie Laboratory and the code will be kept blind to personnel involved in the counting of the cells.

6.3.7. Pulmonary Function Tests (PFTs)

Throughout the study, it is preferable that for any individual subject at all study visits the same pulmonologist, technician or nurse administers pulmonary function tests, in order to ensure consistency of technique.

Forced expiratory volume in 1 second (FEV_1) forced vital capacity (FVC), slow vital capacity (SVC), and FEV_1/FVC ratio will be measured according to the BTPS (Body Temperature and Pressure Standard) convention. The spirometer should be calibrated and maintained to acceptable respiratory function laboratory standards [ERS Consensus Statement, 1995; Standardisation of Lung Function Tests, 1993]. At each assessment, PFTs will be performed three times. For each set of three FVC, SVC, and FEV_1 measurements, the highest measurement must be taken.

Hand held spirometers should be used during the sputum induction process and for the biopsy procedure.

6.3.7.1. Pulmonary Function Test and Reversibility

Visit 1

At visit 1, the highest of 3 technically acceptable measurements of FEV_1 will be recorded before and 30 minutes after inhalation of 400mcg salbutamol delivered via an MDI inhaler and a **VOLUMATIC** spacer. Subjects should have refrained from taking short acting $beta_2$-agonists and anticholinergics for at least 6 hours before the visit. The % predicted normal value for FEV_1 would be calculated and recorded in the CRF using the highest of the 3 measurements.

- All predicted normal values will be taken from the ECCS tables provided [Standardisation of Lung Function Tests, 1993]. At Visit 1, reversibility will be calculated as a percentage of the predicted normal FEV_1 using the following formula:

$$\textbf{Reversibility} = \left[\frac{\textbf{Highest Post-bronchodilator } FEV_1 \textbf{ - Highest Pre-bronchodilator } FEV_1}{\textbf{Predicted normal } FEV_1}\right] \times 100$$

- In addition to FEV_1, FVC and SVC measurements, both pre and post 400mcg salbutamol will also be recorded in the CRF.

6.3.7.2. Subject Eligibility Prior to Randomisation

Subjects must meet the following criteria, before being randomised at Visit 3

- A reversibility defined as ≤10% increase in FEV_1 as a percentage of the predicted normal value OR <200mls absolute improvement, 30 minutes following inhalation of 400mcg salbutamol via the MDI and a **VOLUMATIC** spacer, must be demonstrated at Visit 1.

6.3.7.3. Pulmonary Function Tests

All other Visits (except Visit 1)

- For all other visits, pulmonary function test (SVC) will be assessed more than 6 hours after the last dose of salbutamol and/or ipratropium bromide or Combivent. Subjects will also be asked to refrain from smoking in the 2 hours before their PFTs.
- SVC will be performed both pre-and post salbutamol.
- In addition, at Visits 2/2A and 6/6A and at EWV (if applicable), before the biopsy procedures, FEV_1 (before and after the administration of salbutamol 400mcg via an MDI and a **VOLUMATIC** spacer) will be measured and the results recorded in the Biopsy Safety Form. FVC data generated while measuring the FEV_1 should be recorded in the subject's source notes.
- At Visits 3 and 7, FEV_1 (before and after the administration of salbutamol 400mcg via an MDI and a **VOLUMATIC** spacer) will be measured as part of the sputum induction procedure. These results are not recorded in the CRF but are kept with the subject's source notes.

6.3.7.4. Spirometry Procedures

- Before Visit 1 only, subjects should refrain from using their short-acting bronchodilators (e.g. **VENTOLIN**†) and their anticholinergics including Combivent for at least 6 hours.

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† **VENTOLIN** is a Trademark of the GlaxoSmithKline Group of Companies. Registered in US Patent and Trademark Office.

- Where possible pulmonary function measurements should be performed at the same time of day under BTPS conditions using the same spirometer at each visit. The subject should be in the same position (i.e. sitting or standing) at each visit.
- The spirometer should be regularly calibrated according to the manufacturer's recommendations. The calibration logs should be stored.
- It is mandatory to use spirometers that can print out a hard copy of the FEV_1measurements.
- All spirometer printouts (at each spirometry measurement) should be kept in the subject's notes and labelled appropriately with the subject number, clinic visit and date and time of measurement. It should also be initialled and dated by the person generating the data. The person generating the data, should also sign and date all the hard copies of all the traces which should then be kept with the subject's notes.

6.4. Outline of Study Procedures at Each Visit

A table showing the study assessments and timing of these assessments is provided in the Time and Events Schedule in Appendix 1. Details of the assessments performed at each visit are given below.

For each scheduled study visit, subjects will be required to attend the clinic in the morning, at the same time and after breakfast (except on the days when biopsies are taken where they will not have breakfast before the biopsy). Clinic visits should be scheduled at the same time of day (± 2 hours) and should be conducted preferably in the morning.

Smoking and the use of relief medication must be avoided during the clinic stay if at all possible.

Each subject will be provided with a Run-In and Treatment Daily Record Card(s) for use during the study. During the Run-In and the Treatment periods, subjects will be asked to record any exacerbations that they may experience. During the Treatment period, subjects will be required to record their compliance of the study medication. The Daily Record Card (DRC) data will not be databased, although relevant information from the DRC regarding exacerbations and compliance will be recorded in the CRF.

6.4.1. Visit 1: Screening and Start of the 4-Week Run-In Period

Subjects considered by the investigator, as potential candidates for entry into the study will attend the clinic for a screening visit. They should have refrained from taking their $beta_2$-agonists and short-acting anticholinergics including Combivent for at least 6 hours prior to the clinic visit. If this is not the case, a 6-hour period should elapse before pulmonary function tests are performed. Subjects will be asked to stop taking their relief short acting $beta_2$-agonist and/or short acting anticholinergic or Combivent medication at Visit 1 and will be provided with salbutamol and/or ipratropium bromide or Combivent for the duration of the study.

The following procedures will be conducted at Visit 1:

- Written informed consent will be obtained, before the patient is asked to stop taking any medication mentioned in Section 5.2.2 Exclusion Criteria number 11.
- Any adverse event that the subject may experience from the time consent is obtained from the subject. AEs may include pre or post-treatment events that occur as a result of protocol mandated procedures (i.e.invasive procedures, modifications of the subject's previous therapeutic regimen). Adverse events will be recorded in the Adverse Event Section of the CRF and followed up, as appropriate (see Section 10).
- A full medical history and surgical history. A physical examination including (height and weight, respiratory examination) as well as a full examination of major organ systems will be performed (see Section 6.2.3)
- Cigarette smoking history and smoking status will be recorded (see Section 6.1.3)
- COPD history and duration, (including history and duration of chronic bronchitis), demography (see Section 6.1.1)
- Resting SaO_2 will be measured by pulse oximetry (see Section 6.2.5)
- Chest X-ray: The investigator will review a current postero-anterior (P-A) chest radiograph (performed within 9 weeks prior to Visit 1). If a prior film is not available for review by the Investigator, a new film should be obtained and results must be available at Visit 2 prior to the biopsy. Review of written reports without the accompanying films is not acceptable (see Section 6.1.2)
- An assessment of COPD exacerbations will be made. Subjects with poorly controlled COPD, defined as the occurrence of moderate or severe exacerbations (see Section 6.2.2.1) are not eligible to participate
- All medication for COPD, taken during the 12 weeks preceding this visit will be recorded together with all other medication taken during 4 weeks preceding this visit. For prohibited respiratory medications see Section 8.2. All oral/inhaled corticosteroids, long-acting anticolinergics, and xanthines must have been withdrawn at least 4 weeks before the start of Visit 1. Subjects must have stopped all inhaled, oral and nebulised long acting $beta_2$-agonists 2 weeks before the start of Visit 1.

At least 6 hours after the subject's last $beta_2$-agonist administration,

- PFTs will be performed and salbutamol reversibility will be calculated (see Section 6.3.7.1)

Following completion of the above procedures, a checklist of the inclusion and exclusion criteria will be completed.

- Clinical laboratory tests [Chemistry, Haematology, Urinalysis and pregnancy testing for females of childbearing potential]. All clinically significant abnormal laboratory findings are to be repeated until the values return to normal.
- A blood sample will be taken for pre-biopsy analysing of blood clotting tests, prior to Visit 2. Samples are to be processed at the site where possible and results must be available before the biopsy procedure is conducted.

- Issue study run-in medication, salbutamol and/or ipratropium bromide or Combivent as relief medication as appropriate (see Section 8.1)
- Issue the subject with Run-In Daily Record Card and explain how to record exacerbations and relief medication
- Telephone RAMOS, specify the subject number and RAMOS will register the subject into the study
- Issue the FOB kit, and ask the subject to bring the test sample to the next visit

Reminders

- Subjects will be asked to return to the clinic for Visit 2 (Week -1) in 21 ±3 days at the same time of day and reminded:
  - To take their salbutamol and/or ipratropium bromide or Combivent as prescribed. If the subject experiences symptoms that do not respond adequately to salbutamol and/or ipratropium bromide or Combivent , the subject must contact the investigator
  - **Not** to eat or drink anything for 8 hours before the bronchial biopsy at Visit 2
  - **Not** to use Aspirin/NSAIDs in the 5-day period before Visit 2
  - To refrain from using their salbutamol and/or ipratropium bromide or Combivent medication for at least 6 hours immediately preceding Visit 2
  - To refrain from smoking for 2 hours immediately preceding the next visit
  - To bring any remaining salbutamol and/or ipratropium bromide or Combivent medication with them to Visit 2
  - To bring their Run-In Daily Record Card , and the run-in medication to Visit 2

6.4.2. Visit 2 (Week -1): Continuation of the 4-Week Run-In Period

At Visit 2, the following assessments will be completed:

- Document the date and time of the subject's last dose of salbutamol and/or ipratropium bromide or Combivent, immediately preceding the visit (subject should not be taking this medication in the morning of the clinic visit, or the last dose must have been taken 6 hours before the clinic visit).
- If the subject is a current smoker, document if the subject has smoked during the 2 hours preceding the visit (see Section 6.1.3)
- Any adverse experiences, which have occurred, will be recorded in the Adverse Event section of the CRF and followed up, as appropriate (see Section 10)
- Any changes or additions to the subject's concomitant medication or additions to medical procedures will be recorded in the CRF (see Section 8)
- A COPD exacerbation assessment will be made to determine if the subject has experienced any exacerbations during the period between Visits 1 and 2. Check the

DRC for any record of exacerbations. Subjects who experience moderate or severe exacerbations during the Run-In period are not eligible to be randomised to the double-blind Treatment Period.

- Review a current postero-anterior (P-A) chest radiograph (performed within 9 weeks prior to Visit 1) if not previously reviewed. Review of written reports without accompanying films is not acceptable (see Section 6.1.2)
- For any subject who discontinues from the study, the End of Study Record page in the CRF should be completed

At least 6 hours after the subject's last salbutamol and/or ipratropium bromide or Combivent medication

- Vital signs will be measured after the subject has been sitting for 5 minutes (see Section 6.2.4)
- SVC will be performed (see Section 6.3.7.3)
- FOB test should be assessed
- A bronchial biopsy will be performed (only if safety criteria listed in the BBP document and in Section 6.3.4.2 are met, otherwise the biopsy procedure should be rescheduled within 1 to 7 days (Visit 2A)
- Issue relief medication, salbutamol and/or ipratropium bromide or Combivent as appropriate (see Section 8.1)
- Ask the subject to record any exacerbations in the Run-In Daily Record Card
- Check study run-in medication compliance

Reminders If Biopsy is not Rescheduled

- Subjects will be asked to return to the clinic for Visit 3 in 7±3 days at the same time of day. Subjects will be reminded:
  - To take their salbutamol and/or ipratropium bromide or Combivent as prescribed. If the subject experiences symptoms that do not respond adequately to salbutamol and/or ipratropium bromide or Combivent, the subject must contact the investigator
  - To refrain from using their salbutamol and/or ipratropium bromide or Combivent medication for at least 6 hours immediately preceding Visit 3
  - To refrain from smoking for **2** hours immediately preceding Visit 3
  - To bring their salbutamol and/or ipratropium bromide medication or Combivent medication with them to Visit 3
  - To bring their Run-In DRC to Visit 3

Reminders If Biopsy is Rescheduled for Visit 2A

- Subjects will be asked to return to the clinic for Visit 2A in 7 (± 3) days at the same time of day. Subjects will be reminded:

- To take their salbutamol and/or ipratropium bromide or Combivent as prescribed. If the subject experiences symptoms that do not respond adequately to salbutamol and/or ipratropium bromide or Combivent, the subject must contact the investigator
- To refrain from using their salbutamol and/or ipratropium bromide or Combivent medication for 6 hours immediately preceding Visit 2A
- To refrain from smoking for 2 hours immediately preceding Visit 2A
- **Not** to eat or drink anything for 8 hours before the bronchial biopsy at Visit 2A
- **Not** to use Aspirin/NSAIDs in the 5-day period before Visit 2A
- To bring the salbutamol and/or ipratropium bromide or Combivent medication with them to Visit 2A
- To bring their Run-In Daily Record Card to Visit 2A, and the run-in medication

6.4.3. Visit 2A (Only if Biopsy Has Been Rescheduled)

The same procedures, and reminders as outlined in visit 2 should be completed, and followed.

Note: If results of any assessment made at Baseline (Visit 2/2A) are not available at the time of assessment and subsequently preclude continuation in the study, the subject must be withdrawn immediately and a safety Follow-Up visit scheduled (see Section 6.4.11)

6.4.4. Visit 3 (Week 0): Start of the Double-Blind Treatment

The following assessments will be made **BEFORE** the first dose of double-blind study medication is inhaled in the clinic.

- Document the date and time of the subject's last dose of salbutamol and/or ipratropium bromide or Combivent, immediately preceding the visit (subject should not be taking this medication in the morning of the clinic visit, or the last dose must have been taken 6 hours before the clinic visit).
- If the subject is a current smoker, document if the subject has smoked during the 2 hours preceding this visit
- Any adverse experiences, which have occurred since the last visit, will be recorded on the Adverse Event Section of the CRF and followed up, as appropriate (see Section 10).
- Any changes or additions to the subject's concomitant medication or additions to medical procedures will be recorded in the CRF (see Section 8).
- A COPD exacerbation assessment will be made to determine if the subject has experienced any exacerbations during the period between Visits 2/2A and 3. Check the Run-In DRC for any record of exacerbations. Subjects who experience moderate or severe exacerbations during the Run-In period are not eligible to be randomised to the double-blind Treatment Period(see Section 6.2.2.1).

- For subjects who discontinue from the study, the End of Study Record page in the CRF should be completed.
- Check study run-in medication compliance.

At least 6 hours after the subject's last salbutamol and/or ipratropium bromide or Combivent medication:

- *Vital signs will be measured after the subject has been sitting for 5 minutes* (Section 6.2.4)
- SVC will be performed (see Section 6.3.7.3)
- Sputum induction and sample preparation will be performed (see SP document)

Randomisation Criteria

If the subject meets the Randomisation Criteria in Section 5.2.3, the following assessments will be made:

- Telephone RAMOS and specify the subject number (the number shown on the subject's CRF.
- RAMOS will randomise the subject, assign a random number and will read the appropriate container number for each of the 4 bottles to be dispensed to the subject for the duration of the treatment period. Each random number and container number must only be allocated by RAMOS. The investigator is advised to give the subject one bottle at each of the visits during the treatment period, rather than give all 4 bottles to the subject at this visit. If the subject were likely to delay his/her next visit for some reason, it would be appropriate to provide another bottle at the discretion of the investigator. The subject should be reminded to use the bottles sequentially
- Issue relief medication, salbutamol and/or ipratropium bromide or Combivent as appropriate (see Section 8.1)
- The first dose of double-blind study treatment will be taken by the subject in the clinic and this will be recorded in the CRF and in the subject's DRC.

Subjects who do not meet the randomisation criteria must be withdrawn from the study.

Reminders:

- Subjects will be asked to return to the clinic for Visit 4 (Week +4) in 28 ±3 days at the same time of day and reminded:
  - To take their study medication as demonstrated. **Not to take** their morning dose of study medication at home on the morning of their next clinic visit, but to bring their medication with them to the clinic
  - Issue relief medication, salbutamol and/or ipratropium bromide or Combivent as appropriate (see Section 8.1)

- To refrain from using their salbutamol and/or ipratropium bromide or Combivent for at least 6 hours immediately preceding Visit 4 (subject should not be taking this medication in the morning of the clinic visit, or the last dose must have been taken 6 hours before the clinic visit).
- To refrain from smoking for **2** hours immediately preceding Visit 4
- To bring any remaining study medication, salbutamol and/or ipratropium bromide or Combivent medication with them to Visit 4
- Issue the subject with a Treatment DRC and explain how to record the use of the study medication and to record any exacerbations. Remind the subject to bring the Treatment DRC to Visit 4

- If the subject is withdrawing at this visit, the subject should complete all scheduled visit assessments for this visit. A safety Follow-Up visit should be scheduled for 7±3 days) later (see Section 6.4.11)

6.4.5. Visit 4: (Week 4 of the Double-Blind Treatment Period)

At Visit 4, the following procedures will be completed:

- Document the date and time of the subject's last dose of salbutamol and/or ipratropium bromide or Combivent, immediately preceding the visit (subject should not be taking this medication in the morning of the clinic visit, or the last dose must have been taken 6 hours before the clinic visit).
- If the subject is a current smoker, document if the subject has smoked during the 2 hours preceding this visit
- Any adverse experiences, which have occurred since the last visit, will be recorded on the Adverse Event Section of the CRF and followed up, as appropriate (Section 10).
- Any changes or additions to the subject's concomitant medication or additions to medical procedures will be recorded in the CRF (see Section 8).
- A COPD exacerbation assessment will be made to determine if the subject has experienced any exacerbations during the period between Visits 3 and 4. Check the Treatment DRC for any record of exacerbations (see Section 6.2.2.1).
- SVC will be performed (see Section 6.3.7.3)
- Issue relief medication, salbutamol and/or ipratropium bromide or Combivent as appropriate (see Section 8.1)
- Check study medication compliance against the DRC. To continue in the study, subjects **must show ≥ 80% and ≤ 120% compliance in taking their study medication.** Subjects who do not meet this criterion should be withdrawn from the study.

Reminders:

- Subjects will be asked to return to the clinic for Visit 5 (Week 8) in 56±3 days at the same time of day and reminded:

- To take their study medication as demonstrated. **Not to take** their morning dose of study medication at home on the morning of their next clinic visit, but to bring their medication with them to the clinic
- To take their salbutamol and/or ipratropium bromide or Combivent as prescribed. If the subject experiences symptoms that do not respond adequately to salbutamol and/or ipratropium bromide or Combivent, the subject must contact the investigator
- To refrain from using their salbutamol and/or ipratropium bromide or Combivent for at least the 6 hours immediately preceding Visit 5
- To refrain from smoking for **2** hours immediately preceding Visit 5
- To bring any remaining study medication, salbutamol and/or ipratropium bromide or Combivent medication with them to Visit 5
- Issue the subject with a new Treatment DRC. Ask the subject to record the use of the study medication and to record any exacerbations. Remind the subject to bring the Treatment DRC to Visit 5

- For subjects who discontinue from the study, the End of Study Record page in the CRF should be completed.
- If the subject is withdrawing at this visit, the subject should complete all scheduled visit assessments for this visit. A safety Follow-Up visit should be scheduled for 7±3 days after discontinuation of the study medication (see Section 6.4.11)

6.4.6. Visit 5: (Week 8 of the Double-Blind Treatment Period)

At Visit 5, the following procedures will be completed:

- Document the date and time of the subject's last dose of salbutamol and/or ipratropium bromide or Combivent, immediately preceding the visit.
- If the subject is a current smoker, document if the subject has smoked during the 2 hours preceding this visit
- Any adverse experiences, which have occurred since the last visit, will be recorded on the Adverse Event Section of the CRF and followed up, as appropriate (see Section 10).
- Any changes or additions to the subject's concomitant medication or additions to medical procedures will be recorded in the CRF (see Section 8).
- A COPD exacerbation assessment will be made to determine if the subject has experienced any exacerbations during the period between Visits 4 and 5. Check the Treatment DRC for any record of exacerbations (see Section 6.2.2.1)
- SVC will be performed (see Section 6.3.7.3)
- Check study medication compliance against the DRC. To continue in the study, subjects **must show ≥ 80% and ≤ 120% compliance in taking their study**

medication. Subjects who do not meet this criterion should be withdrawn from the study.

- Issue relief medication, salbutamol and/or ipratropium bromide or Combivent as appropriate (see Section 8.1)
- Collect any used study medication

Reminders:

- Subjects will be asked to return to the clinic for Visit 6 (Week +12) in 84 ±3 days at the same time of day and reminded:
  - To take their study medication as demonstrated. **Not to take** their morning dose of study medication at home on the morning of their next clinic visit, but to bring their medication with them to the clinic
  - To take their salbutamol and/or ipratropium bromide or Combivent medication as prescribed. If the subject experiences symptoms that do not respond adequately to salbutamol and/or ipratropium bromide or Combivent , the subject must contact the investigator
  - **Not** to eat or drink anything for 8 hours before the bronchial biopsy at Visit 6
  - **Not** to use Aspirin/NSAIDs in the 5-day period before Visit 6
  - To refrain from using their salbutamol and/or ipratropium bromide or Combivent medication for 6 hours immediately preceding Visit 6
  - To refrain from smoking for **2** hours immediately preceding Visit 6
  - To bring any remaining study medication, salbutamol and/or ipratropium bromide or Combivent medication to Visit 6
  - Ask the subject to record the use of the study medication and to record any exacerbations. Remind the subject to bring the Treatment DRC to Visit 6
- For subjects who discontinue from the study, the End of Study Record page in the CRF should be completed.
- If the subject is withdrawing at this visit, the subject should complete all scheduled visit assessments for this visit. A safety Follow-Up visit should be scheduled for 7±3 days after discontinuation of the study medication (see Section 6.4.11)
- **Note:** Subjects will be asked to provide a blood sample for pre-biopsy analysis of blood clotting test within 4 weeks prior to Visit 6. **Samples are to be processed at the site where possible and results must be available before the biopsy procedure is conducted.**

6.4.7. Visit 6: (Week 12 of the Double-Blind Treatment Period)

At Visit 6, the following procedures will be completed:

- Document the date and time of the subject's last dose of salbutamol and/or ipratropium bromide or Combivent, immediately preceding the visit (subject should

not be taking this medication in the morning of the clinic visit, or the last dose must have been taken 6 hours before the clinic visit).

- If the subject is a current smoker, document if the subject has smoked during the 2 hours preceding this visit
- Any adverse experiences, which have occurred since the last visit, will be recorded on the Adverse Event Section of the CRF and followed up, as appropriate (Section 10).
- Any changes or additions to the subject's concomitant medication or additions to medical procedures will be recorded in the CRF (see Section 8).
- A COPD exacerbation assessment will be made to determine if the subject has experienced any exacerbations during the period between Visits 5 and 6. Check the Treatment DRC for any record of exacerbations (see Section 6.2.2.1)
- Check study medication compliance against the Treatment DRC.
- For any subject who discontinues from the study, the End of Study Record page in the CRF should be completed (see Section 6.4.11)

At least 6 hours after the subject's last salbutamol and/or ipratropium bromide or Combivent medication:

- Vital signs will be measured after the subject has been sitting for 5 minutes (see Section 6.2.4)
- SVC will be performed (see Section 6.3.7.3)
- A bronchial biopsy will be performed **(only if safety criteria listed in the BBP document and in Section 6.3.4.2 are met, otherwise the biopsy procedure should be rescheduled within 1 to 7 days (Visit 6A)**
- Issue relief medication, salbutamol and/or ipratropium bromide or Combivent as appropriate (see Section 8.1)
- Issue the FOB kit and ask the subject to bring the test sample to the next visit.

Reminders If Biopsy is not Rescheduled:

- Subjects will be asked to return to the clinic for Visit 7 (Week 13) in 91±3 days at the same time of day and reminded:
  - To take their study medication as demonstrated. **Not to take** their morning dose of study medication at home on the morning of their next clinic visit, but to bring their medication with them to the clinic
  - To take their salbutamol and/or ipratropium bromide or Combivent as prescribed. If the subject experiences symptoms that do not respond adequately to salbutamol and/or ipratropium bromide or Combivent, the subject must contact the investigator
  - To refrain from using their salbutamol and/or ipratropium bromide or Combivent for at least 6 hours immediately preceding Visit 7
  - To refrain from smoking for **2** hours immediately preceding Visit 7

  - To bring any remaining study medication, salbutamol and/or ipratropium bromide or Combivent with them to Visit 7
  - Ask the subject to record the use of the study medication and any exacerbations. Remind the subject to bring the Treatment DRC to Visit 7
- For subjects who discontinue from the study, the End of Study Record page in the CRF should be completed.
- If the subject is withdrawing at this visit, the subject should complete all scheduled visit assessments for this visit. A safety Follow-Up visit should be scheduled for 7±3 days after discontinuation of the study medication (see Section 6.4.11)

Reminders: If Biopsy is Rescheduled for Visit 6A:

- Subjects will be asked to return to the clinic for Visit 6A in 7±3 days at the same time of the day. Subjects will be reminded :
  - To take their study medication as demonstrated. **Not to take** their morning dose of study medication at home on the morning of their next clinic visit, but to bring their medication with them to the clinic
  - To take their salbutamol and/or ipratropium bromide or Combivent medication as prescribed. If the subject experiences symptoms that do not respond adequately to salbutamol and/or ipratropium bromide or Combivent, the subject must contact the investigator
  - **Not** to eat or drink anything for 8 hours before the bronchial biopsy at Visit 6A
  - **Not** to use Aspirin/NSAIDs in the 5-day period before Visit 6A
  - To refrain from using their salbutamol and/or ipratropium bromide or Combivent medication for 6 hours immediately preceding Visit 6A
  - To refrain from smoking for **2** hours immediately preceding Visit 6A
  - To bring any remaining study medication, salbutamol and/or ipratropium bromide or Combivent medication with them to Visit 6A
  - Ask the subject to record the use of the study medication and to record any exacerbations. Remind the subject to bring the Treatment Daily Record Card to Visit 6A
- For subjects who discontinue from the study, the End of Study Record page in the CRF should be completed.
- If the subject is withdrawing at this visit, the subject should complete all scheduled visit assessments for this visit. A safety Follow-Up visit should be scheduled for 7±3 days after discontinuation of the study medication (see Section 6.4.10)

6.4.8. Visit 6A (Only if Biopsy Has Been Rescheduled)

- The same procedures and reminders as outlined in visit 6 should be completed, and followed.

- If the subject is withdrawing at this visit, the subject should complete all scheduled visit assessments for this visit. A safety Follow-Up visit should be scheduled for 7±3 days after discontinuation of the study medication (see Section 6.4.11)

6.4.9. Visit 7: (Week 13 - End of the Double-Blind Treatment Period)

At Visit 7, the following procedures will be completed:

- Document the date and time of the subject's last dose of salbutamol and/or ipratropium bromide or Combivent, immediately preceding the visit (subject should not be taking this medication in the morning of the clinic visit, or the last dose must have been taken 6 hours before the clinic visit).
- If the subject is a current smoker, document if the subject has smoked during the 2 hours preceding this visit
- Any adverse experiences, which have occurred since the last visit, will be recorded on the Adverse Event Section of the CRF and followed up, as appropriate (Section 10) Any changes or additions to the subject's concomitant medication or additions to medical procedures will be recorded in the CRF (see Section 8).
- A COPD exacerbation assessment will be made to determine if the subject has experienced any exacerbations during the period between Visits 6 and 7. Check the Treatment DRC for any record of exacerbations (see Section 6.2.2.1)
- Collect the remaining study medication
- Check study medication compliance against the Treatment DRC.

At least 6 hours after the subjects last salbutamol and/or ipratropium bromide or Combivent administration:

- Vital signs will be measured after the subject has been sitting for 5 minutes (see Section 6.2.4)
- Clinical laboratory tests [Chemistry, Haematology, Urinalysis, Faecal Occult Blood test (FOB), and pregnancy testing for females of childbearing potential]. All clinically significant abnormal laboratory findings are to be repeated until the values return to normal
- Issue the FOB kit only if a repeat sample is required, and if so, ask the subject to bring the test sample to the next visit
- SVC will be performed (see Section 6.3.7.3)
- Issue relief medication, salbutamol and/or ipratropium bromide or Combivent as appropriate (see Section 8.1)
- Sputum induction and sample preparation will be performed (see SP document and Section 6.3.5)

Reminders:

- Subjects will be asked to return to the clinic for Visit 8 (Week +14) in 98±3 days at the same time of day and reminded:
  - To take their salbutamol and/or ipratropium bromide or Combivent as prescribed. If the subject experiences symptoms that do not respond adequately to salbutamol and/or ipratropium bromide or Combivent, the subject must contact the investigator
  - To resume their usual COPD medication
  - To refrain from using their salbutamol and/or ipratropium bromide or Combivent medication during the 6 hours immediately preceding Visit 8
  - To refrain from taking any other COPD medication for at least 6 hours immediately preceding Visit 8
- For subjects who discontinue from the study, the End of Study Record page in the CRF should be completed.
- If the subject is withdrawing at this visit, the subject should complete all scheduled visit assessments for this visit. A safety Follow-Up visit should be scheduled for 7±3 days after discontinuation of the study medication (see Section 6.4.11)

6.4.10. Visit 8: Safety Follow-Up Visit

A safety Follow-Up visit (Visit 8, Week +14) in 98 ±3 days is required for all subjects who **complete the study at Visit 7** (end of the double-blind period) and any subject who **withdraws from the double-blind therapy prior to completion of Week 13.** This visit will occur 7 ±3 days after Week 13 or following the EWV. Subjects will be asked to refrain from using salbutamol and/or ipratropium bromide or Combivent medication (or other COPD medication) for at least 6 hours and from smoking during the 2 hours immediately preceding the Follow-Up visit.

At Visit 8, the following procedures will be completed:

- Document the date and time of the subject's last dose of salbutamol and/or ipratropium bromide or Combivent, immediately preceding the visit (subject should not be taking this medication in the morning of the clinic visit, or the last dose must have been taken 6 hours before the clinic visit).
- Any adverse experiences, which have occurred since the last visit, will be recorded on the Adverse Event Section of the CRF and followed up, as appropriate (see Section 10)
- Any changes or additions to the subject's concomitant medication or additions to medical procedures will be recorded in the CRF (see Section 8)
- A COPD exacerbation assessment will be made to determine if the subject has experienced any exacerbations during the period between Visits 7 and 8

- A physical examination including (respiratory examination) as well as a full examination of major organ systems will be performed (see Section 6.2.3)
- Telephone RAMOS and specify the subject number and record Follow-Up visit

At least 6 hours after the subjects last salbutamol and/or ipratropium bromide or Combivent and/or other COPD administration:

- Vital signs will be measured after the subject has been sitting for 5 minutes (Section 6.2.4)
- SVC will be performed (see Section 6.3.7.3)
- FOB test should be assessed if applicable
- All clinically significant abnormal laboratory findings from V7 or EWV should be repeated at this visit, and until the values return to normal

6.4.11. Early Withdrawal Visit

Randomised subjects who withdraw from the study at a scheduled visit should complete the assessments scheduled at that visit.

A physical examination, including a respiratory examination and temperature measurement, and clinical laboratory tests will be performed, if not already included in the scheduled visit assessments. Call RAMOS, specify the subject number and log the subject as withdrawn.

If the subject is withdrawing at visits 4, or 5 a bronchial biopsy should be performed 1 week after the withdrawal visit as long as all the safety criteria in Section 6.3.4.2 and in the Bronchial Biopsy Procedures document are met. If possible, sputum induction should be performed 7 days later if possible.

Subjects who withdraw from the study between scheduled clinic visits will be instructed to return to the clinic within 24 hours of stopping study medication for an EWV. At this visit, subjects will complete the following: SVC, vital signs, physical examination, and clinical laboratory tests (including FOB test if applicable). Medication compliance, concomitant medications, adverse events and smoking status will be evaluated, and 1 week after the EWV the biopsy and/or sputum should be performed if possible.

A safety Follow-Up visit is required for all subjects who withdraw from the study following the start of the double-blind medication and before completion of the assessments up to and including those scheduled at Week 13. This assessment should be performed 7 ±3 days after discontinuation of study medication (Section 6.4.11).

7. INVESTIGATIONAL PRODUCT(S)

7.1. Description of Investigational Product

GSK will supply the following investigational products for this study:

Cilomilast (SB 207499) will be provided as an yellow, round, convex tablet containing 15 mg of SB 207499. Matching placebo tablets will also be provided.

7.1.1. Rescue Medication

The following rescue medication will be provided for use during the Run-In period and the 13-Week Treatment period.

- Salbutamol and/or ipratropium bromide or Combivent will be provided as relief medication for the duration of the study
- Salbutamol and/or ipratropium bromide or Combivent via the nebuliser will be provided for use before the bronchial biopsy procedure

7.2. Dosage and Administration

Subjects who fulfil the Randomisation Criteria will enter a 13-week double-blind treatment phase. Subjects will be randomised to receive either Cilomilast (SB 207499) 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. Subjects will be reminded **not to take their morning dose of study medication** at home on Clinic Visit days, but to bring their study medication with them to the clinic.

7.3. Dose Rationale

A randomized, 24-week, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy, safety and tolerability of Ariflo (15 mg twice daily) in patients with chronic obstructive pulmonary disease (COPD) (SB 207499/039)

The primary objectives were to demonstrate the clinical efficacy of SB 207499 15 mg twice daily versus placebo by assessment of forced expiratory volume in 1 second (FEV1) at trough and of the total score of the St. George's Respiratory Questionnaire (SGRQ) over 24 weeks in patients with COPD. Secondary measures of efficacy were post-exercise breathlessness, summary symptom score, clinic FVC at trough, exercise performance (6-minute walk test), and COPD exacerbation rates. COPD exacerbations were defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy . COPD exacerbations were categorized as Level 1, 2, or 3, based on the treatment received by the patient.

This study provides definitive evidence of efficacy for SB 207499 15 mg twice daily over a 24-week treatment period in patients with COPD. SB 207499 was shown to have

statistically significant effects on the co-primary endpoints of change from baseline averaged over 24 weeks in trough FEV1 and in SGRQ.

A 6 week multicenter, double-blind, placebo-controlled, parallel group study to determine the safety, tolerability and efficacy of oral SB 207499 (5, 10 and 15 mg bid) as therapy in out-patients with chronic obstructive pulmonary disease (COPD) (SB 207499/032)

The primary efficacy variable was pre-bronchodilator FEV1 measured at trough drug levels at study endpoint. Secondary efficacy variables were other tests of pulmonary function (FVC, PEFR, FEF25-75, FEF75), first dose effects on pulmonary function tests, exercise tolerance test, use of beta-2 agonists, dyspnea during usual daily activities, other symptoms of COPD, SaO2 at rest, COPD exacerbation and Quality of Life assessments (St. George's Hospital Respiratory Questionnaire (SGRQ) and SF-36).

At a dose of 15 mg bid, SB 207499 was statistically superior to placebo with respect to improvements in pulmonary function in patients with COPD. The superiority of the 15 mg bid regimen was supported by positive trends in symptoms (dyspnea), quality of life and a significant reduction in beta-2 agonist use. Although a greater degree of benefit was observed with 15 mg bid than with the other dosages of SB 207499, no clear dose ordering was observed.

7.4. Blinding

Cilomilast (SB 207499) 15 mg tablets and SB 207499-matched placebo tablets will be identical in appearance and the double-blind medication drug labels will identify only the container number.

All medication for randomised subjects will be blinded to both the investigator and the subject. The blind will be maintained by GSK who will maintain an updated copy of the master randomisation code.

Individual subject code breaks will be provided to the Investigator with the study medication. These will identify the container number and the corresponding treatment allocation.

Only in the case of an emergency, when knowledge of the investigational product is essential for the clinical management or welfare of the subject, the investigator may unblind a subject's treatment assignment. If the blind is broken for any reason, the investigator must notify GSK **immediately** of the unblinding incident without revealing the subject's study treatment assignment. In addition, the investigator will record the date and reason for revealing the blinded treatment assignment for that subject in the appropriate CRF.

If a serious adverse event (SAE; as defined in Section 10.2, "Definition of a SAE") is reported to GSK, Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for the individual subject. If an expedited regulatory report to one or more regulatory agencies is required, the report will identify the subject's

treatment assignment. When applicable, a copy of the regulatory report may be sent to investigators in accordance with relevant regulations, GSK policy, or both.

7.5. Treatment Assignment

Once the Run-In period has been successfully completed at Visit 3/3A, eligible subjects will be assigned to a study treatment in accordance with the central randomisation schedule. Randomisation will be balanced at site level. GSK's Registration and Medication Ordering System (RAMOS), using an Interactive Voice Response System (IVRS) will be used to allocate the dispensing packs. Details of the drug allocation procedure using RAMOS will be provided to each investigator.

Medication will be allocated by use of 3 numbers as follows:

- Each subject who is screened will be allocated a **CRF Number (Subject Number)**. This number is unique to each subject and will be assigned from a list provided to the site in chronological order
- Each subject who satisfies the randomisation criteria will be assigned a unique **Random Number** by IVRS. Once a **Random Number** has been assigned to a subject, it cannot be reassigned to any other subject. Neither the subject nor the investigator will know which treatment has been allocated to the subject
- At visit 3, following randomisation, RAMOS will allocate four double blind treatment bottles via the IVRS system. Each bottle labeled with a 6 digit **Container Number** is unique and corresponds to the study medication pack to be dispensed to the subject. The investigator is advised to give the subject one bottle at each of the visits during treatment period, rather than give all 4 bottles to the subject at this visit. If the subject were to delay his/her next visit for some reason, it would be appropriate to provide another bottle at the discretion of the investigator. The subject should be reminded to use the bottles sequentially.

RAMOS should be called on the following occasions:

- At Visit 1, the investigator or designee will telephone RAMOS, specify the subject number (the number shown on the CRF) and RAMOS will register the subject
- At Visit 3, the investigator or designee will telephone RAMOS, specify the subject number. In addition the investigator or designee will be asked to enter the smoking status of the patient (based on the criteria listed in Section 6.1.3: Smoking History). At this point RAMOS will stratify the patient. This stratification cannot be re-entered (though confirmation of stratification must be obtained by pressing the # key). If the wrong stratification is selected from the phone menu, and is confirmed, please contact the RAMOS help desk at the number provided on the RAMOS worksheet.
- RAMOS will randomise the subject, assign the treatment umber and assign the study medication, by reading the appropriate Container **Numbers** of the **four** Treatment **bottles** to be dispensed to the subject.

- If the subject is withdrawn from the study at any time, between Visits 3/3A and 7, the investigator or designee will telephone RAMOS, specify the subject number and log the subject as withdrawn.
- **At Follow-up visit (visit 8), the investigator or designee will telephone RAMOS to specify the subject number and record Follow-Up visit**
- **On each occasion the IVRS is called, the minimum information required will be the unique centre number, (allocated to each centre prior to centre approval) and the CRF number.**

Although study medication will be stored at each site, the investigator (or designee) **must** telephone RAMOS to obtain the Container Numbers of the Treatment bottles to be dispensed to each subject. All calls to RAMOS are confirmed with faxes, which are sent to the investigator upon completion of each call. Worksheets to aid use of RAMOS will be provided at the start of the study. All RAMOS faxes and completed worksheets must be retained in the investigator's study file.

7.6. Packaging

The contents of the label will be in accordance with all applicable regulatory requirements.

Study medication for the 13-week double-blind treatment period will be presented in double-blind bottles. For the double-blind treatment phase, bottles will contain either 70 tablets of Cilomilast (SB 207499) 15 mg or matching placebo. Each bottle will provide a 35-day supply of study medication (28 days worth and an additional 7 days overage).

7.7. Labeling and Preparation

The contents of the label will be in accordance with all applicable regulatory requirements.

A single set of individual patient code breaks will be provided to the centre for use in emergency situations only. These will be supplied at the point of distribution and will detail the 6 digit RAMOS container number and corresponding treatment allocation.

Labels will contain the following:

- Container number (for double-blind study medication)
- Space to enter subject initials, date dispensed, and visit number (Run-In medication bottles only)
- Quantity statement
- Protocol number
- Packaging (job) number
- Dosing directions

- Storage conditions (room temperature)
- Keep out of reach of children
- Appropriate caution statements
- Company Address

7.8. Handling and Storage

Investigational product must be dispensed or administered according to procedures described herein. Only subjects enrolled in the study may receive investigational product, in accordance with all applicable regulatory requirements. Only authorized site staff may supply or administer investigational product. All investigational products must be stored in a secure area with access limited to the investigator and authorized site staff and under physical conditions that are consistent with investigational product-specific requirements.

Prior to dispensing, all study medication will be kept safely locked, in a dry place at room temperature 20°C- 25°C (at or below 30°C).

7.9. Product Accountability

The investigator is responsible for investigational product accountability, reconciliation, and record maintenance. In accordance with all applicable regulatory requirements, the investigator or designated site staff must maintain investigational product accountability records throughout the course of the study. This person(s) will document the amount of investigational product received from GSK, the amount supplied and/or administered to and returned by subjects, if applicable.

Accountability records or logs must be maintained for study medication. Subjects will be asked to return all used and unused study medication. The investigator or designee must reconcile and resolve any discrepancies between what was dispensed to the subject and what is returned.

7.10. Assessment of Compliance

At each treatment visit (from Visits 3/3A to Visit 7) including unscheduled visits where medication is returned, the number of remaining doses from each blinded study treatment prescribed to the subject is to be counted.

Compliance will be calculated by using the formula below:

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

Compliance (%) will be entered into the CRF.

Subjects must show ≥ 80% and ≤ 120% compliance in taking study medication at each treatment visit to continue in the study.

7.11. Treatment of Investigational Product Overdose

In the event of an overdose, general symptomatic and supportive measures should be initiated promptly and maintained for as long as necessary. The investigator should consult the approved product labels for further information on treatment of overdose.

7.12. Occupational Safety

Investigational product is not expected to pose significant occupational safety risk to site staff under normal conditions of use and administration. A Material Safety Data Sheet (MSDS) describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

8. CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

8.1. Permitted Medications

All concomitant medications taken during the study will be recorded in the CRF with indication, dose information, and dates of administration. Any changes must be clearly recorded in the CRF

The following concurrent medications may be permitted:

- Treatment for smoking cessation (any changes in the smoking status; starting or stop smoking will withdrawal subject from the PP population)
- Salbutamol (prn) and/or ipratropium bromide or Combivent for use as relief medication will be provided throughout the study. Salbutamol and/or ipratropium bromide or Combivent for use via a nebuliser will be provided for use as part of the bronchial biopsy, and sputum induction procedures. The use of this medication must be recorded in the concomitant medication of the CRF. Investigators must ensure that at each visit, the subject has sufficient rescue medication to last at least until the following visit. If the subject experiences symptoms that do not respond adequately to salbutamol and/or ipratropium bromide or Combivent, the subject must contact the investigator
- Between Visits 1 and 7, the subject should NOT take any additional bronchodilators that they possess at home, with the exception of salbutamol and/or ipratropium bromide or Combivent. *If the subject experiences symptoms, which do not respond adequately to* salbutamol *and/or* ipratropium bromide or Combivent*, the subject must contact the investigator*

8.2. Prohibited Medications

Except in the short-term management of COPD exacerbations, the following medications are prohibited between Visit 1 and Visit 8.

- Inhaled, oral and systemic corticosteroids (should be stopped 4 weeks before Visit 1)
- Long-acting β_2-agonists (e.g. salmeterol and formoterol should be stopped 2 weeks before Visit 1)
- Oral β_2-agonists (e.g.bambuterol) and nebulised β_2-agonists (except as part of the biopsy or sputum induction procedures)
- Long-acting anticholinergics e.g. tiotropium bromide (should be stopped 4 weeks before Visit 1)
- Xanthines (should be stopped 4 weeks before Visit 1)
- Leukotriene modifiers
- Sodium cromoglycate and nedocromil sodium
- NACs (N-Acetyl Cysteine)

8.3. Medical Devices

The following GSK devices are provided for this study:

- MDI inhaler
- **VOLUMATIC** spacer

8.4. Non-Drug Therapies

Non-drug therapies for conditions other than COPD may be used during the study if their use is not considered to have an impact on the subject's COPD.

9. SUBJECT COMPLETION AND WITHDRAWAL

9.1. Subject Completion

A subject will be defined as having completed the study if they complete the Run-In, Treatment and Follow-Up phases of the study as defined in this protocol.

9.2. Subject Withdrawal

Any subject 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.

9.2.1. Subject Withdrawal from Study

Subjects who withdraw from the study prior to randomisation to study medication are discussed in Section 9.3 below.

Once randomised, subjects will be considered to have withdrawn from the study if they are withdrawn from the investigational product or if they do not complete the Follow-Up contact (Visit 8).

9.2.2. Subject Withdrawal from Investigational Product

Randomised subjects who do not complete the 13-week Treatment period and/or who do not attend all required clinic visits up to and including Visit 7 will be defined as having withdrawn from the investigational product. Reason for withdrawal includes adverse events, lack of efficacy of study medication, COPD exacerbations requiring hospitalisations or the use of oral corticosteroids (see Section 6.2.1.1), lost to follow-up, did not meet entry criteria, protocol violation, consent withdrawal or other reasons. The investigator will record the primary reason for the subject's withdrawal in the CRF. Further information regarding withdrawals due to adverse events is provided in Section 10.

Subjects may be withdrawn from study treatment at any time by the investigator if it is considered detrimental for them to continue in the study. Subjects are also free to withdraw themselves from the study at any time, although every effort should be taken to persuade them to return to the clinic for a follow-up visit and to return all study-related materials. Subjects who experience a severe COPD exacerbation during the Treatment period will be withdrawn from the study (see definitions in Section 6.2.1.1) and any subject who experiences a moderate COPD exacerbation requiring the use of oral corticosteroids will also be withdrawn from the study. Subjects who change their smoking status (start or stop smoking) will be excluded from per protocol population. Subjects who experience **one** moderate exacerbation requiring the use of antibiotics during the Treatment Period, will be allowed to continue. However, subjects experiencing **more than one** moderate exacerbation requiring the use of antibiotics during the Treatment Period will be withdrawn from the study, and the withdrawal procedures followed as described below. The reason for withdrawal will be recorded as COPD exacerbation.

At withdrawal, all study medication and rescue medication should be collected from the subject. Drug accountability records or logs must be completed. If possible the following assessments should be completed when the subject is withdrawn and the data recorded in the CRF.

- Review of adverse events
- Review of concurrent medications
- Clinic pulmonary function tests
- Review of exacerbations

- Physical examination
- Clinical laboratory tests [Chemistry, Haematology, Urinalysis, Faecal Occult Blood test (FOB), and pregnancy testing for females of childbearing potential]

A Follow-Up visit or telephone call should be performed 1 week±3 days after the withdrawal visit. The 'End of Study Record' in the CRF must be completed.

9.3. Screen and Baseline Failures

For subjects who enter the Run-In period but who do not meet the eligibility criteria for entry to the Treatment period and who are not randomised or who discontinue the study during the Run-In period, the following information will be recorded in the CRF:

- All Visit 1 data
- Adverse events (including exacerbations if any)
- Concurrent medication (if any)
- End of Study record in CRF (including reason for withdrawal and date of withdrawal)

No follow-up contact will be required for subjects who are withdrawn prior to randomisation to study medication at Visit 3, unless they experienced a serious adverse event (SAE) – see Section 10.2, 'Definition of a SAE') or they were withdrawn due to an adverse event. For these subjects, a Follow-Up visit (phone-call) will be carried out 2 weeks from the date of withdrawal and the Follow-Up visit forms in the CRFs will be completed.

9.4. Early Withdrawal Assessments in the Treatment Period

Randomised subjects who withdraw from the study at a scheduled visit should complete the assessments scheduled at that visit. These include the following:

- A physical examination including a respiratory examination
- Subjects who withdraw from the study between scheduled clinic visits will be instructed to return to the clinic within 24 hours of stopping study medication for an EWV. At this visit, subjects will complete the following: SVC, vital signs, physical examination, and clinical laboratory tests (including FOB test if applicable). Medication compliance, concomitant medications, adverse events and smoking status will be evaluated, and 1 week after the EWV the biopsy and/or sputum should be performed if possible
- A safety Follow-Up visit is required for all subjects who withdraw from the study following the start of the double-blind medication and before completion of the assessments up to and including those scheduled at Week 13. This assessment should be performed 7 ±3 days after discontinuation of study medication (Section 6.4.10).
- Medication compliance, concomitant medications, medical procedures and smoking status will be evaluated.

10. ADVERSE EVENTS (AE) AND SERIOUS ADVERSE EVENTS (SAE)

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE as provided in this protocol. During the study, when there is a safety evaluation, the investigator or site staff will be responsible for detecting AEs and SAEs, as detailed in this section of the protocol.

Additional monitoring for gastrointestinal adverse events:

In order to address concerns identified pre-clinically with SB 207499 and drugs of a similar pharmacological class for an effect on the gut vasculature or heart, the gastrointestinal adverse experience profile will be defined. Particular attention will be paid to collection of data on gastrointestinal adverse experiences with extensive monitoring (physical exam, laboratory assessments, faecal occult blood, orthostatic heart rate and blood pressure) for events of potential concern. Gastrointestinal adverse experiences (i.e., bloody or black stool, abdominal discomfort such as pain or cramps, diarrhoea, vomiting) which cause the patient concern or interfere with daily activities (including eating and sleeping) will be assessed by the Investigator within 24 hours of occurrence. The Investigator will review the results of the initial assessment and arrange further follow-up as appropriate. All events should be followed to resolution. The investigator should record the GI AEs on the separate GI AE forms provided, and report the GI AEs to the GSK monitor within 24 hours of the first assessment.

10.1. Definition of an AE

Any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

Examples of an AE **includes**:

- Significant or unexpected worsening or exacerbation of the condition/indication under study. See Section 10.3, “Lack of Efficacy”, for additional information.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- Significant failure of expected pharmacological or biological action. See Section 10.3, "Lack of Efficacy" for additional information.

Examples of an AE **does not include** a/an:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

For GSK clinical studies, AEs may include pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e., invasive procedures, modification of subject's previous therapeutic regimen).

10.2. Definition of a SAE

A serious adverse event is any untoward medical occurrence that, at any dose:

a results in death.

b is life-threatening.

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c requires hospitalization or prolongation of existing hospitalization.

NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-subject setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d results in disability/incapacity, or

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e is a congenital anomaly/birth defect.

f Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3. Lack of Efficacy

"Lack of efficacy" per se will not be reported as an AE. The signs and symptoms or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the AE or SAE definition (including clarifications).

10.4. Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs and SAEs

Abnormal laboratory findings (e.g., clinical chemistry, hematology, urinalysis) or other abnormal assessments (e.g., X-rays, etc.) that are judged by the investigator as **clinically significant** will be recorded as AEs or SAEs if they meet the definition of an AE, as defined in Section 10.1 ("Definition of an AE"), or SAE, as defined in Section 10.2 ("Definition of a SAE"). Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject's condition, or that are present or detected at the start of the study and do not worsen, will **not** be reported as AEs or SAEs.

The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

10.5. Time Period, Frequency, and Method of Detecting AEs and SAEs

The time period for collecting AEs and SAEs will begin from the time consent is obtained from the subject when prohibited medication is withdrawn from the subject to the end of the Follow-Up period. SAEs that are related to study participation (e,g. procedures, invasive tests, a change from existing therapy) or are related to a concurrent medication will be collected and recorded from the time the subject consents to participate in the study until he/she withdraws or completes the study.

The investigator will inquire about the occurrence of AEs/SAEs at every visit/contact during the study and Follow-up

The investigator will ask the following question at every visit in order to capture AEs/SAEs

"Have you had any (other) medical problems since your last visit/assessment?

10.6. Recording of AEs and SAEs

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE/SAE on the CRF. It is not acceptable for the investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the appropriate AE/SAE CRF pages. However, there may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to GSK.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

10.7. Evaluating AEs and SAEs

10.7.1. Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study. The assessment will be based on the investigator's clinical judgement. The intensity of each AE and SAE recorded in the CRF should be assigned to one of the following categories:

Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.

Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities.

Severe: An event that prevents normal everyday activities.

An AE that is assessed as severe should not be confused with a SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as 'serious' when it meets one of the pre-defined outcomes as described in Section 10.2, "Definition of a SAE".

10.7.2. Assessment of Causality

The investigator is obligated to assess the relationship between investigational product and the occurrence of each AE/SAE. The investigator will use clinical judgement to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational product will be considered and investigated. The investigator will also consult the CIB/IB and/or Product Information, for marketed products, in the determination of his/her assessment.

There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, it is very important that the investigator always make an assessment of causality for every event prior to transmission of the SAE CRF to GSK. The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE CRF accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

The investigator will provide the assessment of causality as per instructions on the SAE form in the CRF.

10.8. Follow-Up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject and provide further information to GSK on the subject's condition.

All AEs and SAEs documented at a previous visit/contact and are designated as ongoing, will be reviewed at subsequent visits/contacts.

All AEs and SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up. Once resolved, the appropriate AE/SAE CRF page(s) will be updated. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

GSK may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obligated to assist. If a subject

dies during participation in the study or during a recognized follow-up period, GSK will be provided with a copy of any post-mortem findings, including histopathology.

New or updated information will be recorded on the originally completed "SAE" CRF, with all changes signed and dated by the investigator. The updated SAE CRF should be resent to GSK within the time frames outlined in Section 10.9.

10.9. Prompt Reporting of SAEs to GSK

SAEs will be reported promptly to GSK as described in the following table once the investigator determines that the event meets the protocol definition of an SAE.

10.9.1. Timeframes for Submitting SAE Reports to GSK

	Initial SAE Reports		Follow-up Information on a Previously Reported SAE	
Type of SAE	Time Frame	Documents	Time Frame	Documents
All SAEs	24 hrs	"SAE" CRF pages	24 hrs	Updated "SAE" CRF pages

10.9.2. Completion and Transmission of the SAE Reports

Once an investigator becomes aware that an SAE has occurred in a study subject, she/he will report the information to GSK within 24 hours as outlined in Section 10.9, "Prompt Reporting of SAEs to GSK". The SAE CRF will always be completed as thoroughly as possible with all available details of the event, signed by the investigator (or designee), and forwarded to GSK within the designated time frames. If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying GSK of the event and completing the form. The form will be updated when additional information is received.

The investigator will always provide an assessment of causality at the time of the initial report as described in Section 10.7.2, "Assessment of Causality".

Facsimile transmission of the "SAE" CRF is the preferred method to transmit this information to the project contact for SAE receipt. In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of the "SAE" CRF sent by overnight mail. Initial notification via the telephone does not replace the need for the investigator to complete and sign the SAE CRF within the time frames outlined in Section 10.9, "Prompt Reporting of SAEs to GSK".

GSK will provide a list of project contacts for SAE receipt, fax numbers, telephone numbers, and mailing addresses.

The following pages of the CRF must accompany the SAE forms that are forwarded to GSK: “Demography”, “Medical History”, “Concomitant Medications”, “Study Medication Records.

10.10. Regulatory Reporting Requirements For SAEs

The investigator will promptly report all SAEs to GSK in accordance with the procedures detailed in Section 10.9 "Prompt Reporting of SAEs to GSK." GSK has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to the appropriate project contact for SAE receipt is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met.

The investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to regulatory authorities and the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

Expedited Investigator Safety Reports (EISR) are prepared according to GSK policy and are forwarded to investigators as necessary. An EISR is prepared for a SAE that is both attributable to investigational product and unexpected. The purpose of the EISR is to fulfill specific regulatory and Good Clinical Practice (GCP) requirements, regarding the product under investigation.

An investigator who receives an EISR describing a SAE or other specific safety information from GSK will file it with the Investigator Brochure and will notify the IRB or IEC, if appropriate according to local requirements.

10.11. Post-study AEs and SAEs

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE detection period defined in Section 10.5, “Time Period, Frequency, and Method of Detecting AEs and SAEs”, of the protocol.

Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the investigational product, the investigator will promptly notify GSK.

10.12. SAEs Related to Study Participation

An SAE considered related to study participation (e.g., procedures, invasive tests, a change in existing therapy), even if it occurs during the pre- or post-treatment period, will be reported promptly to GSK (see Section 10.9, "Prompt Reporting of SAEs to GSK").

11. MEDICAL DEVICES – INCIDENTS AND NEAR-INCIDENTS (INCLUDING MALFUNCTIONS)

GSK medical devices are being provided for use in this study. In order to fulfil international reporting obligations the investigator is responsible for the detection and documentation of events meeting the definitions of incident, near-incident, or malfunction that occur during the study with such devices.

11.1. Definitions of a Medical Device, Incident, Near-Incident, Malfunction, and Remedial Action

Medical Device – Any instrument, apparatus, appliance, material or other article, the principal intended action of which is typically fulfilled by physical means (including mechanical action, physical barrier, replacement of, or support to, organs or body functions). Examples of medical devices include measuring spoons, syringes, spacers and spring-loaded auto-injectors.

The detection and documentation procedures described in this protocol apply to all GSK medical devices provided for use in the study.

Incident – Any medical occurrence that occurs in a study subject, user, or other person with a GSK medical device, provided for use in the study, **which results in death or a serious deterioration in the state of health** whether or not due to a malfunction of the device.

Incidents include for example:

- inhalation of an object that has accidentally entered a spacer device and resulted in tracheal obstruction.

Incidents do not include for example:

- medical occurrences associated with metered-dose inhalers that do not fulfill the definition of a medical device (such events will be reported as medicinal product AEs)
- non-serious medical occurrences which have no further safety implications for the subject or the device

Near-incident – Any potential incident occurring with a GSK medical device provided for use in the study. Near-incidents are events that could have jeopardized the study subject, user, or other person, causing death or a serious deterioration of health, if medical intervention or other fortunate circumstances had not occurred. This would include deficiencies or inaccuracies in the instructions for use of the device and/or malfunctions.

Near-incidents include for example:

- discovery of caustic damage to the plastic parts of a device caused by contamination with an ointment, where no actual injury to a subject occurred but the reporter

recognized that such an event could happen in normal medical use of the device and could kill or seriously harm a subject.

Malfunction – A failure of a device to perform in accordance with its intended purpose when used in accordance with the manufacturer's instructions.

Remedial Action – Any action other than routine maintenance or servicing of a device where such action is necessary to prevent recurrence of an incident or near-incident. This includes any amendment to the design to prevent recurrence.

11.2. Time Period for Detecting Medical Device Incidents and Near-Incidents

Medical device incidents, near-incidents or malfunctions will be detected, documented and reported during all periods of the study in which the GSK medical devices that are provided are available for use.

11.3. Documenting Medical Device Incidents and Near-Incidents

Any medical device incident or near-incident occurring during the study will be documented in the subject's medical records, in accordance with the investigator's normal clinical practice, and on the "Medical Device Incident Report Form". **In addition, for incidents and near-incidents fulfilling the definition of an AE or an SAE, the appropriate pages of the CRF will be completed as described in Section 10, "Adverse Events (AEs) and Serious Adverse Events (SAEs).**

The "Medical Device Incident Report Form" will be completed as thoroughly as possible and signed by the investigator or his/her designee before transmittal to GSK, or designee. It is **very important** that the investigator provides his/her assessment of causality to the medical device provided by GSK at the time of the initial report, and describes any corrective or remedial actions taken to prevent recurrence of the incident.

11.4. Follow-up of Medical Device Incidents and Near-Incidents

All medical device incidents, and near-incidents involving an AE, will be followed until resolution of the event, until the condition stabilizes, until the condition is otherwise explained, or until the subject is lost to follow-up. The investigator is responsible for ensuring that follow-up includes any supplemental investigations as may be indicated to elucidate as completely as practical the nature and/or causality of the incident.

New or updated information will be recorded on the originally completed "Medical Device Incident Report Form", with all changes signed and dated by the investigator.

11.5. Prompt Reporting of Medical Device Incidents and Near-Incidents to GSK

Medical device incidents and near-incidents will be reported promptly to GSK as described below once the investigator determines that the event meets the protocol definition of a medical device incident or near-incident.

11.5.1. Timeframes for Submitting Medical Device Incident and Near-Incident Reports to GSK

Initial Medical Device Incident/Near-Incident Reports			Additional Information on a Previously Reported Medical Device Incident/Near-Incident	
Type of Event	Time Frame	Documents	Time Frame	Documents
Incident and Near-Incident	24 hrs	"Medical Device Incident Report Form"	24 hrs	Updated "Medical Device Incident Report Form"

11.5.2. Transmission of Medical Device Incident and Near-Incident Reports

Facsimile transmission of the "Medical Device Incident Report Form" is the preferred method to transmit this information to the GSK project contact. The same individual will be the GSK project contact for receipt of medical device reports and SAEs. In the absence of facsimile equipment, notification by telephone is acceptable for incidents, with a copy of the "Medical Device Incident Report Form" sent by overnight mail. For near-incidents, telephone notification, in the absence of facsimile equipment, is not acceptable. Instead, a copy of the "Medical Device Incident Report Form" will be sent by overnight mail.

11.6. Regulatory Reporting Requirements For Medical Devices

The investigator will promptly report all incidents and near-incidents occurring with any GSK medical device provided for use in the study, in accordance with the procedures detailed in Section 11.5, “Prompt Reporting of Medical Device Incidents and Near-Incidents to GSK”. GSK has a legal responsibility to notify appropriate regulatory bodies and other entities about certain safety information relating to medical devices being used in clinical studies. Prompt notification of incidents and near-incidents by the investigator to the appropriate project contact is essential in order to meet legal obligations and ethical responsibility towards the safety of other subjects.

The investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements relating to the reporting of incidents and near-incidents to regulatory bodies, and the IRB/IEC.

11.7. Post-Study Medical Device Incidents and Near-Incidents

Investigators are not obliged to actively seek reports of medical device incidents or near-incidents in former study participants. However, if the investigator learns of any incident or near-incident at any time after a subject has been discharged from the study, and such incident/near-incident is reasonably related to a GSK medical device provided for the study, the investigator will promptly notify GSK.

12. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

12.1. Hypotheses

The null hypothesis is that the mean change from baseline of Cilomilast is the same as that of placebo in both CD68 and CD8 cell counts per area tissue. The alternative hypothesis is that either is not the same.

12.2. Sample Size Considerations

12.2.1. Target Sample Size

In order to obtain 86 patients for per protocol analysis, the study will enroll 116 patients in equal ratio (placebo or cilomilast).

The sample size estimates are obtained based on the results of study 076. The proposed sample size will ensure 90% power to detect an approximate difference of 175 (assumed common standard deviation 230) in CD8+ between cilomilast and placebo at significance level of 2.5%. The target sample size will ensure more than 99% power to detect a difference of 80 (assumed common standard deviation 75) in CD+68 between cilomilast and placebo at significance level of 2.5%.

12.2.2. Sample Size Sensitivity

Sample size sensitivity was assessed with various standard deviations as illustrated in the following table. The sample sizes do not change too much as standard deviation changes.

CD8	Standard Deviation	Sample size
	210	36
	220	40
	230	**43**
	240	47
	250	51
CD68	55	12
	65	17
	75	**22**
	85	29
	95	36

12.3. Method of Randomization

Patients will be randomised in a 1:1 ratio to receive either SB 207499 15 mg twice daily or placebo. The randomisation code will be generated by the GSK Biometrics Unit.

12.4. Planned Efficacy Analysis

12.4.1. Primary Efficacy Variables

- The numbers of sub-epithelial CD68+ (macrophages) per area of biopsy tissue
- The numbers of sub-epithelial CD8+ (cytotoxic T-lymphocytes) per area of biopsy tissue

12.4.2. Secondary Efficacy Variables

In sub-epithelial cells per area of biopsy tissue:

- Neutrophil elastase positive cells (neutrophils)
- CD4+ lymphocytes
- IL-8 mRNA positive cells
- TNFα mRNA positive cells
- CD45 positive cells
- Mucin expression

In sputum cells per unit volume

- Sputum total cell count
- Macrophages as a percentage of total cells
- Neutrophils as a percentage of total cells
- Eosinophils as a percentage of total cells
- Lymphocytes as a percentage of total cells
- IL-8

NB: *Additional secondary efficacy variables may be analysed before the study final statistical results, depending on sample availability and results of initial analysis*

Tertiary Efficacy Endpoints

- Slow vital Capacity

12.4.3. Derivation of Efficacy Variables for Analysis

For bronchial biopsies samples will be taken from the lobar and sub-segmental areas of the lung. Assuming no differences in results are observed between areas, the average of the two evaluations will be used in the analysis. For clinic pulmonary function parameter (SVC), three readings will be collected at each scheduled evaluation. The highest of the three readings will be used in the analysis. If more than one set of readings is available for a particular assessment, the later of the two readings will be used in the analysis. All statistical inferences on clinic pulmonary function tests, inflammatory cell profiles, and bronchial biopsy evaluations will be based on the change from baseline defined as the difference between the value at the evaluation of interest and the value at the pre-dose assessment at Visit 3 (i.e., immediately prior to administration of double-blind medication) or at Visit 2 for biopsy evaluations.

12.4.4. Comparisons of Interest

For sputum and biopsy measures the primary comparison will be the comparison between groups in the per-protocol population at endpoint, defined as the last evaluable (measured prior to occurrence of protocol violation) observation in the double blind treatment period for each patient , Hochberg method will be used to adjust the p-value (Hochberg; Biometrika, 1988).

Secondary comparisons of interest will be the comparison between groups at Week 13 for sputum and Week 12 for biopsy measures.

For lung function measures, the comparison of interest between the groups will be in the intent to treat population at all scheduled visit (Weeks 4, 8, 12 and 13) and endpoint (defined as the last on therapy measurement in the double blind treatment period for each patient.

12.4.5. Populations to be Evaluated

The intent-to-treat population will include all patients who receive randomised study medication, have 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 will be excluded from the analysis.

The primary analysis for efficacy in this study will be based on the per-protocol population. Per-Protocol population will consist of ITT patients who do not have major protocol violations. Because of their potential to confound measurement of the primary endpoint, any data collected subsequent to the onset of a patient's initial COPD exacerbation will also be excluded from the per-protocol analysis. Protocol violations resulting in exclusion of data from the per-protocol analysis will be documented in full prior to unblinding the study.

12.4.6. Methods of Analysis

Descriptive statistics will be provided for all demographic and baseline characteristics.

The assessment of treatment differences for the primary efficacy variables will be based on an analysis of variance model with effects for smoking status, centre and treatment group. Least squares means along with associated 95% confidence intervals will be calculated for each treatment group. Least squares means and ninety-five percent (95%) confidence intervals will also be calculated for the difference between placebo and cilomilast. Primary endpoints will also be analyzed by smoking stauts.

The robustness of the inference from the above model will be explored with respect to inclusion/exclusion of covariates, treatment by center interaction, and normality of the underlying data. Testing for treatment-by-center interaction will be performed at a significance level of 0.10. The degree and effects of departures from normality will be assessed through graphical analysis of residuals.

All continuous secondary and tertiary efficacy variables will be analysed using analysis of variance models described above for the primary variable.

The response of CD8+, CD68+ in biopsy, and neutrophil positive cells in sputum to treatment will also be explored by fitting a Poisson model to the data, adjusting for center, treatment, baseline smoking status and baseline value. These analyses are also considered to be supportive, and the p-values that are obtained will not be adjusted.

The distribution of time to the first COPD exacerbation will be estimated using the Kaplan-Meier product limit method.

12.5. Planned Safety Evaluation

Evaluation of safety data will include all randomised patients and will be based on comparisons of patient experience by assigned medication regimen. Clinical interpretation will be based on review of displays of adverse experiences. Principal considerations in this evaluation will be time-to-onset, severity and Investigator-reported relationship of the adverse experience to study medication. Descriptive statistics will also be used in the evaluation of safety.

12.6. Interim Analysis

There are no interim analyses planned for this study.

13. STUDY ADMINISTRATION

13.1. Regulatory and Ethical Considerations

13.1.1. Regulatory Authority Approval

GSK will obtain approval to conduct the study from the appropriate regulatory agency in accordance with any applicable country-specific regulatory requirements prior to a site initiating the study in that country.

13.1.2. Ethical Conduct of the Study and Ethics Approval

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

The investigator (or sponsor, where applicable) is responsible for ensuring that this protocol, the site's informed consent form, and any other information that will be presented to potential subjects (e.g., advertisements or information that supports or supplements the informed consent) are reviewed and approved by the appropriate IEC/IRB. The investigator agrees to allow the IEC/IRB direct access to all relevant documents. The IEC/IRB must be constituted in accordance with all applicable regulatory requirements. GSK will provide the investigator with relevant document(s)/data that are needed for IEC/IRB review and approval of the study. Before investigational product(s) and CRFs can be shipped to the site, GSK must receive copies of the IEC/IRB approval, the approved informed consent form, and any other information that the IEC/IRB has approved for presentation to potential subjects.

If the protocol, the informed consent form, or any other information that the IEC/IRB has approved for presentation to potential subjects is amended during the study, the investigator is responsible for ensuring the IEC/IRB reviews and approves, where applicable, these amended documents. The investigator must follow all applicable regulatory requirements pertaining to the use of an amended informed consent form including obtaining IEC/IRB approval of the amended form before new subjects consent to take part in the study using this version of the form. Copies of the IEC/IRB approval of the amended informed consent form/other information and the approved amended informed consent form/other information must be forwarded to GSK promptly.

IEC/IRB approval of the PG consent forms must be obtained in addition to the approval given for the clinical study. Regulatory review and approval may be required in some countries before IEC/IRB approval can be sought.

13.1.3. Informed Consent

Informed consent will be obtained before the subject can participate in the study. The contents and process of obtaining informed consent will be in accordance with all applicable regulatory requirements.

GSK will provide the investigator with copies of the information leaflet about the study and the consent form translated into the appropriate local language. It will be reviewed and approved by the appropriate IEC/IRB (see Section 13.1.2, "Ethical Conduct of the Study and Ethics Approval")

The investigator or his/her designee will provide the subject with the information leaflet and the consent form and will explain the study, its purpose and the purpose of the informed consent form to the subject before any non-routine clinical procedures specific for the study are carried out. Clinical procedures that would routinely be performed as a part of normal clinical practice, such as diagnosis or treatment of a disease or medical

condition that would have been done irrespective of the subject's intended participation in the clinical study are permissible, prior to explaining to the subject the consent process and the information on the clinical study.

13.1.4. Investigator Reporting Requirements

As indicated in Section 10.10, the investigator (or sponsor, where applicable) is responsible for reporting SAEs to the IEC/IRB, in accordance with all applicable regulations. Furthermore, the investigator may be required to provide periodic safety updates on the conduct of the study at his or her site and notification of study closure to the IEC/IRB. Such periodic safety updates and notifications are the responsibility of the investigator and not of GSK.

13.2. Study Monitoring

In accordance with applicable regulations, GCP, and GSK procedures, GSK monitors will contact the site prior to the subject enrollment to review the protocol and data collection procedures with site staff. In addition, the monitor will periodically contact the site, including conducting on-site visits. The extent, nature and frequency of on-site visits will be based on such considerations as the study objective and/or endpoints, the purpose of the study, study design complexity, and enrollment rate.

During these contacts, the monitor will:

- Check the progress of the study.
- Review study data collected.
- Conduct source document verification.
- Identify any issues and address their resolution.

This will be done in order to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol (and any amendments), GCP, and all applicable regulatory requirements.

The investigator agrees to allow the monitor direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the monitor to discuss findings and any relevant issues.

At study closure, monitors will also conduct all activities described in Section 13.4, "Study and Site Closure."

A standard Clarification Agreement (SCA) will be used in this study. This will specify any clarifications to data that can be made by GSK personnel without reference back to the investigator. The items in the SCA will be agreed with the investigator at the start of the study.

The source verification strategy and the definition of source data for all data items in the CRF will be discussed with the investigator at the start of the study.

13.3. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

13.4. Study and Site Closure

Upon completion of the study, the monitor will conduct the following activities in conjunction with the investigator or site staff, as appropriate:

- Return of all study data to GSK.
- Data queries.
- Accountability, reconciliation, and arrangements for unused investigational product(s).
- Review of site study records for completeness.
- Return of treatment codes to GSK.

In addition, GSK reserves the right to temporarily suspend or prematurely discontinue this study either at a single site or at all sites at any time for reasons including, but are not limited to, safety or ethical issues or severe non-compliance. If GSK determines such action is needed, GSK will discuss this with the Investigator (including the reasons for taking such action) at that time. When feasible, GSK will provide advance notification to the investigator of the impending action prior to it taking effect.

GSK will promptly inform all other investigators and/or institutions conducting the study if the study is suspended or terminated for safety reasons, and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the investigator must inform the IEC/IRB promptly and provide the reason for the suspension or termination.

If the study is prematurely discontinued, all study data must be returned to GSK. In addition, arrangements will be made for all unused investigational product(s) in accordance with the applicable GSK procedures for the study.

Financial compensation to investigators and/or institutions will be in accordance with the agreement established between the investigator and GSK.

13.5. Records Retention

Following closure of the study, the investigator must maintain all site study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (e.g., audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must assure that all reproductions are legible and are a true and accurate copy of the original, and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, or GSK standards/procedures; otherwise, the retention period will default to 15 years.

The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, the following: archival at an off-site facility, transfer of ownership of the records in the event the investigator leaves the site.

13.6. Provision of Study Results and Information to Investigators

When a clinical study report is completed, GSK will provide the major findings of the study to the investigator.

In addition, details of the study treatment assignment will be provided to the investigator to enable him/her to review the data to determine the outcome of the study for his/her subject.

GSK will not routinely inform the investigator or subject of the test results, because the information generated from this study will be preliminary in nature, and the significance and scientific validity of the results will be undetermined at such an early stage of research. Individual genotype results will only be shared with an investigator or subject if this is a requirement of a governmental agency or other legal authority.

13.7. Information Disclosure and Inventions

Ownership:

All information provided by GSK and all data and information generated by the site as part of the study (other than a subject's medical records) are the sole property of GSK.

All rights, title, and interests in any inventions, know-how or other intellectual or indusstudy property rights which are conceived or reduced to practice by site staff during the course of or as a result of the study are the sole property of GSK, and are hereby assigned to GSK.

If a written contract for the conduct of the study which includes ownership provisions inconsistent with this statement is executed between GSK and the study site, that contract's ownership provisions shall apply rather than this statement.

Confidentiality:

All information provided by GSK and all data and information generated by the site as part of the study (other than a subject's medical records) will be kept confidential by the investigator and other site staff. This information and data will not be used by the investigator or other site personnel for any purpose other than conducting the study. These restrictions do not apply to: (1) information which becomes publicly available through no fault of the investigator or site staff; (2) information which it is necessary to disclose in confidence to an IEC or IRB solely for the evaluation of the study; (3) information which it is necessary to disclose in order to provide appropriate medical care to a study subject; or (4) study results which may be published as described in the next paragraph. If a written contract for the conduct of the study which includes confidentiality provisions inconsistent with this statement is executed, that contract's confidentiality provisions shall apply rather than this statement.

Publication:

For multicenter studies, the first publication or disclosure of study results shall be a complete, joint multicenter publication or disclosure coordinated by GSK. Thereafter, any secondary publications will reference the original publication(s).

Prior to submitting for publication, presentation, use for instructional purposes, or otherwise disclosing the study results generated by the site (collectively, a "Publication"), the investigator shall provide GSK with a copy of the proposed Publication and allow GSK a period of at least thirty (30) days [or, for abstracts, at least five (5) working days] to review the proposed Publication. Proposed Publications shall not include either GSK confidential information other than the study results or personal data on any subject, such as name or initials.

At GSK's request, the submission or other disclosure of a proposed Publication will be delayed a sufficient time to allow GSK to seek patent or similar protection of any inventions, know-how or other intellectual or indusstudy property rights disclosed in the proposed Publication.

If a written contract for the conduct of the study, which includes publication provisions inconsistent with this statement is executed, that contract's publication provisions shall apply rather than this statement.

13.8. Data Management

Subject data are collected by the investigator or designee using the Case Report Form (CRF) defined by GSK. Subject data necessary for analysis and reporting will be entered/transmitted into a validated database or data system. Clinical data management will be performed in accordance with applicable GSK standards and data cleaning procedures. Database freeze will occur when data management quality control procedures are completed. Original CRFs will be retained by GSK, while the investigator will retain a copy.

13.8.1. Data Collection

Data will be collected in the CRF and in the Biopsy and Sputum Worksheets.

Data Management will be performed in accordance with applicable GSK standards and data cleaning procedures. All completed CRFs will be collected by the study monitor and returned to GSK or their designee for entry into the database.

The investigator or designee must record all required subject data using paper CRF defined by GSK. An explanation must be documented for missing data. The investigator must sign and date a declaration on the CRF attesting to his/her responsibility for the quality of all data recorded and that the data represents a complete and accurate record of each subject's participation in the study.

Data will be converted to electronic form by use of a data entry package. The data will then be loaded into a database management system. Data will be reviewed and validated according to checks listed in the Data Validation Documentation. Data Queries (DQs) for inconsistencies and anomalies will be created by data management and will either be sent directly to the sites or will be sent via the study monitors. Upon resolution, sites will return signed DQs directly to GSK data management or their designee. The database will be updated accordingly until all data are deemed "clean".

Quality control procedures will be applied to ensure that the quality of the data in the final database meets the expected standards. Access to the data will be strictly controlled.

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15. APPENDICES

15.1. Appendix 1: Time and Events Table

Visit	1	2/2A[9]	3	4	5	6/6A[9]	7	8	EWV[1]
Period	Screen	Baseline	Start of double-blind Treatment	Treatment				Follow-Up	
Duration (Weeks ± days)	-4 ± 3 days	-1 ± 3 days	0 ± 3 days	4 ± 3 days	8 ± 3 days	12± 3 days	13± 3 days	14± 3 days	
Signed written informed consent	X								
Inclusion/Exclusuion criteria	X		X						
Demography	X								
Medical & surgical history	X								
Postero-anterior chest radiograph [2]	X								
Pulmonary history & symptoms	X								
Concurrent Medication history	X								
Current Medical Conditions	X								
Compliance of Study Medication				X	X	X	X	X	X
Concomitant medication/medical procedures	X	X	X	X	X	X	X	X	X
Adverse Events	X*	X	X	X	X	X	X	X	X
Smoking history	X						X		X
Exacerbation assessment	X	X	X	X	X	X	X	X	X
Physical examination [3]	X							X	X[4]
Vital signs (BP,HR)		X	X			X	X	X	X
Resting SaO_2 [5]	X								
Salbutamol reversibility [6]	X								
Pre-and Post bronchodilator PFTs [7]	X	X	X	X	X	X	X	X	X
Sputum induction and sample preparation			X				X		X[8]
Blood clotting tests	X				X				X
Bronchial biopsy and sample preparation		X				X			X[8]
Clinical Laboratory & pregnancy testing	X						X		X
Faecal Occult Blood test (FOB)[10]		X					X	X[11]	X[11]
Dispense double-blind medication			X	X	X	X			
Collect study medication				X	X	X	X	X	X

1. Subjects who withdraw between clinic visits will attend the clinic within 24 hours for an early withdrawal visit (EWV)
2. Postero-anterior chest X-ray must be is available to the Investigator by Visit 2 prior to taking the biopsy.
3. To include a respiratory examination
4. If abnormalities are present at previous visit for subjects who complete Week 13 or withdraw from the study
5. Resting SaO_2 will be measured by pulse oximetry.
6. Before and 30 minutes after administration of 400mcg salbutamol via MDI and spacer to determine %predicted normal FEV_1, and FVC
7. Includes FEV_1, FVC, and SVC measured by the same person at each visit (please note only SVC at all other visits except visit 1)
8. Sputum should be performed, if possible 7 days after Bronchial biopsies which is done 1 week after the Early Withdrawal visit
9. The baseline and end of treatment bronchial biopsies will only be performed, if the safety criteria are met, otherwise the biopsy procedure should be rescheduled within 1 to 7 days (Visit 2A and Visit 6A respectively).
10. Assessment of FOB (for which, the kit was given to subject at the previous visit)
11. Assessment of FOB if applicable

15.2. Appendix 2: Protocol Amendment 1

Changes are highlighted in bold in the amended text, however if text is deleted from the original version these are highlighted in bold in the original version.

The amendment includes the following general changes throughout the protocol and are therefore not highlighted in bold:

PFTs has been changed to **SVC** for all visits except visit 1.

"**Not to take the morning dose of study medication at home on the day of Visit**" has been removed from all visits.

"Collect any used study medication" has been removed from all visits, and replaced by "**Check the study medication compliance"**.

Secondary Endpoints (summary and Section 3.2, Section 6.3.2, and Section 12.4.2)

Original Text:

NB: *Additional secondary efficacy variables may be analysed at a future date, depending on sample availability and results of initial analysis*

Amended Text:

NB: *Additional secondary efficacy variables may be analysed before the study final statistical results, depending on sample availability and results of initial analysis.*

Safety Endpoints (summary and Section 6.1)

Original Text:

- Clinical laboratory tests (chemistry and haematology)
- **Electrocardiograms (12-lead ECGs) at start and end of the study**

Amended Text:

Clinical laboratory tests **[Chemistry, Haematology, Urinalysis, Faecal Occult Blood test (FOB), and pregnancy testing for females of childbearing potential]**

Study Plan (summary and Section 4)

Original Text:

PFT -Pulmonary Function Tests

Amended Text:

PFT -Pulmonary Function Tests **at V1 (and only SVC at all other visits)**

Study Assessments and Procedures (summary and Section 6.1)

Original Text:

Chest X-ray (if one has not been taken recently i.e. not more than 12 weeks before Visit 1) to exclude the possibility of any abnormality that may mimic or co-exist with COPD (e.g. pneumothorax, bronchial carcinoma or active pulmonary TB)

Amended Text:

Chest X-ray (if one has not been taken recently i.e. not more than **9 weeks** before Visit 1) to exclude the possibility of any abnormality that may mimic or co-exist with COPD (e.g. pneumothorax, bronchial carcinoma or active pulmonary TB)

VISIT TIMINGS (Section 4)

Original Text:

Visits should be scheduled at the same time of day (± 2 hours) and may be conducted **either morning (preferred) or evening with a minimum of 8 hours following last dose of the study medication for individual subjects.**

Amended Text:

Visits should be scheduled at the same time of day (± 2 hours) and **should be conducted preferably in the morning.**

INCLUSION CRITERIA (Section 5.2.1)

Original Text:

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

Amended Text:

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.

Original Text:

3. Subjects with a smoking history of ≥ 10 pack years (1 pack year = 20 cigarettes smoked per day for 1 year or equivalent). (Ex-smokers are defined as those who have stopped smoking for at least 6 months prior to Visit 1. Ex-smokers are eligible to enter the study provided they have at least 10 pack years smoking history).

Amended Text:

3. Subjects with a smoking history **(current or ex-smoker)** of ≥ 10 pack years (1 pack year = 20 cigarettes smoked per day for 1 year or equivalent). *(Ex-smokers are defined as those who have stopped smoking for at least 6 months prior to Visit 1. Ex-smokers are eligible to enter the study provided they have at least 10 pack years smoking history).*

Original Text:

6. (Predicted normal values will be taken from the report of the working party of the European Community for Coal and Steel, 1983)

Amended Text:

6. (Predicted normal values will be taken from the report of the working party of the European Community for Coal and Steel, **1993**)

EXCLUSION CRITERIA (5.2.2)

Original Text:

7. Subjects with clinically significant gastrointestinal or hepatic **that are controlled or uncontrolled on permitted therapy.**

Amended Text:

7. Subjects with clinically significant gastrointestinal or hepatic abnormalities.

Original Text:

11. Subjects receiving treatment with inhaled cromolyn sodium or nedocromil, inhaled long-acting beta$_2$-agonists, and/or oral beta$_2$-agonists, xanthines, leukotriene modifiers, mucolytics, oral/inhaled corticosteroids, or NACs N-Acetyl Cysteine. **All COPD medications except anticholinergic medication or salbutamol should be withdrawn prior to or at Visit 1 (Screening). All oral/inhaled corticosteroids must be withdrawn at least four weeks prior to Visit 1.**

Amended Text:

11. Subjects receiving treatment with inhaled cromolyn sodium or nedocromil, inhaled long-acting beta$_2$-agonists, and/or oral beta$_2$-agonists, **long acting anticolinergic (e.g. tiotropium bromide)** xanthines, leukotriene modifiers, mucolytics, oral/inhaled

corticosteroids, or NACs N-Acetyl Cysteine. **All COPD medications except short-acting anticholinergic medication or salbutamol should be withdrawn prior to or at Visit 1 (Screening). All oral/inhaled corticosteroids, long-acting anticolinergic (e.g. tiotropium bromide), xanthines must be withdrawn at least four weeks prior to Visit 1.**

Exclusion Criteria at randomisation visit (visit 3)

Original Text:

Subjects with clinically significant orthostatic changes in blood pressure or heart rate at Visit 1 or 3 (if required by regulatory agencies)

Amended Text:

The original criterion has been removed.

Study Assessments and Procedures (Section 6)

Original Text:

If a subject is withdrawing at the unscheduled visit **at Week 10 or 11** a biopsy should be performed **and sputum induction at the EWV**. If possible, a sputum induction should be performed 7 days after the biopsy procedure

Amended Text:

If a subject is withdrawing at the unscheduled visit a biopsy should be performed **1 week after the EWV**. If possible, a sputum induction should be performed 7 days after the biopsy procedure

Original Text:

Pulmonary Function Tests (PFT s) include measurements of FEV_1, SVC and FVC **which** will be conducted before and after administration of salbutamol 400mcg via an MDI and **VOLUMATIC** spacer. All other procedures are outlined in the Time and Events Schedule (see Appendix 1)

Amended Text:

Pulmonary Function Tests (PFT s) include measurements of FEV_1, SVC and FVC **will be conducted at visit 1, and only SVC will be measured at all other visits** before and after administration of salbutamol 400mcg via an MDI and **VOLUMATIC** spacer. All other procedures are outlined in the Time and Events Schedule (see Appendix 1)

Demographic and Baseline Assessments (Section 6.1)

Original Text:

Pulmonary Function Tests (PFTs) FEV_1 and FVC including reversibility after administration of 400mcg of salbutamol, and slow vital capacity (VC)

Amended Text:

Pulmonary Function Tests (PFTs); FEV_1 and FVC including reversibility after administration of 400mcg of salbutamol **only at V1, and slow vital capacity (SVC) at all other visits**

Chest X-ray (Section 6.1.2 and Section 6.4.2)

Original Text:

A postero-anterior (P-A) chest radiograph (X-ray) should be performed **at 12 weeks prior to Visit 2** and the results (including film) must be made available by Visit 2 prior to taking the biopsy. Abnormal findings not consistent with the diagnosis of COPD should be documented in the CRF and followed up as appropriate.

Amended Text:

A postero-anterior (P-A) chest radiograph (X-ray) should have been performed **within 9 weeks prior to Visit 1** and the results (including film) must be made available by Visit 2 prior to taking the biopsy. Abnormal findings not consistent with the diagnosis of COPD should be documented in the CRF and followed up as appropriate.

Safety (Section 6.2)

Original Text:

Pregnancy testing: urine pregnancy tests will be conducted in all female subjects of child-bearing potential.

Amended Text:

Clinical laboratory tests [Chemistry, Haematology, Urinalysis, Faecal Occult Blood test (FOB), and pregnancy testing for females of childbearing potential]

Pregnancy (Section 6.2.1)

Original Text:

6.2.1.1. Pregnancy testing

A urine pregnancy test will be conducted at Visits 1 and **8** in all women of childbearing potential. Subjects will be asked to provide approximately 20mls of urine sample for

pregnancy testing. Subjects with a positive pregnancy test should be excluded from entry to the study. If a subject becomes pregnant during the course of the study, she must be withdrawn. A follow-up pregnancy test should be conducted at Visit 8

6.2.1.2. Time period for collecting pregnancy information

The time period for collecting pregnancy information includes the period between Visit 1 and **the Follow-Up** period (i.e. between Visit 1 and Visit **8**. A pregnancy occurring during this period will be followed up for the times specified below.

Amended Text:

6.2.1.1. Pregnancy testing

A urine or **serum** pregnancy test will be conducted at Visits 1 and **7** in all women of childbearing potential. Subjects will be asked to provide approximately 20mls of urine sample for pregnancy testing. Subjects with a positive pregnancy test should be excluded from entry to the study. If a subject becomes pregnant during the course of the study, she must be withdrawn.

6.2.1.2. Time period for collecting pregnancy information

The time period for collecting pregnancy information includes the period between Visit 1 and the **end of treatment** period (i.e. between Visit 1 and Visit **7**). A pregnancy occurring during this period will be followed up for the times specified below.

Clinical Laboratory tests (Section 6.2.6)

Original Text:

Blood will be collected from the subject to analysis blood clotting tests. These will be measured at the **hospital's local laboratory** (where possible) 4 weeks prior to taking the bronchial biopsy.

Note: A blood sample will be taken for a blood clotting tests at EWV, and a biopsy needs to be taken at 1 week after the EWV.

Amended Text:

Approximately 20 ml of blood and a urine sample will be collected at visit 1, 7 and/or EWV for laboratory analyses. Patients who complete the study or withdraw will have blood and urine samples collected at the Safety Follow-up Visit, only if abnormalities were observed at V7 and/or EWV. Clotting parameters (prothrombin time, thrombin time and activated partial thromboplastin time), haemoglobin concentration and platelet counts will also be measured **at the hospital's local laboratory** (where possible) within 4 weeks of bronchial biopsy. **The Investigator is responsible for arranging with the local laboratories for these tests to be made and reported.**

The following parameters will be measured:

Haematology: Haemoglobin concentration, haematocrit, red cell count, white cell count with differential, platelet count.

Clinical chemistry: Blood urea, creatinine, aspartate transaminase (ASAT/SGOT), alanine transaminase (ALAT/SGPT), gamma glutamyl-transferase (GGT), alkaline phosphatase (ALP), total protein, albumin, total bilirubin, sodium, potassium, chloride, glucose, uric acid.

Amylase will be measured at Visit 1 (Screening), Visit 7 (End of treatment), and at early withdrawal (also for patients who report gastrointestinal symptoms which are of concern to them or interfere with daily activities).

Faeces: Faecal occult blood tests between Visit 1 (Screening), and visit 2, visit 7 and Visit 8 (End of treatment), or early withdrawal (three tests collected on consecutive bowel movements, if possible). The tests are to be performed according to the instructions provided with the faecal occult blood kits. Faecal occult blood will also be tested in patients who report gastrointestinal symptoms which are of concern to them or interfere with daily activities. **Please note that the FOB kit test should be done at home before the clinic visits (V2, V8, or EWV).**

Urinalysis: Blood, glucose, protein, ketones.

Pregnancy: Urine/Serum beta-HCG for women of childbearing potential
Urinary beta-HCG for women of child bearing potential at the Safety Follow-up Visit.

Additional laboratory tests will be performed where indicated for patients who report gastrointestinal adverse experiences, which are of concern to them or interfere with their daily activities or sleep.

All clinically significant abnormal laboratory findings are to be repeated until the values return to normal. If such values do not return to normal within a period judged reasonable by the Investigator, the aetiology should be identified and the sponsor notified. Clinically significant worsenings in laboratory findings must be recorded in the Baseline Signs and Symptoms or Adverse Experiences section of the CRF. Values outside of the reference range, but of no clinical significance, should be marked "NCS" by the Investigator on the printed laboratory report sheet. Faecal occult blood tests are analysed at each site. If positive, 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.

Pulmonary Function Tests (Section 6.3.7.3)

Original Text:

- For all other visits, pulmonary function tests (PFTs) will be assessed more than 6 hours after the last dose of salbutamol and/or ipratropium bromide Subjects will also be asked to refrain from smoking in the 2 hours before their PFTs
- PFTs will be performed in the absence of salbutamol and will be performed as trough (pre-dose) plasma levels of study medication.

Amended Text:

- For all other visits, pulmonary function test **(SVC)** will be assessed more than 6 hours after the last dose of salbutamol and/or ipratropium bromide. Subjects will also be asked to refrain from smoking in the 2 hours before their PFTs
- **SVC** will be performed pre-and post salbutamol

Screening and Start of the 4-Week Run-In Period (Section 6.4.1)

Original Text:

Written informed consent will be obtained.

Amended Text:

- Written informed consent will be obtained **(Subjects who are on inhaled corticosteroids should give their consent 4 weeks prior to V1).**

Original Text:

Urine sample will be taken for pregnancy testing in women of child-bearing potential (see Section 6.2.1.1)

Amended Text:

- **Clinical laboratory tests [Chemistry, Haematology, Urinalysis, Faecal Occult Blood test (FOB), and pregnancy testing for females of childbearing potential].**

All clinically significant abnormal laboratory findings are to be repeated until the values return to normal.

Section 6.2.2.1, Section 6.4.2 and Section 6.4.4

Original Text:

A COPD exacerbation assessment will be made to determine if the subject has experienced any exacerbations during the period between Visits 1 and 2. Check the DRC for any record of exacerbations. **Subjects who take any corticosteroids and/or antibiotics or who are hospitalised for the treatment of a COPD exacerbation during the Run-In must be withdrawn**

Amended Text:

A COPD exacerbation assessment will be made to determine if the subject has experienced any exacerbations during the period between Visits 1 and 2. Check the DRC for any record of exacerbations. **Subjects who experience moderate or severe exacerbations during the Run-In period are not eligible to be randomised to the double-blind Treatment Period.**

Section 6.4.1

Original Text:

- Issue study run-in medication, salbutamol and/or ipratropium bromide as relief medication as appropriate (see Section 8.1)

Amended Text:

- Issue **study run-in medication**, salbutamol and/or ipratropium bromide as relief medication as appropriate (see Section 8.1)
- **Issue the FOB kit, and ask the subject to bring the sample to the next visit (Also added on Section 6.4.9)**

Section 6.4.2

Original Text:

- **All subjects must demonstrate stability in clinic trough FEV_1 (i.e. the absolute value in the absence of salbutamol must not have increased or decreased by > 20% between Visit 1 and Visit 2). Subjects who fail this criterion must be withdrawn from the study (see Section 6.3.7.2).**

Amended Text:

FOB test should be assessed (also added on Section 6.4.10)

Week 8 of the Double-Blind Treatment Period (Section 6.4.6)

Original Text:

Note: Subjects will be asked to provide a blood sample for pre-biopsy analysis of blood clotting test 4 weeks prior to Visit 6. Samples are to be processed at the site where possible and results must be available before the biopsy procedure is conducted.

Amended Text:

Note: Subjects will be asked to provide a blood sample for pre-biopsy analysis of blood clotting test **within** 4 weeks prior to Visit 6. Samples are to be processed at the site where possible and results must be available before the biopsy procedure is conducted.

Week 13 - End of the Double-Blind Treatment Period (Section 6.4.9)

Original Text:

- Vital signs will be measured after the subject has been sitting for 5 minutes (see Section 6.2.4)
- **PFTs** will be performed (see Section 6.3.7.3)

Amended Text:

- Vital signs will be measured after the subject has been sitting for 5 minutes (see Section 6.2.4)
- **Clinical laboratory tests [Chemistry, Haematology, Urinalysis, Faecal Occult Blood test (FOB), and pregnancy testing for females of childbearing potential]. All clinically significant abnormal laboratory findings are to be repeated until the values return to normal**
- **SVC** will be performed (see Section 6.3.7.3)

Visit 8: Safety Follow-Up Visit (Section 6.4.10)

Original Text:

- **Urine sample will be taken for pregnancy testing in women of child-bearing potential (see Section 6.2.1)**
- Telephone RAMOS and specify the subject number and record Follow-Up visit

At least 6 hours after the subjects last salbutamol and/or ipratropium bromide and/or other COPD administration:

- Vital signs will be measured after the subject has been sitting for 5 minutes (Section 6.2.4)
- **PFTs** will be performed (see Section 6.3.7.3)

Amended Text:

- Telephone RAMOS and specify the subject number and record Follow-Up visit

At least 6 hours after the subjects last salbutamol and/or ipratropium bromide and/or other COPD administration:

- Vital signs will be measured after the subject has been sitting for 5 minutes (Section 6.2.4)
- **SVC** will be performed (see Section 6.3.7.3)
- **All clinically significant abnormal laboratory findings from V7 or EWV should be repeated at this visit, and until the values return to normal.**

Early Withdrawal Visit (Section 6.4.11 and Section 9.4)

Original Text:

A physical examination, including a respiratory examination and temperature measurement, and **oropharyngeal examination** will be performed, if not already included in the scheduled visit assessments. Call RAMOS, specify the subject number and log the subject as withdrawn.

Subjects who withdraw from the study between scheduled clinic visits will be instructed to return to the clinic within 24 hours of stopping study medication for an EWV. At this visit, subjects will complete the following: **PFTs**, vital signs, and physical examination. Medication compliance, concomitant medications, adverse events and smoking status will be evaluated, and 1 week after the EWV the biopsy and/or sputum should be performed if possible.

Amended Text:

A physical examination, including a respiratory examination and temperature measurement, **and clinical laboratory tests** will be performed, if not already included in the scheduled visit assessments. Call RAMOS, specify the subject number and log the subject as withdrawn.

Subjects who withdraw from the study between scheduled clinic visits will be instructed to return to the clinic within 24 hours of stopping study medication for an EWV. At this visit, subjects will complete the following: **SVC**, vital signs, physical examination, **and clinical laboratory tests (including the FOB test)**. Medication compliance, concomitant

medications, adverse events and smoking status will be evaluated, and 1 week after the EWV the biopsy and/or sputum should be performed if possible.

Dosage and Administration (Section 7.2)

Original Text:

Subjects who fulfil the Randomisation Criteria will enter a 13-week double-blind treatment phase. Subjects will be randomised to receive either Cilomilast (SB 207499) 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. ***Subjects 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.***

Amended Text:

Subjects who fulfil the Randomisation Criteria will enter a 13-week double-blind treatment phase. Subjects will be randomised to receive either Cilomilast (SB 207499) 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.

Treatment of Investigational Product Overdose (Section 7.11)

Original Text:

In the event of an overdose, general symptomatic and supportive measures should be initiated promptly and maintained for as long as necessary. The investigator should consult the approved product labels for further information on treatment of overdose.

Any instance of a suspected or confirmed overdose must be fully documented as a Serious Adverse Experience (Section 10.6) and communicated to the GSK Medical Monitor within 24 hours.

Amended Text:

In the event of an overdose, general symptomatic and supportive measures should be initiated promptly and maintained for as long as necessary. The investigator should consult the approved product labels for further information on treatment of overdose.

Permitted Medications (Section 8.1)

Original Text:

Salbutamol and/or ipratropium bromide for use as relief medication on an "as needed " (p.r.n.) basis will be provided throughout the study. Salbutamol and/or ipratropium bromide for use via a nebuliser will be provided for use as part of the bronchial biopsy, and sputum induction procedures

Amended Text:

Salbutamol (prn) and/or ipratropium bromide for use as relief medication will be provided throughout the study. Salbutamol and/or ipratropium bromide for use via a nebuliser will be provided for use as part of the bronchial biopsy, and sputum induction procedures.

Subject Withdrawal from Investigational Product (Section 9.2.2)

Original Text:

- Urinary pregnancy test (female subjects of child-bearing potential only)

Amended Text:

- **Clinical laboratory tests [Chemistry, Haematology, Urinalysis, Faecal Occult Blood test (FOB), and pregnancy testing for females of childbearing potential]**

Sputum Induction (Section 6.3.5.1)

Original Text:

The sputum will be collected and processed as described in the Sputum Procedures (SP) document. It is essential that the methodology described in the SP document be followed precisely. The induced sputum sample taken at **Visit 3 for the first subject** at each centre, (fixed slides and frozen supernatants) will be sent via QUEST Laboratories to John Hunter Hospital, Australia to confirm sputum sample quality and logistics. Each site must await confirmation from the John Hunter Hospital, Australia that the sample quality is acceptable**. If suitable, then this sample will be the Visit 3 sample**.

Amended Text:

The sputum will be collected and processed as described in the Sputum Procedures (SP) document. It is essential that the methodology described in the SP document be followed precisely. **An induced sputum sample should be taken, as a pilot sample at each centre**, (fixed slides and frozen supernatants) which will be sent via QUEST Laboratories to John Hunter Hospital, Australia to confirm sputum sample quality and logistics. Each site must await confirmation from the John Hunter Hospital, Australia that the sample quality is acceptable **prior to induction, and processing of any recruited subject sample**.

Bronchial Biopsy (Section 6.3.4)

Original Text:

Bronchial biopsies will be performed prior to randomisation (Visit 2/2A, week -1) and after 12 weeks of treatment (Visit 6/6A) or 7 days after early withdrawal from the study (if possible), **following the procedure of Dr** [redacted] The full procedure is described in the Bronchial Biopsy Procedures (BBP) document. It is essential that the methodology described in the BBP document be followed precisely. The following is

intended only as a summary of the procedures and should only be used in conjunction with the full methodology.

Amended Text:

Bronchial biopsies will be performed prior to randomisation (Visit 2/2A, week -1) and after 12 weeks of treatment (Visit 6/6A) or 7 days after early withdrawal from the study (if possible). The full procedure is described in the Bronchial Biopsy Procedures (BBP) document. It is essential that the methodology described in the BBP document be followed precisely. The following is intended only as a summary of the procedures and should only be used in conjunction with the full methodology.

Visit 1: Screening and Start of the 4-Week Run-In Period (Section 6.4.1)

Original Text:

Subjects considered by the investigator, as potential candidates for entry into the study will attend the clinic for a screening visit. They should have refrained from taking their $beta_2$-agonists and anticholinergics for at least 6 hours prior to the clinic visit. If this is not the case, a 6-hour period should elapse before pulmonary function tests are performed. Subjects will be asked to stop taking relief **VENTOLIN** at Visit 1 and will be provided with salbutamol and/or ipratropium bromide for the duration of the study.

Amended Text:

Subjects considered by the investigator, as potential candidates for entry into the study will attend the clinic for a screening visit. They should have refrained from taking their $beta_2$-agonists and **short-acting** anticholinergics for at least 6 hours prior to the clinic visit. If this is not the case, a 6-hour period should elapse before pulmonary function tests are performed. Subjects will be asked to stop taking relief **VENTOLIN** at Visit 1 and will be provided with salbutamol and/or ipratropium bromide for the duration of the study.

Prohibited Medications (Section 8.2)

Original Text:

- Long-acting anticholinergics e.g. tiotropium bromide
- Xanthines

Amended Text:

- Long-acting anticholinergics e.g. tiotropium bromide **(should be stopped 4 weeks before Visit 1)**
- Xanthines **(should be stopped 4 weeks before Visit 1)**

Time and Events Table (Appendix 1)

Original Text:

Visit	1	2/2A[9]	3	4	5	6/6A[9]	7	8	EWV[1]
Period	Screen	Baseline	Start of double-blind Treatment	Treatment				Follow-Up	
Duration (Weeks ± days)	-4 ± 3 days	-1 ± 3 days	0 ± 3 days	4 ± 3 days	8 ± 3 days	12± 3 days	13± 3 days	14± 3 days	
Signed written informed consent	X								
Inclusion/Exclusuion criteria	X		X						
Demography	X								
Medical & surgical history	X								
Postero-anterior chest radiograph [2]	X								
Pulmonary history & symptoms	X								
Concurrent Medication history	X								
Current Medical Conditions	X								
Compliance of Study Medication				X	X	X	X	X	X
Concomitant medication/medical procedures	X	X	X	X	X	X	X	X	X
Adverse Events	X*	X	X	X	X	X	X	X	X
Smoking history	X						X		X
Exacerbation assessment	X	X	X	X	X	X	X	X	X
Physical examination [3]	X							X	X[4]
Vital signs (BP,HR)		X	X			X	X	X	X
Resting SaO_2 [5]	X								
Salbutamol reversibility [6]	X								
Post bronchodilator PFTs [7]	X	X	X	X	X	X	X	X	X
Sputum induction and sample preparation			X				X		X[8]
Blood clotting tests	X				X				X
Bronchial biopsy and sample preparation		X				X			X[8]
Pregnancy testing	X							X	
Dispense double-blind medication			X						
Collect study medication				X	X	X	X	X	X

1. Subjects who withdraw between clinic visits will attend the clinic within 24 hours for an early withdrawal visit (EWV)
2. Postero-anterior chest X-ray must be is available to the Investigator by Visit 2 prior to taking the biopsy.
3. To include a respiratory examination
4. If abnormalities are present at previous visit for subjects who complete Week 13 or withdraw from the study
5. Resting SaO2 will be measured by pulse oximetry.
6. Before and 30 minutes after administration of 400mcg salbutamol via MDI and spacer to determine %predicted normal FEV1, and FVC
7. Includes FEV1, FVC, and SVC measured by the same person at each visit
8. Sputum should be performed, if possible 7 days after Bronchial biopsies which is done 1 week after the Early Withdrawal visit
9. The baseline and end of treatment bronchial biopsies will only be performed, if the safety criteria are met, otherwise the biopsy procedure should be rescheduled within 1 to 7 days (Visit 2A and Visit 6A respectively).

* Only SAEs related to study participation will be collected and reported from screening, all AEs should be collected.

Amended Text:

Visit	1	2/2A[9]	3	4	5	6/6A[9]	7	8	EWV[1]
Period	Screen	Baseline	Start of double-blind Treatment	Treatment				Follow-Up	
Duration (Weeks ± days)	-4 ± 3 days	-1 ± 3 days	0 ± 3 days	4 ± 3 days	8 ± 3 days	12± 3 days	13± 3 days	14± 3 days	
Signed written informed consent	X								
Inclusion/Exclusuion criteria	X		X						
Demography	X								
Medical & surgical history	X								
Postero-anterior chest radiograph [2]	X								
Pulmonary history & symptoms	X								
Concurrent Medication history	X								
Current Medical Conditions	X								
Compliance of Study Medication				X	X	X	X	X	X
Concomitant medication/medical procedures	X	X	X	X	X	X	X	X	X
Adverse Events	X*	X	X	X	X	X	X	X	X
Smoking history	X						X		X
Exacerbation assessment	X	X	X	X	X	X	X	X	X
Physical examination [3]	X							X	X[4]
Vital signs (BP,HR)		X	X			X	X	X	X
Resting SaO_2 [5]	X								
Salbutamol reversibility [6]	X								
Pre-and Post bronchodilator PFTs [7]	X	X	X	X	X	X	X	X	X
Sputum induction and sample preparation			X				X		X[8]
Blood clotting tests	X				X				X
Bronchial biopsy and sample preparation		X				X			X[8]
Clinical Laboratory & pregnancy testing	X						X		X
Faecal Occult Blood test (FOB)	X	X[10]					X	X[10]	X
Dispense double-blind medication			X						
Collect study medication				X	X	X	X	X	X

1. Subjects who withdraw between clinic visits will attend the clinic within 24 hours for an early withdrawal visit (EWV)
2. Postero-anterior chest X-ray must be is available to the Investigator by Visit 2 prior to taking the biopsy.
3. To include a respiratory examination
4. If abnormalities are present at previous visit for subjects who complete Week 13 or withdraw from the study
5. Resting SaO2 will be measured by pulse oximetry.
6. Before and 30 minutes after administration of 400mcg salbutamol via MDI and spacer to determine %predicted normal FEV1, and FVC
7. Includes FEV1, FVC, and SVC measured by the same person at each visit (please note only SVC at all other visits except visit 1)
8. Sputum should be performed, if possible 7 days after Bronchial biopsies which is done 1 week after the Early Withdrawal visit
9. The baseline and end of treatment bronchial biopsies will only be performed, if the safety criteria are met, otherwise the biopsy procedure should be rescheduled within 1 to 7 days (Visit 2A and Visit 6A respectively).
10. Assessment of FOB kit (which was given to subject at previous visit)

* Only SAEs related to study participation will be collected and reported from tscreening, all AEs should be collected.

15.3. Appendix 3: Protocol Amendment 2

AMENDMENTS:

Timing of Pre-Treatment biopsy Clarification

Protocol Summary

Study Design, 2nd paragraph, 1st sentence

Original Text:

Bronchial biopsies will be performed one week prior to randomisation for the baseline sample (i.e. at Week –1, Visit 2), at the end of **13 weeks'** treatment at Visit 6, or 1 week after Early Withdrawal Visit (EWV).

Amended Text:

Bronchial biopsies will be performed one week prior to randomisation for the baseline sample (i.e. at Week –1, Visit 2), at the end of **12 weeks'** treatment at Visit 6, or 1 week after Early Withdrawal Visit (EWV).

Clarification of Subject Withdrawals for Biopsy and Sputum

Main Body of Protocol
Section 6, 2nd Bullet Point

Original Text

- If the baseline biopsy sample is unevaluable (as ascertained by the central laboratory) the 2nd biopsy will not be performed. Similarly, if the baseline sputum is unevaluable (as acertained by the Central Laboratory) further samples will not be induced.

Amended Text

- If for any reason, both the baseline biopsy sample and the sputum sample are unobtainable, the subject should be withdrawn
- If the baseline biopsy sample is unobtainable but the baseline sputum sample is obtainable, the post-treatment biopsy should not be taken, but the sputum sample should be induced at the visit scheduled for sputum induction

3rd Bullet point, 1st sentence

Original Text

- In cases where the baseline sputum sample is evaluable but the baseline biopsy sample is unevaluable then a 2nd biopsy will not be taken but sputum samples will be induced at the visits sheduled for sputum induction

Amended Text

- If the baseline sputum sample is unobtainable, no further sputum samples should be taken, but biopsy samples should be taken as scheduled

Sputum Induction

Main Body of Protocol
Section 6.3.5.1, 1st sentence

Original Text:

Sputum induction will be conducted at Visit 3 (0) weeks, Visit 7 (+13 weeks), or 1 week after EWV if the biopsy was not possible to be taken.

Amended Text

Sputum induction will be conducted at Visit 3 (0) weeks, Visit 7 (+13 weeks), and if applicable at EWV, a week after taking the biopsy at EWV

Timings of Pulmonary Function Tests

Protocol Summary
Study Design, 3rd paragraph

Original Text:

At visit 1 pulmonary function tests (FEV_1, FVC, and slow SVC) will be conducted before and after administration of salbutamol 400mcg via an MDI and a **VOLUMATIC** spacer.

Amended Text:

At visit 1 pulmonary function tests (FEV_1, FVC, and slow SVC) will be conducted before and after administration of salbutamol 400mcg via an MDI and a **VOLUMATIC** spacer. At Visits, 2-8 and including the Early Withdrawal Visit (EWV), Slow Vital Capacity (SVC), (before and after the administration of salbutamol 400mcg via an MDI and a **VOLUMATIC** spacer) will be measured and recorded in the CRF.

In addition, at Visits 2/2A and 6/6A and at EWV (if applicable), before the biopsy procedures, FEV_1 (before and after the administration of salbutamol 400mcg via an MDI and a **VOLUMATIC** spacer) will be measured and the results recorded in the Biopsy Safety Form. FVC data generated while measuring the FEV_1 should be recorded in the subject's source notes.

At Visits 3 and 7, FEV_1 (before and after the administration of salbutamol 400mcg via an MDI and a **VOLUMATIC** spacer) will be measured as part of the sputum induction procedure. These results are not recorded in the CRF but are kept with the subject's source notes.

MAIN BODY OF PROTOCOL
Section 4 STUDY DESIGN, 3rd paragraph

Original Text:

At all visits pulmonary function tests (FEV_1, FVC, and SVC) will be conducted before and after administration of salbutamol 400mcg via an MDI and a **VOLUMATIC** spacer.

Amended Text:

At visit 1 pulmonary function tests (FEV_1, FVC, and slow SVC) will be conducted before and after administration of salbutamol 400mcg via an MDI and a **VOLUMATIC** spacer. At Visits, 2-8 and including the Early Withdrawal Visit (EWV), Slow Vital Capacity (SVC), (before and after the administration of salbutamol 400mcg via an MDI and a **VOLUMATIC** spacer) will be measured and recorded in the CRF.

In addition, at Visits 2/2A and 6/6A and at EWV (if applicable), before the biopsy procedures, FEV_1 (before and after the administration of salbutamol 400mcg via an MDI and a **VOLUMATIC** spacer) will be measured and the results recorded in the Biopsy Safety Form. FVC data generated while measuring the FEV_1 should be recorded in the subject's source notes.

At Visits 3 and 7, FEV_1 (before and after the administration of salbutamol 400mcg via an MDI and a **VOLUMATIC** spacer) will be measured as part of the sputum induction procedure. These results are not recorded in the CRF but are kept with the subject's source notes.

Footnote at the bottom of the Study Plan

Original Text:

PFT- Pulmonary Function Tests only at V1 (and only SVC at all other visits)

Amended Text:

PFT – Pulmonary Function Tests see Section 6.3.7 for details

Section 6 STUDY ASSESSMENTS AND PROCEDURES,

Last paragraph after last bullet point

Original Text:

Pulmonary Function Tests (PFT s) include measurements of FEV_1, SVC and FVC will be conducted at visit 1, and only SVC will be measured at all other visits before and after administration of salbutamol 400mcg via an MDI and VOLUMATIC spacer. All other procedures are outlined in the Time and Events Schedule (see Appendix 1**)**

Amended Text:

Pulmonary Function Tests (PFTs) will be conducted as outlined in Section 6.3.7. All other procedures are outlined in the Time and Events Schedule (see Appendix 1)

Section 6.1 Demographic and Baseline Assessments, Bullet point Number 10

Original Text:

- Pulmonary Function Tests (PFTs); FEV_1 and FVC including reversibility after administration of 400mcg of salbutamol only at V1, and slow vital capacity (SVC) at all other visits

Amended Text:

- Pulmonary Function Tests (PFTs): FEV_1, FVC and SVC including reversibility after administration of 400mcg of salbutamol will be conducted at Visit 1.

Section 6.3.7.1 Pulmonary Function Test and Reversibility Visit 1, 1st paragraph

Addition of bullet point after the formula:

- In addition to FEV_1, FVC and SVC measurements, both pre and post 400mcg salbutamol will also be recorded in the CRF.

Section 6.3.7.3 Pulmonary Function Tests All other visits (except Visit 1)

Original Text:

- For all other visits, pulmonary function test (SVC) will be assessed more than 6 hours after the last dose of salbutamol and/or ipratropium bromide. Subjects will also be asked to refrain from smoking in the 2 hours before their PFTs
- SVC will be performed in pre-and post salbutamol

Amended Text: Addition of 2 further bullet points after last bullet point :

- For all other visits, pulmonary function test (SVC) will be assessed more than 6 hours after the last dose of salbutamol and/or ipratropium bromide. Subjects will also be asked to refrain from smoking in the 2 hours before their PFTs
- SVC will be performed both pre-and post salbutamol
- In addition, at Visits 2/2A and 6/6A and at EWV (if applicable), before the biopsy procedures, FEV_1 (before and after the administration of salbutamol 400mcg via an MDI and a **VOLUMATIC** spacer) will be measured and the results recorded in the Biopsy Safety Form. FVC data generated while measuring the FEV_1 should be recorded in the subject's source notes.

- At Visits 3 and 7, FEV_1 (before and after the administration of salbutamol 400mcg via an MDI and a **VOLUMATIC** spacer) will be measured as part of the sputum induction procedure. These results are not recorded in the CRF but are kept with the subject's source notes.

FOB tests

Section 6.2.6 Clinical Laboratory tests [including Pre-Biopsy Test for blood clotting analysis Prior to Visits 2/2A and 6/6A and EWV (if appropriate)

Faeces:

1st sentence

Original Text:

Faecal occult blood tests between visit 1 (Screening), and Visit 2, visit 7 and visit 8 (End of treatment), or early withdrawal (three tests collected on consecutive bowel movements, if possible)

Amended Text:

Faecal occult blood tests will be conducted at Visits 2 and 7, and if applicable at Visits 8 (Follow-Up) and Early Withdrawal Visit (EWV) (three tests collected on consecutive bowel movements)

Last sentence:

Original Text:

Please note the FOB kit test should be done at home before the clinic visits (V2,V8 or EWV)

Amended Text:

Please note the FOB test should be done at home prior to the designated clinic visit

Section 6.4.1, Visit 1, Screening and Start of the 4-Week Run-In Period

11th bullet point

Amended Text:

Faecal Occult Blood Test (FOB) is removed

Section 6.4.7 Visit 6: (Week 12 of the Double-Blind Treatment Period)

Addition of a bullet point before the heading Reminders if Biopsy is not Rescheduled:

- Issue the FOB kit and ask the subject to bring the test sample to the next visit.

Section 6.4.9 Visit 7: (Week 13 Endof the Double-Blind Treatment Period)

9th Bullet point

Amended Text

- Issue the FOB kit only if a repeat sample is required, and if so, ask the subject to bring the test sample to the next visit

Section 6.4.11. Early Withdrawal Visit
4th paragraph, 2nd sentence

Original Text

At this visit, subjects will complete the following: SVC, vital signs, physical examination, and clinical laboratory tests (including FOB test)

Amended Text

At this visit, subjects will complete the following: SVC, vital signs, physical examination, and clinical laboratory tests (including FOB test if applicable)

Section 9.4 Early Withdrawal Assessments in the Treatment Period

2nd bullet point, 2nd sentence (end of sentence)

Original Text:

At this visit, subjects will complete the following : SVC, vital signs, physical examination, and clinical laboratory tests.

Amended Text:

At this visit, subjects will complete the following : SVC, vital signs, physical examination, and clinical laboratory tests (including FOB test if applicable).

Section 15.1 Appendix 1: Time and Events Table

Amended Text:

In the row for Faecal Occult Blood test (FOB), 10 has been added as superscript above the word FOB and the superscript 10 has been removed from above the X at Visits 2/2A and Visit 8. The superscript 11, has been added instead to the X at Visits 8 and EWV. A footnote for 11 has been added at the bottom of the Table which says " Assessment of FOB if applicable"

Physical Examination

Section 6.2.3 Visits 1, 8 and EWV, Last sentence

Original Text:

Any changes should be documented as a Baseline Sign or Symptom at Visit 1 or an Adverse Event at Visit 8, or the EWV.

Amended Text:

Any changes should be documented as an Adverse Event at Visit 8, or the EWV

Blinding Issues

Section 6.3.6, 1st sentence

Original Text:

To prevent the potential for reader bias based on knowledge of visit number; the slides (biopsy and sputum) produced for each subject visit will be assigned a random code number generated by GSK (a Slide Identification Number).

Amended Text:

To prevent the potential for reader bias based on knowledge of visit number; the sputum slides produced for each subject visit will be assigned a random code number generated by GSK (a Slide Identification Number). The biopsy tissue blocks for each subject will be identified by a unique number, generated by the Meakins-Christie Laboratory and the code will be kept blind to personnel involved in the counting of the cells.

Timing of Taking Consent

Section 6.4.1 Visit 1 Screening and Start of the 4-week Run-In Period Bullet point Number 1

Original Text:

- Written informed consent will be obtained **(Subjects who are on inhaled corticosteroids should give their consent 4 weeks prior to V1).**

Amended Text:

- Written informed consent will be obtained, before the patient is asked to stop taking any medication mentioned in Section 5.2.2 Exclusion Criteria number 11.

Provision of Rescue Medication

Section 5.2.3 Exclusion Criteria at Randomisation Visit (Visit 3)

Original Text:

1. Subjects who have had any changes to their COPD medication (other than salbutamol and/or Atrovent), received corticosteroids (oral or inhaled) for respiratory disease, or hospitalised for COPD/lower respiratory tract infections during the run-in period.

Amended Text:

1. Subjects who have had any changes to their COPD medication (other than salbutamol, ipratropium bromide or **Combivent**), received corticosteroids (oral or inhaled) for respiratory disease, or hospitalised for COPD/lower respiratory tract infections during the run-in period.

Section 8.1 Permitted Medications, Bullet point Number 2

Original Text:

- Salbutamol (prn) and/or ipratropium bromide (qid) for use as relief medication will be provided throughout the study. Salbutamol and/or ipratropium bromide for use via a nebuliser will be provided for use as part of the bronchial biopsy, and sputum induction procedures. The use of this medication must be recorded in the concomitant medication of the CRF.

Amended Text:

- Salbutamol (prn) and/or ipratropium bromide (prn) or Combivent for use as relief medication will be provided throughout the study. Salbutamol and/or ipratropium bromide or Combivent for use via a nebuliser will be provided for use as part of the bronchial biopsy, and sputum induction procedures. The use of this medication must be recorded in the concomitant medication of the CRF. Investigators must ensure that at each visit, the subject has sufficient rescue medication to last at least until the following visit. If the subject experiences symptoms that do not respond adequately to salbutamol and/or ipratropium bromide or Combivent, the subject must contact the investigator.

Section 8.1 Permitted Medications, 4th Bullet point

Amended Text

This bullet point referring to Combivent has been removed and incorporated in the text.

Section 6.3.7.3 – Section 7.1.1

Amended Text

Combivent has been added to references made in relation to rescue medication

Container Number

Section 6.4.4 Visit 3 (Week 0) Start of the Double-Blind Treatment Randomisation Criteria
Bullet Points Number 2 and 3 and addition of bullet point number 4

Original Text:

- RAMOS will randomise the subject, assign a treatment number (random number) and will read the appropriate container number of the treatment pack to be dispensed to the subject. Each random number and container number must only be allocated by RAMOS.
- Dispense the study medication for the 13 weeks of treatment and salbutamol and/or ipratropium bromide medication. Remind the subject to use the study treatment medication sequentially

Amended Text:

- RAMOS will randomise the subject, assign a random number and will read the appropriate container number for each of the 4 bottles to be dispensed to the subject for the duration of the treatment period. Each random number and container number must only be allocated by RAMOS. The investigator is advised to give the subject one bottle at each of the visits during the treatment period, rather than give all 4 bottles to the subject at this visit. If the subject were likely to delay his/her next visit for some reason, it would be appropriate to provide another bottle at the discretion of the investigator. The subject should be reminded to use the bottles sequentially
- Issue relief medication, salbutamol and/or ipratropium bromide or Combivent as appropriate (see Section 8.1)

Section 7.5 Treatment Assignment
Bullet points Number 2, 3 and 5 (last sentence)

Original Text:

- Each subject who satisfies the randomisation criteria will be assigned a unique Randomisation Number by IVRS. Once a randomisation number has been assigned to a subject, it cannot be reassigned to any other subject. Neither the subject nor the investigator will know which treatment has been allocated to the subject
- At visit 3, the subject will be provided with a double blind treatment bottle labeled with a 6 digit **Container Number**. Every **Container Number** is unique and corresponds to the study medication pack to be dispensed to the subject at this visit

- RAMOS will randomise the subject, assign the treatment umber and assign the study medication, by reading the appropriate Container Number of the Treatment bottle to be dispensed to the subject.

Amended Text:

- Each subject who satisfies the randomisation criteria will be assigned a unique **Random Number** by IVRS. Once a **Random Number** has been assigned to a subject, it cannot be reassigned to any other subject. Neither the subject nor the investigator will know which treatment has been allocated to the subject
- At visit 3, following randomisation, RAMOS will allocate four double blind treatment bottles via the IVRS system. Each bottle labeled with a 6 digit **Container Number** is unique and corresponds to the study medication pack to be dispensed to the subject. The investigator is advised to give the subject one bottle at each of the visits during treatment period, rather than give all 4 bottles to the subject at this visit. If the subject were to delay his/her next visit for some reason, it would be appropriate to provide another bottle at the discretion of the investigator. The subject should be reminded to use the bottles sequentially.
- RAMOS will randomise the subject, assign the treatment umber and assign the study medication, by reading the appropriate Container **Numbers** of the **four** Treatment **bottles** to be dispensed to the subject.

Study Medication Taken At Clinic Visits

Section 6.4.4 Visit 3 (week 0): Start Of the Double-Blind Treatment to Section 6.4.7 (Visit 6A (Only if Biopsy Has Been Rescheduled) Reminders: 1st point after bullet point number 1

Original Text:

– To take their study medication as demonstrated

Amended Text:

– To take their study medication as demonstrated. **Not to take** their morning dose of study medication at home on the morning of their next clinic visit, but to bring their medication with them to the clinic

Section 7.2 Dosage and Administration

Additional sentence at the end of last sentence

Original Text:

Subjects who fulfil the Randomisation Criteria will enter a 13-week double-blind treatment phase. Subjects will be randomised to receive either Cilomilast (SB 207499) 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.

Amended Text:

Subjects who fulfil the Randomisation Criteria will enter a 13-week double-blind treatment phase. Subjects will be randomised to receive either Cilomilast (SB 207499) 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. Subjects will be reminded **not to take their morning dose of study medication** at home on Clinic Visit days, but to bring their study medication with them to the clinic.

ECG

Section 10 ADVERSE EVENTS (AE) AND SERIOUS ADVERSE EVENTS Additional monitoring for gastrointestinal adverse events:

1st and last sentences

Original Text:

In order to address concerns identified pre-clinically with SB 207499 and drugs of a similar pharmacological class for an effect on the gut vasculature or heart, the gastrointestinal adverse experience profile will be defined and the ECG effects of SB 207499 will be assessed. Particular attention will be paid to collection of data on gastrointestinal adverse experiences with extensive monitoring (physical exam, laboratory assessments, faecal occult blood, orthostatic heart rate and blood pressure) for events of potential concern. Gastrointestinal adverse experiences (i.e., bloody or black stool, abdominal discomfort such as pain or cramps, diarrhoea, vomiting) which cause the patient concern or interfere with daily activities (including eating and sleeping) will be assessed by the Investigator within 24 hours of occurrence. The Investigator will review the results of the initial assessment and arrange further follow-up as appropriate. All events should be followed to resolution. The investigator should report the GI AEs to the GSK monitor within 24 hours of the first assessment.

Amended Text:

In order to address concerns identified pre-clinically with SB 207499 and drugs of a similar pharmacological class for an effect on the gut vasculature or heart, the gastrointestinal adverse experience profile will be defined. Particular attention will be paid to collection of data on gastrointestinal adverse experiences with extensive monitoring (physical exam, laboratory assessments, faecal occult blood, orthostatic heart rate and blood pressure) for events of potential concern. Gastrointestinal adverse experiences (i.e., bloody or black stool, abdominal discomfort such as pain or cramps, diarrhoea, vomiting) which cause the patient concern or interfere with daily activities (including eating and sleeping) will be assessed by the Investigator within 24 hours of occurrence. The Investigator will review the results of the initial assessment and arrange further follow-up as appropriate. All events should be followed to resolution. The investigator should record the GI AEs on the separate GI AE forms provided, and report the GI AEs to the GSK monitor within 24 hours of the first assessment.

Timing of Collecting AEs and SAEs

Protocol Summary
Study Assessments and Procedures
Bullet Point Number 6

Original Text:

- Any adverse events that the subject may have experienced during the study period

Amended Text:

Any adverse event that the subject may experience following consent (and the subject is asked to withdraw any prohibited medication), until the Follow-Up period

Section 6.1 Demographic and Baseline Assessments
Bullet Point Number 6

Original Text:

- Any adverse events that the subject may have experienced during 18 weeks of Visit 1

Amended Text:

- Any adverse event that the subject may experience from the time consent is obtained from the subject until the end of the Follow-Up period. AEs may include pre or post-treatment events that occur as a result of protocol mandated procedures (i.e. invasive procedures, modification of the subject's previous therapeutic regimen)

Section 6.4.1 2nd Bullet Point

Original Text:

- Any adverse experiences, which have occurred within the 4 weeks preceding this Visit, will be recorded on the Adverse Event Section of the CRF and followed up, as appropriate (see Section 10).

Amended Text:

- Any adverse event that the subject may experience from the time consent is obtained from the subject. AEs may include pre or post-treatment events that occur as a result of protocol mandated procedures (i.e. invasive procedures, modification of the subject's previous therapeutic regimen). Adverse events will be recorded on the Adverse Event Section of the CRF and followed up, as appropriate (see Section 10).

Section 10.6 Time Period, Frequency, and Method of Detecting AEs and SAEs
1st sentence

Original Text:

The time period for collecting other AEs will begin at randomisation or the first receipt of investigational product until the end of the follow-up period. SAEs that are related to study participation (e,g. procedures, invasive tests, a change from existing therapy) or are related to a concurrent medication will be collected and recorded from the time the subject consents to participate in the study until he/she withdraws or completes the study.

Amended Text:

The time period for collecting other AEs and SAEs will begin from the time consent is obtained from the patient till the end of the Follow-Up period. SAEs that are related to study participation (e,g. procedures, invasive tests, a change from existing therapy) or those that are related to a concurrent medication will be collected and recorded from the time the subject consents to participate in the study until he/she withdraws or completes the study.

Section 15.1 APPENDIX 1: Time and Events Table
Last footnote (*) at the bottom of the Time and Events Table

Original Text

Only SAEs related to study participation will be collected and reported from screening , all AEs should be collected

Amended Text

Any adverse event from the time of consent when subjects may be asked to withdraw their current medication till the Follow-Up period.

Timing of Clinic Visits

Section 6.4 Outline of Study Procedures at each Clinic Visit
2nd paragraph, 2nd sentence

Original Text:

Clinic visits should be scheduled at 10.00 am ± 2 hours

Amended Text:

Clinic visits should be scheduled at the same time of day (± 2 hours) and should be conducted preferably in the morning

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Document Type:	Reporting and Analysis Plan	**Study Identifier:**	SB-207499/181
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Reporting and Analysis Plan for SB-207499/181. A 13-Week Randomised, Multicentre, Double-blind, Parallel-group Study to Compare the Anti-inflammatory Activity of Oral Cilomilast (15 mg bd) with Placebo Twice Daily in Subjects with Chronic Obstructive Pulmonary Disease (COPD).

Abstract: (For Internal Use Only)

A 13-week randomised, double-blind, placebo-controlled, parallel-group multicentre study to compare the bronchial anti-inflammatory activity of oral Cilomilast (15 mg bd) with placebo twice daily in subjects with Chronic Obstructive Pulmonary Disease (COPD)

Authors: [redacted]

Compound Numbers/Keywords (if applicable): SB207499/181

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Study Title: A 13-Week Randomised, Multicentre, Double-blind, Parallel-group Study to Compare the Anti-inflammatory Activity of Oral Cilomilast (15 mg bd) with Placebo Twice Daily in Subjects with Chronic Obstructive Pulmonary Disease (COPD).

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Type Name Type Approver's Title and Functional Area	_____	_____

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Reporting and Analysis Plan for SB-207499/181. A 13-week randomised, Multicentre, Double-blind, Parallel-group Study to compare the Anti-inflammatory Activity of oral Cilomilast (15 mg bd) with placebo Twice Daily in subjects with Chronic Obstructive Pulmonary Disease (COPD).

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Date of Issue:

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1. INTRODUCTION 6

2. STUDY OBJECTIVE(S) AND ENDPOINT(S) 6

2.1. STUDY OBJECTIVE(S) 6

2.2. STUDY ENDPOINT(S) 6

2.2.1. Primary Endpoints 6
2.2.2. Secondary Endpoints 7
2.2.3. Tertiary Endpoints 7
2.2.4. Safety Endpoints 7

2.3. STATISTICAL HYPOTHESES 8

3. STUDY DESIGN 8

4. PLANNED ANALYSES 8

4.1. INTERIM ANALYSES 8

4.2. META-ANALYSIS 9

5. SAMPLE SIZE CONSIDERATIONS 9

5.1. SAMPLE SIZE SENSITIVITY 9

5.2. SAMPLE SIZE RE-ESTIMATION 9

6. ANALYSIS POPULATIONS 10

6.1. RANDOMISED POPULATION 10

6.2. PER-PROTOCOL (PP) POPULATION 10

6.3. INTENT-TO-TREAT (ITT) POPULATION 10

6.4. PROTOCOL VIOLATIONS 10

6.4.1. Violations of Eligibility Criteria 10
6.4.2. Excluded Medication 11
6.4.3. Visit Specific Protocol Violations 11
6.4.4. Conduct of Study Deviations 11

7. TREATMENT COMPARISONS 12

7.1. PRIMARY COMPARISONS OF INTEREST 12

7.2. OTHER COMPARISONS OF INTEREST 12

8. GENERAL CONSIDERATIONS FOR DATA ANALYSES 12

8.1. POOLING OF CENTRES FOR EFFICACY ANALYSIS 12

8.2. MULTIPLICITY 12

8.3. SUB-POPULATIONS OF INTEREST 13

8.4. MULTICENTRE STUDIES 13

8.5. OTHER STRATA AND COVARIATES 13

8.6. EXAMINATION OF SUBGROUPS 13

8.7. MULTIPLE COMPARISONS AND MULTIPLICITY 13

9. DATA HANDLING CONVENTIONS 13

9.1. MISSING DATA 13

9.2. DERIVED DATA 13
9.2.1. Baseline and Endpoint 13
9.2.2. Duplicate or repeated observations 14
9.2.3. Study Medication Record 14
9.2.4. Compliance 15
9.2.5. Visit Dates 15
9.2.6. Last Study Day 15
9.2.7. Prior, Concomitant and Post-therapy Medications 16
9.2.8. Pulmonary Function Tests (PFTs) 16
9.2.9. COPD Exacerbation 16
9.2.10. Bronchial Biopsy 16
9.2.11. Sputum Induction 17
9.2.12. Adverse Events 17
9.2.13. Clinical Laboratories /Vital Signs /Orthostatic Vital Signs 17
9.3. ASSESSMENT WINDOWS 19
9.4. VALUES OF CLINICAL CONCERN 19

10. STUDY POPULATION 20
10.1. DISPOSITION OF SUBJECTS 20
10.2. PROTOCOL DEVIATIONS 20
10.3. DEMOGRAPHIC AND BASELINE CHARACTERISTICS 20
10.4. TREATMENT COMPLIANCE 20

11. EFFICACY ANALYSES 20
11.1. PRIMARY EFFICACY ANALYSES 20
11.1.1. Primary Analysis of CD68+ and CD8+ in Biopsy 21
11.1.2. Sensitivity Analysis to Access Impact on Primary Analysis 21
11.1.3. Treatment by Centre Interaction 21
11.1.4. Normality of Underlying Data 21
11.2. SECONDARY EFFICACY ANALYSES 21
11.3. OTHER EFFICACY ANALYSIS 21

12. SAFETY ANALYSES 22
12.1. EXTENT OF EXPOSURE 22
12.2. ADVERSE EVENTS 22
12.3. DEATHS AND SERIOUS ADVERSE EVENTS 22
12.4. DEVICE INCIDENTS AND NEAR INCIDENTS 22
12.5. ADVERSE EVENTS LEADING TO DISCONTINUATION OF INVESTIGATIONAL PRODUCT AND/OR WITHDRAWAL FROM THE STUDY AND OTHER SIGNIFICANT ADVERSE EVENTS 22
12.6. PREGNANCIES (AS APPLICABLE) 22
12.7. CLINICAL LABORATORY EVALUATIONS 22
12.8. OTHER SAFETY MEASURES 23

13. HEALTH OUTCOMES ANALYSES 23

14. CLINICAL PHARMACOLOGY DATA ANALYSES 23

15. BIOMARKER DATA ANALYSIS 23

16. PHARMACOGENETIC DATA ANALYSES 23

17. VIRAL GENOTYPING/PHENOTYPING 23

18. REFERENCES 23

19. ATTACHMENTS 24

19.1. TABLE OF CONTENTS FOR DATA DISPLAY SPECIFICATIONS 24

19.2. DATA DISPLAY SPECIFICATIONS 33

Demographic *33*
Efficacy *49*
Safety *61*
Figures *75*
Appendix *79*

List of Abbreviations

AE	adverse Event
BBPD	Bronchial Biopsy Procedures Document
bd	Twice daily
BTPS	Body temperature and Pressure , saturated with water vapour (referring to conditions in the lung) All spirometric recordings should be corrected to BTPS conditions
CD4, 8, 45 and 68	Cluster of Differential molecules 4, 8, 45 and 68
CIB	Clinical Investigator's Brochure
COPD	Chronic Obstructive Pulmonary Disease
CRF	Clinical Record Form
D-PBS	Dulbecco's-Phosphate buffered saline
DRC	Daily Record Card
DQ	Data Queries
ECCS	European Community for Coal and Steel
EISR	Expedited Investigator Safety Report
EWV	Early Withdrawal Visit
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilence
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GSK	GlaxoSmithKline
IEC	Independent Ethics Committee
IFN	Interferon gamma
IL-8	Interlukin -8
IRB	Institutional Review Board
ITT	Intent-To-Treat
IUD	Intrauterine Device
IVRS	Interactive Voice Response System
LTOT	Long Term Oxygen Therapy
MDI	Metered Dose Inhaler
NSAID (s)	Non-Steroidal Anti-Inflammatory Drug (s)
PFT	Pulmonary Function test
PP	Per Protocol
RAMOS	Registration and Medication Ordering System
SAE	Serious Adverse Event
SCA	Standard Clarification Agreement
SaO_2	Saturated Oxygen
SPD	Sputum Procedures Document

1. INTRODUCTION

A previous multicentre study (207499/076), which was design to evaluate the anti-inflammatory effects of Cilomilast, has been completed successfully. Study 181 is a similar design to further explore the potential for Cilomilast to demonstrate anti-inflammatory effects in subject with COPD. This is a randomised, double-blind, placebo-controlled, parallel-group multicentre study in subjects with moderate to severe COPD involving 8 visits over an 18-week. A four week single-blind placebo run-in period will be followed by 13 weeks of treatment with double-blind study medication. A follow-up visit will be conducted within 7 ± 3 days of the completion of the 13-week double-blind phase or withdrawal from the study.

Patients eligible to enter the double-blind period must meet the randomisation criterion as defined in the protocol. Qualifying patients will be randomised in a 1:1 ratio to receive either Cilomilast or matching placebo tablets twice daily (bd).

2. STUDY OBJECTIVE(S) AND ENDPOINT(S)

2.1. Study Objective(s)

A previous multicentre study (207499/076), which was design to evaluate the anti-inflammatory effects of Cilomilast, has been completed successfully. Study 181 is a similar design to further explore the potential for Cilomilast to demonstrate anti-inflammatory effects in subject with COPD. This is a randomised, double-blind, placebo-controlled, parallel-group multicentre study in subjects with moderate to severe COPD involving 8 visits over an 18-week period. A four week single-blind placebo run-in period will be followed by 13 weeks of treatment with double-blind study medication. A follow-up visit will be conducted within 7 ± 3 days of the completion of the 13-week double-blind phase or withdrawal from the study.

Patients eligible to enter the double-blind period must meet the Randomisation Criterion as defined in the protocol. Qualifying patients will be randomised in a 1:1 ratio to receive either Cilomilast or matching placebo tablets twice daily.

2.2. Study Endpoint(s)

2.2.1. Primary Endpoints

The co-primary variables in this study are the changes from baseline to end of therapy of,

(1) sub-epithelial CD68+ (macrophages) per area of biopsy tissue and,

(2) sub-epithelial CD8+ (cytotoxic T-lymphocytes) per area of biopsy.

2.2.2. Secondary Endpoints

Secondary endpoints can be classified into two categories.

(1) **For Biopsy**: Compare the number of the following sub-epithelial cells per area of biopsy tissue from subjects treated with Cilomilast and placebo:

- Neutrophil elastase positive cells (neutrophils)
- CD4+ lymphocytes
- IL-8 mRNA positive cells
- TNFα mRNA positive cells
- CD45 positive cells
- Mucin expression

(2) **For Sputum**: Compare the number of the following cells in sputum per unit volume from subjects treated with Cilomilast and placebo:

- Sputum total cell count and differential cell counts
- Macrophages as a percentage of total cells and as a total cell count per unit volume
- Eosinophils as a percentage of total cells and as a total cell count per unit volume
- Lymphocytes as a percentage of total cells and as a total cell count per unit volume
- Neutrophil elastase
- IL-8

2.2.3. Tertiary Endpoints

- Slow Vital Capacity (SVC).

2.2.4. Safety Endpoints

- Incidence of adverse events
- Vital signs

- Clinical laboratory tests [Chemistry, Haematology, Urinalysis, Faecal Occult Blood test (FOB), and pregnancy testing for females of childbearing potential].

2.3. Statistical Hypotheses

The primary null hypotheses of this study are the mean changes from baseline, in CD68 and CD8 cell counts per tissue area, are the same for placebo and Cilomilast. That is the null hypotheses are $H_0 : \mu_{CD68(c)} = \mu_{CD68(p)}$ and $H_0 : \mu_{CD8(c)} = \mu_{CD8(p)}$ where *c* represents the Cilomilast group and *p* represents the placebo group. The alternative hypotheses are that the mean changes are not the same, $H_a : \mu_{CD68(c)} \neq \mu_{CD68(p)}$ and $H_a : \mu_{CD8(c)} \neq \mu_{CD8(p)}$. Change from baseline is the difference between the value at endpoint (Week 12, Visit 6 or one week after the Early Withdrawal Visit) and at baseline (Week –1, Visit 2).

3. STUDY DESIGN

This is a randomised, double-blind, placebo-controlled, parallel-group multicentre study in subjects with moderate to severe COPD. Subjects will complete a four week single blind placebo run-in period before randomisation to Cilomilast 15mg bd or placebo bd for thirteen weeks. This will be followed by a one week follow-up period.

Bronchial biopsies will be performed one week prior to randomisation for the baseline sample (i.e. at Week –1, Visit 2), at the end of 12 week's treatment at visit 6, or 1 week after the Early Withdrawal Visit. The baseline and end of treatment bronchial biopsies will only be performed, if the safety criteria listed in the Bronchial Biopsy Procedures Document are met, otherwise the biopsy procedure should be rescheduled within 1 to 7 days (Visit 2A and Visit 6A respectively). An induced sputum sample will be collected at visit 3 (Week 0), at Visit 7 (at the end of 13 week's treatment) and at the Early Withdrawal Visit if a biopsy was not done.

In addition to the above, at visit 1, pulmonary function tests (FEV1, FVC and SVC) will be conducted before and after administration of salbutamol 400mcg via an MDI and a VOLUMATIC spacer. The randomisation schedule will be generated in blocks using RANDALL and the GlaxoSmithKline Registration and Medication Ordering System (GSK RAMOS).

4. PLANNED ANALYSES

Data will be unblinded and the database will be frozen after quality of the data has met GSK standards.

4.1. Interim Analyses

There is no planned interim analysis for this study.

4.2. Meta-Analysis

There is no planned Meta-analysis for this study.

5. SAMPLE SIZE CONSIDERATIONS

The study population will consist of approximately 86 patients for per protocol analysis. In order to reach that number, the study will enrol 116 patients in a 1: 1 ratio to receive either Cilomilast 15 mg twice daily or placebo. The GSK Biometrics Unit will generate the randomisation code.

The sample size estimates are obtained based on the results of study 076. The proposed sample size will ensure 90% power to detect a difference of 175 in CD8+ between Cilomilast and placebo at significant level of 2.5% with an assumed common standard deviation 230. The target sample size will also ensure more than 99% power to detect a difference of 80 in CD68+ between Cilomilast and placebo at significant level of 2.5% with an assumed common standard deviation 75.

5.1. Sample Size Sensitivity

Calculating the required sample sizes for various standard deviations assessed the sample size sensitivity. The results are illustrated in Table 1. From Table 1 it is clear that the sample size is reasonably insensitive to changes of standard deviation.

Table 1 Sample Size Sensitivity (sample size = 43/arm)

Hypothesis	Standard Deviation	Sample Size
CD8	210	36
	220	40
	230	43
	240	47
	250	51
CD68	55	12
	65	17
	75	22
	85	29
	95	36

5.2. Sample Size Re-estimation

There is no planned sample size re-estimation for this study

6. ANALYSIS POPULATIONS

There are two defined populations of interest, an Intent-To-Treat (ITT) population and a Per-Protocol (PP) population. The results from the Per-Protocol population are of primary interest. The randomised population is also of interest for subject accountability.

6.1. Randomised Population

This population consists of all patients who have a randomisation id number assigned and are confirmed to receive at least one dose of double-blind study medication. All safety variables will be analysed for this population.

6.2. Per-protocol (PP) Population

The primary analysis for efficacy in this study will be based on the per-protocol population. Patients with violations of eligibility criteria will be excluded entirely from this analysis. Patients with violations occurring post-randomisation will have data collected subsequent to the violation excluded. Because of their potential to confound measurement of the primary endpoint, any data collected subsequent to the onset of a patient's initial COPD exacerbation will also be excluded from the per-protocol analysis. Protocol violations resulting in exclusion of data from the per-protocol analysis will be documented in full prior to unblinding the study.

6.3. Intent-to-treat (ITT) Population

The intent-to-treat population will include all patients who receive randomised study medication, have 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 will be excluded from the analysis.

6.4. Protocol Violations

Subject data will be examined for evidence of protocol violations in order to assess how well the protocol was followed.

6.4.1. Violations of Eligibility Criteria

For the following violations all primary endpoint data are excluded from the per-protocol analysis,

- Pre- bronchodilator FEV_1/FVC ratio > 0.7 at Visit 1,
- Increase in FEV_1 of > 10% of predicted normal and > 200 ml following salbutamol at Visit 1,

- Post- salbutamol FEV_1 <40% or >80% of predicted value at Visit 1,
- O_2 saturation < 88%.

6.4.2. Excluded Medication

Unless stated otherwise any primary endpoint data collected after the initiation of an excluded medication, listed below, is excluded from per-protocol analysis,

- Inhaled, oral and systemic corticosteroids use within 4 weeks prior to Visit 1,
- Concomitant oral or IV xanthine use within 4 weeks prior to Visit 1,
- Concomitant oral or inhaled long-acting beta-2 agonist use within 2 weeks prior to Visit 1,
- Oral beta-2 agonist and nebulised beta-2 agonists,
- Long-acting Anticholinergic use that is discontinued within 4 weeks prior to Visit 1,
- Concomitant leukotriene modifiers
- Sodium cromoglycate and nedocromil sodium
- NACs(N-Acetyl Cysteine).

6.4.3. Visit Specific Protocol Violations

For these violations data collected at the visit is excluded from the per-protocol analysis,

- Study medication compliance <80% or >120% during active, on-therapy dosing,
- Salbutamol/albuterol and/or anticholinergic medication within 6 hours of pulmonary function testing. This protocol violation will only apply to the pulmonary function tests.

6.4.4. 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),

- Moderate or severe exacerbation of COPD within 6 weeks prior to visit 3,
- Smoking within 2 hours of pulmonary function testing (at visit 3 or later).

7. TREATMENT COMPARISONS

7.1. Primary Comparisons of Interest

For biopsy measures the primary analysis will be a comparison between groups in the per-protocol population at endpoint. Endpoint, for any measurement, is defined as the last evaluable (measured prior to occurrence of protocol violation) observation in the double blind treatment period. The primary comparisons will be based on an ANOVA model. A comparison will be done for the difference in change from baseline at endpoint between the Cilomilast group and the placebo group in both CD68 and CD8 cell counts per area tissue, while controlling for centre effect and if present centre by treatment interaction. The primary comparisons will be performed at an alpha level of 0.05. Hochberg method will be used to adjust the p-value (Hochberg; Biometriks, 1988).

7.2. Other Comparisons of Interest

Secondary comparisons of interest will be the comparison between treatment groups at Week 13 for sputum and Week 12 for biopsy measures.

For lung function measure, SVC, the comparison of interest between groups will be in the intent to treat population at all scheduled visit (Week 4, 8, 12 and 13) and endpoint (defined as the last on therapy measurement in the double blind treatment period for each patient).

8. GENERAL CONSIDERATIONS FOR DATA ANALYSES

8.1. Pooling of Centres for Efficacy Analysis

For the analysis of the primary endpoint centres will not be pooled unless it is found that it is impossible to perform the analysis without doing so. In this situation centres will be pooled by country or region for the analysis.

8.2. Multiplicity

The comparison between Cilomilast and placebo, based on the Per-Protocol population for the primary endpoints CD68+ and CD8+ are of primary interest.

As there are two primary endpoints of interest, the modified Bonferroni procedure of Hochberg[1] will be used to adjust for primary endpoints.

8.3. Sub-populations of Interest

Statistical analysis for the primary efficacy variables (CD68+ and CD8+) will be performed by smoking status (Smoker and non-smoker). ANOVA models will be used with the population subsetted by baseline smoking status. Multiplicity issues will not be addressed.

8.4. Multicentre Studies

8.5. Other Strata and Covariates

8.6. Examination of Subgroups

8.7. Multiple Comparisons and Multiplicity

9. DATA HANDLING CONVENTIONS

9.1. Missing Data

Missing data arising from patients sporadically missing visits or assessments at visits will be assumed missing completely at random. No attempts will be made to assess the impact of missing data arising by this mechanism.

9.2. Derived Data

9.2.1. Baseline and Endpoint

9.2.1.1. Baseline

In general the last non-missing evaluation prior to the first dose is defined as baseline. The baseline bronchial biopsy will be performed prior to randomisation (visit 2/2A, week –1) and the baseline sputum induction will be conducted at visit 3 (week 0).

If the baseline biopsy sample is unevaluable (as ascertained by the central laboratory) the second biopsy will not performed. Similarly, if the baseline sputum is unevaluable, further sputum samples will not be induced.

[1] Hochberg Y. 1988. A sharper Bonferroni procedure for multiple tests of significance. Biometrika, 75, 800-802.

For vital signs and temperature, evaluations occurring within fifteen minutes post first dose of double-blind study medication will be considered for baseline.

For laboratory evaluations, only date is compared. Laboratory samples collected in association with Gastro-intestinal Adverse Events (GI AEs) of concern on the date of the randomisation visit or prior to the date of the randomisation visit will not be considered for baseline.

9.2.1.2. Endpoint

Endpoint will be defined as the last non-missing on-therapy assessment collected for a patient regardless of the type of visit the assessment was collected at. For bronchial biopsy, the endpoint will be defined as the assessment at week 12 of treatment (Visit 6/6A) or one week after Early Withdrawal. The endpoint for sputum is defined as the assessment at visit 7 (13 weeks).

9.2.2. Duplicate or repeated observations

Multiple biopsy and sputum results, for the efficacy endpoints for each subject at each visit, will be provided. These observations will be averaged. In all other cases where multiple observations are available or tests are repeated for a particular visit, the latest evaluation will be used in the analysis. If a latest evaluation can not reasonably be determined based on date and/or time then the average of the multiple evaluations will be taken.

9.2.3. Study Medication Record

9.2.3.1. Date of First Dose in the Double-blind Period

The date of the first dose of study medication will be taken from the start date of double-blind medication field on the investigational product panel. If this date is missing then the visit date for visit 3 will be used.

9.2.3.2. Date of Last Dose in the Double-blind Period

Date of the last dose will be taken from stop date of the treatment period double-blind medication field on the investigational product panel. If this date is missing then the visit date for visit 7 will be used unless the subject withdrew in which case the visit date from the early withdrawal visit will be used.

9.2.3.3. Exposure to Double-blind Study Medication

Exposure to double-blind study medication will be calculated according to the following:

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

A Randomised patient whose date of first dose is not available but are confirmed to have received a dose of double-blind study medication will have an assumed exposure of one day.

Relative Day is defined as,

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

For assessments and events occurring prior to the date of first dose of double-blind study medication, "1" will not be added when calculating the relative day.

9.2.4. Compliance

9.2.4.1. Number of Tablets Consumed

The number of tablets consumed is defined as,

(num. tablets dispensed) – (num. tablets returned) – (num. tablets lost)

9.2.4.2. Number of Days Between Visits

The number of days between visits is defined as,

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

9.2.4.3. Visit Level Compliance

Visit level compliance is defined as,

$$\frac{100 * (\text{number of tablets consumed at a visit})}{2 * (\text{number of days between visits})}$$

9.2.4.4. Overall Compliance

Overall compliance is defined as,

$$\frac{100 * \sum \text{umber of tablets consumed at a visit})}{2 * \sum \text{umber of days between visits})}$$

9.2.5. Visit Dates

The date for each visit will be defined as the date recorded within the CRF for that visit. If this date is not available, the date from the COPD pulmonary function tests will be used. If this date is missing as well the earliest visit date recorded for the visit will be used.

9.2.6. Last Study Day

The last study day is defined as the last visit day regardless of withdrawal.

9.2.7. Prior, Concomitant and Post-therapy Medications

9.2.7.1. Prior Medications

Prior medications are any medication used prior to the date of the first dose including those, which continued beyond the date of first dose of double-blind study medication.

9.2.7.2. Concomitant Medications

Concomitant medications are any medications initiated post the date of the first dose of double-blind study medication and prior to the last dose of double-blind study medication. Medications initiated prior to the date of the first dose of double-blind study medication and continued on or after the date of the first dose of double-blind study medication will also be considered concomitant.

9.2.7.3. Post-therapy Medications

Post-therapy medications are any medication initiated on or after the date of last dose of double-blind study medication. This does not include medications continuing from the double-blind period.

9.2.8. Pulmonary Function Tests (PFTs)

FEV_1, FVC, SVC and FEV_1 / FVC ratio will be measured according to BTPS (Body Temperature and Pressure Standard) convention. At each assessment, pulmonary function test will be performed three times. For each set of three FEV_1, SVC and FVC measurements, the highest measurement will be taken. SVC will be performed in all visits but FEV_1 and FVC will only be measured at visit 1.

9.2.9. COPD Exacerbation

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

9.2.10. Bronchial Biopsy

Bronchial biopsies will be performed prior to randomisation (Visit 2/2A, week –1) and after 12 weeks of treatment (Visit 6/6A) or 7 days after early withdrawal from the study. The full procedure is described in the Bronchial Biopsy Procedure (BBP) Document.

9.2.11. Sputum Induction

Sputum induction will be performed at Visit 3 (Week 0), Visit 7 (Week 13) or one week after early withdrawal from the study. The sputum will be collected and processed in accordance with the Sputum Procedures (SP) document. If the sputum results are found to be below the lowest level of detection, one half of this lower level of detection will be used.

9.2.12. Adverse Events

9.2.12.1. Baseline Signs and Symptoms

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

9.2.12.2. On-therapy Adverse Events

Any event with an onset date on or after the date of first dose of double-blind study medication and prior to two days after the last dose of double-blind study medication.

9.2.12.3. Post-therapy Adverse Event

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

9.2.12.4. Adverse Event Leading to Withdrawal

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

9.2.12.5. 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.

9.2.13. Clinical Laboratories /Vital Signs /Orthostatic Vital Signs

9.2.13.1. On-therapy assessments

Any assessments performed after the first dose of double-blind study medication and no later than one day after the last dose of double-blind study medication. Visit 3 labs associated with GI AEs of concern will also be considered on-therapy.

9.2.13.2. Worst-case On-therapy Assessments

This is defined as the result with the highest concern level observed during the double-blind treatment period. Patients who are beyond the normal range in both the high and low direction during the double-blind period will be presented in both categories.

9.2.13.3. Calculation of Orthostatic Changes

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

$$\text{Orthostatic Change} = \text{measurement}_{\text{dependent}} - \text{measurement}_{\text{supine}}$$

9.3. Assessment Windows

9.4. Values of Clinical Concern

Table 2 Laboratory Values of Interest and Potential Clinical Concern

Parameter	Low Value of Concern	Low	High	High Value of Concern
Hemoglobin	<0.8 x LLN	[0.8 x LLN - 1 x LLN)	(1 x ULN - 1.2 x ULN]	> 1.2 x ULN
Hematocrit	<0.8 x LLN	[0.8 x LLN - 1 x LLN)	(1 x ULN - 1.2 x ULN]	> 1.2 x ULN
WBC	≤3.0 x 103/mm3	(3.0 x 103/mm3 - 1 x LLN)	(1 x ULN - 20.0 x 10^3/mm^3)	≥ 20.0 x 10^3/mm^3
Neutrophil (total)	<0.8 x LLN	[0.8 x LLN - 1 x LLN)	(1 x ULN - 1.5 x ULN]	> 1.5 x ULN
Eosinophil	not defined	not defined	(1 x ULN - 2 x ULN]	> 2 x ULN
Platelet Count	<100 x 109/L	[100 x 109/L - 1 x LLN)	(1 x ULN - 500 x 10^9/L]	> 500 x 10^9/L
AST (SGOT)	not defined	not defined	(1 x ULN - 2 x ULN]	> 2 x ULN
ALT (SGPT)	not defined	not defined	(1 x ULN - 2 x ULN]	> 2 x ULN
GGT	not defined	not defined	(1 x ULN - 2.5 x ULN]	> 2.5 x ULN
Total Bilirubin	not defined	not defined	(1 x ULN - 1.5 x ULN]	> 1.5 x ULN
Alkaline Phosphatase	not defined	not defined	(1 x ULN - 2 x ULN]	> 2.0 x ULN
Creatinine	<0.5 x LLN	[0.5 x LLN – 1 x LLN)	(1 x ULN - 1.5 x ULN]	> 1.5 x ULN
BUN (SI Units)	not defined	not defined	(1 x ULN - 17.85 mmol/L]	> 17.85 mmol/L
BUN (non-SI Units)	not defined	not defined	(1 x ULN - 50 mg/dL]	> 50 mg/dL
Urea	not defined	not defined	(1 x ULN - 17.85 mmol/L]	> 17.85 mmol/L
Sodium (SI Units)	≤130 mmol/L	(130 mmol/L - 1 x LLN)	(ULN - 150 mmol/L)	≥ 150 mmol/L
Sodium (non-SI Units)	≤130 mEq/L	(130 mEq/L - 1 x LLN)	(ULN - 150 mEq/L)	≥ 150 mEq/L
Potassium (SI Units)	≤3.0 mmol/L	(3.0 mmol/L - 1 x LLN)	(ULN - 5.5 mmol/L)	≥ 5.5 mmol/L
Potassium (non-SI Units)	≤3.0 mEq/L	(3.0 mEq/L - 1 x LLN)	(ULN - 5.5 mEq/L)	≥ 5.5 mEq/L
Glucose	<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 3 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 mmHg
Orthostatic Change in Diastolic BP	not defined	not defined	not defined	decrease ≥ 10 mmHg
Orthostatic Change in Heart Rate	not defined	not defined	not defined	increase of ≥ 10 bpm

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

10. STUDY POPULATION

10.1. Disposition of Subjects

Baseline and demographic characteristics will be summarised using 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 GSK Drug dictionary. The number and percentage of patients will be summarised according to generic terms.

Patient compliance will be calculated at each visit. The number of patients below 80% and above 120% will be presented. Descriptive statistics will also be presented

10.2. Protocol Deviations

10.3. Demographic and Baseline Characteristics

10.4. Treatment Compliance

11. EFFICACY ANALYSES

11.1. Primary Efficacy Analyses

All linear models to assess treatment effects for efficacy measures will be performed using SAS procedure MIXED.

11.1.1. Primary Analysis of CD68+ and CD8+ in Biopsy

The assessment of treatment differences for the primary efficacy variables will be based on an analysis of variance model with effects for centre and treatment group. Least squares means along with associated 95% confidence intervals will be calculated for each treatment group. Least squares means and ninety-five percent (95%) confidence intervals will also be calculated for the treatment difference. Differences between treatment groups will be assessed using T-tests on the least square means. Primary endpoints will also be analysed by smoking status.

11.1.2. Sensitivity Analysis to Access Impact on Primary Analysis

The robustness of the inference from the above analysis of variance model will be explored with respect to inclusion/exclusion of covariates, treatment by centre interaction, and normality of the underlying data.

11.1.3. Treatment by Centre Interaction

Testing for treatment-by-centre interaction will be performed 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-centre interaction is observed then further analysis within the centre will be explored.

11.1.4. Normality of Underlying Data

The normality assumption of the underlying data will be explored through graphical examination of the residuals. The degree and effects of departures from normality will be assessed through normal probability plots of residuals and the use of Wilcoxon Sign tests.

11.2. Secondary Efficacy Analyses

The response of CD8+ and CD68+ in biopsy to treatment will also be explored by fitting a Poisson model to the data, adjusting for centre, treatment, baseline smoking status and baseline value. These analyses are also considered to be supportive, and the p-values that are obtained will not be adjusted.

Continuous secondary efficacy variables will be analysed using the main effects models described above for the primary variable.

11.3. Other Efficacy Analysis

Descriptive statistics and a repeated measures model with treatment and baseline as effects will be utilised to analyse SVC.

12. SAFETY ANALYSES

12.1. Extent of Exposure

Evaluation of safety data will include all randomised patients and will be based on comparisons of patient experience by assigned medication regiment. Clinical interpretation will be based on review of displays of adverse experiences, laboratory values, and vital signs. Principal considerations in this evaluation will be time-to-onset, severity and investigator-reported relationship for the adverse experience to study medication. Descriptive statistics will also be used in the evaluation of safety when appropriate.

12.2. Adverse Events

All adverse experiences in the double-blind period will be presented for both treatment groups by body system, severity level (mild, moderate and severe), time of initial onset and action taken.. No formal statistical hypothesis testing will be performed for adverse experiences

12.3. Deaths and Serious Adverse Events

Serious adverse events (including deaths) will be summarised by body system, preferred term, treatment group and on-therapy status. Special attention will be given to gastrointestinal adverse events.

12.4. Device Incidents and Near Incidents

12.5. Adverse Events Leading to Discontinuation of Investigational Product and/or Withdrawal from the Study and Other Significant Adverse Events

Adverse events leading to a patient's withdrawal from the study will be summarised by body system, preferred term, and treatment group.

12.6. Pregnancies (as applicable)

12.7. Clinical Laboratory Evaluations

Descriptive statistics for blood chemistry and haematology by visit/week and treatment group will be provided. Fecal occult blood measurements will be summarised 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.

12.8. Other Safety Measures

Vital signs heart rate, systolic blood pressure, diastolic blood pressure and temperature will be summarised similarly as for clinical laboratory variables.

13. HEALTH OUTCOMES ANALYSES

14. CLINICAL PHARMACOLOGY DATA ANALYSES

15. BIOMARKER DATA ANALYSIS

16. PHARMACOGENETIC DATA ANALYSES

17. VIRAL GENOTYPING/PHENOTYPING

18. REFERENCES

19. ATTACHMENTS

19.1. Table of Contents for Data Display Specifications

DEMOGRAPHIC 33

TABLE 13.01B. SUMMARY OF PATIENT DISPOSITION BY COUNTRY, CENTRE AND TREATMENT GROUP 33

TABLE 13.02. DISTRIBUTION OF RANDOMISED PATIENTS IN STUDY BY VISIT/WEEK AND TREATMENT GROUP 34

TABLE 13.03. REASONS FOR CONCLUDING THE RUN-IN PERIOD 35

TABLE 13.04. REASONS FOR CONCLUDING THE DOUBLE-BLIND PERIOD BY TREATMENT GROUP 36

TABLE 13.06A. SUMMARY OF PROTOCOL VIOLATIONS RESULTING IN EXCLUSION FROM PER-PROTOCOL ANALYSIS BY TREATMENT GROUP 37

TABLE 13.06B. SUMMARY OF PROTOCOL VIOLATIONS RESULTING IN EXCLUSION FROM PER-PROTOCOL ANALYSIS BY TREATMENT GROUP AND VISIT/WEEK 38

TABLE 13.06C. SUMMARY OF CONDUCT OF STUDY DEVIATIONS BY TREATMENT GROUP 39

TABLE 13.07A. SUMMARY OF DEMOGRAPHIC CHARACTERISTICS AT SCREENING BY TREATMENT GROUP – ALL RANDOMISED PATIENTS 40

TABLE 13.07B. SUMMARY OF DEMOGRAPHIC CHARACTERISTICS AT SCREENING BY TREATMENT GROUP - PP 40

TABLE 13.08A. DESCRIPTIVE STATISTICS FOR PULMONARY FUNCTION PARAMETERS AT SCREENING BY TREATMENT GROUP – ALL RANDOMISED PATIENTS 41

TABLE 13.08B. DESCRIPTIVE STATISTICS FOR PULMONARY FUNCTION PARAMETERS AT SCREENING BY TREATMENT GROUP - PP 41

TABLE 13.09A. DESCRIPTIVE STATISTICS FOR SMOKING HISTORY AT SCREENING BY TREATMENT GROUP – ALL RANDOMISED PATIENTS 42

TABLE 13.09B. DESCRIPTIVE STATISTICS FOR SMOKING HISTORY AT SCREENING BY TREATMENT GROUP - PP 42

TABLE 13.10A SUMMARY OF PULMONARY HISTORY BY TREATMENT GROUP – ALL RANDOMISED PATIENTS 43

TABLE 13.10B SUMMARY OF PULMONARY HISTORY BY TREATMENT GROUP-PP 43

TABLE 13.12. SUMMARY OF BASELINE SIGNS AND SYMPTOMS BY MEDRA SOC AND VERBATIM TERM 44

TABLE 13.13A. SUMMARY OF PRIOR MEDICATIONS BY GENERIC TERM AND TREATMENT GROUP 45

TABLE 13.13B. SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND TREATMENT GROUP 45

TABLE 13.13C. SUMMARY OF POST-THERAPY MEDICATIONS BY GENERIC TERM AND TREATMENT GROUP 45

TABLE 13.13D. SUMMARY OF MEDICATIONS GIVEN FOR COPD EXACERBATIONS BY GENERIC TERM AND TREATMENT GROUP 45

TABLE 13.14A. SUMMARY OF STUDY MEDICATION COMPLIANCE (%) BY TREATMENT GROUP AND VISIT/WEEK 46

TABLE 13.14B. DESCRIPTIVE STATISTICS FOR STUDY MEDICATION COMPLIANCE (%) BY TREATMENT GROUP AND VISIT/WEEK 47

TABLE 13.15. SUMMARY OF PATIENT SMOKING STATUS BY BASELINE STATUS AND TREATMENT GROUP AT VISIT 7 48

EFFICACY 49

TABLE 14.01A. SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL CD68+ (MACROPAGES) (CELL/MM^2) BY TREATMENT GROUP - PP 49

TABLE 14.01E. SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL CD68+ (MACROPHAGES) (CELL/MM^2) BY TREATMENT GROUP – PP (SMOKERS) 49

TABLE 14.01F. SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL CD68+ (MACROPHAGES) (CELL/MM^2) BY TREATMENT GROUP – PP (NON-SMOKERS) 49

TABLE 14.02A. SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL CD8+ T-LYMPHOCYTES (CELLS/MM^2) TISSUE BY TREATMENT GROUP – PP 49

TABLE 14.02E. SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL CD8+ T-LYMPHOCYTES (CELLS/MM^2) TISSUE BY TREATMENT GROUP – PP (SMOKERS) 49

TABLE 14.02F. SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL CD8+ T-LYMPHOCYTES (CELLS/MM^2) TISSUE BY TREATMENT GROUP – PP (NON-SMOKERS) 50

TABLE 14.03A. SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL NEUTROPHILS (NE+) (CELLS/MM^2) TISSUE BY TREATMENT GROUP – PP 50

TABLE 14.04A. SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL CD4 + LYMPHOCYTES (CELLS/MM^2)TISSUE BY TREATMENT GROUP – PP 50

TABLE 14.05A. SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL IL-8+MRNA (CELLS/MM^2) TISSUE BY TREATMENT GROUP – PP 50

TABLE 14.06A. SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL TNF-ALPHA+MRNA (CELLS/MM^2) TISSUE BY TREATMENT GROUP - PP 50

TABLE 14.07A. SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL CD45 POSITIVE (CELLS/MM^2) TISSUE BY TREATMENT GROUP – PP 50

TABLE 14.08A1. SUMMARY OF CHANGE FROM BASELINE IN EPITHELIAL MUCIN EXPRESSION (MUC5AC) (CELLS/MM^2) TISSUE BY TREATMENT GROUP – PP 50

TABLE 14.08A2. SUMMARY OF CHANGE FROM BASELINE IN SUB-MUCOSA MUCIN EXPRESSION (MUC5AC) (CELLS/MM^2) TISSUE BY TREATMENT GROUP – PP 50

TABLE 14.08A3. SUMMARY OF CHANGE FROM BASELINE IN EPITHELIAL MUCIN EXPRESSION (MUC5B) (CELLS/MM^2) TISSUE BY TREATMENT GROUP – PP 50

TABLE 14.08A4. SUMMARY OF CHANGE FROM BASELINE IN SUB-MUCOSA MUCIN EXPRESSION (MUC5B) (CELLS/MM^2) TISSUE BY TREATMENT GROUP – PP 50

TABLE 14A.01A. SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL CD68+ MACROPHAGES (CELLS/MM^2) TISSUE BY TREATMENT GROUP - ITT 51

TABLE 14A.02A. SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL CD8+ T-LYMPHOCYTES (CELLS/MM^2) TISSUE BY TREATMENT GROUP - ITT 51

TABLE 14A.03A. SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL NEUTROPHILS (NE+) (CELLS/MM^2) TISSUE BY TREATMENT GROUP – ITT 51

TABLE 14A.04A. SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL CD4 + LYMPHOCYTES (CELLS/MM^2) TISSUE BY TREATMENT GROUP – ITT 51

TABLE 14A.05A. SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL IL-8+MRNA (CELLS/MM^2)TISSUE BY TREATMENT GROUP – ITT 51

TABLE 14A.06A. SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL TNF-ALPHA+MRNA (CELLS/MM^2) TISSUE BY TREATMENT GROUP - ITT 51

TABLE 14A.07A. SUMMARY OF CHANGE FROM BASELINE IN SUB-EPITHELIAL CD45 POSITIVE (CELLS/MM^2) TISSUE BY TREATMENT GROUP – ITT 51

TABLE 14A.08A1. SUMMARY OF CHANGE FROM BASELINE IN EPITHELIAL MUCIN EXPRESSION (MUC5AC) (CELLS/MM^2) TISSUE BY TREATMENT GROUP – ITT 51

TABLE 14A.08A2. SUMMARY OF CHANGE FROM BASELINE IN SUB-MUCOSA MUCIN EXPRESSION (MUC5AC) (CELLS/MM^2) TISSUE BY TREATMENT GROUP – ITT 51

TABLE 14A.08A3. SUMMARY OF CHANGE FROM BASELINE IN EPITHELIAL MUCIN EXPRESSION (MUC5B) (CELLS/MM^2) TISSUE BY TREATMENT GROUP – ITT 51

TABLE 14A.08A4. SUMMARY OF CHANGE FROM BASELINE IN SUB-MUCOSA MUCIN EXPRESSION (MUC5B) (CELLS/MM^2) TISSUE BY TREATMENT GROUP – ITT 51

TABLE 14.10A. SUMMARY OF CHANGE FROM BASELINE IN SPUTUM TOTAL CELL COUNTS (10^6/ML) BY TREATMENT GROUP – PP 52

TABLE 14.11A. SUMMARY OF CHANGE FROM BASELINE IN SPUTUM MACROPHAGES AS A PERCENTAGE OF TOTAL CELLS BY TREATMENT GROUP - PP 52

TABLE 14.12A. SUMMARY OF CHANGE FROM BASELINE IN NEUTROPHILS ELASTASE (NG/ML) BY TREATMENT GROUP – PP 52

TABLE 14.13A. SUMMARY OF CHANGE FROM BASELINE IN SPUTUM EOSINOPHILS (%) BY TREATMENT GROUP – PP 52

TABLE 14.14A. SUMMARY OF CHANGE FROM BASELINE IN SPUTUM LYMPHOCYTES (%) BY TREATMENT GROUP – PP 52

TABLE 14.15A. SUMMARY OF CHANGE FROM BASELINE IN SPUTUM IL-8 (NG/ML) BY TREATMENT GROUP – PP 52

TABLE 14A.10A. SUMMARY OF CHANGE FROM BASELINE IN SPUTUM TOTAL CELL COUNTS (10^6/ML) BY TREATMENT GROUP - ITT 52

TABLE 14A.11A. SUMMARY OF CHANGE FROM BASELINE IN SPUTUM MACROPHAGES AS A PERCENTAGE OF TOTAL CELLS BY TREATMENT GROUP - ITT 53

TABLE 14A.12A. SUMMARY OF CHANGE FROM BASELINE IN NEUTROPHILS ELASTASE (NG/ML) BY TREATMENT GROUP – ITT 53

TABLE 14A.13A. SUMMARY OF CHANGE FROM BASELINE IN SPUTUM EOSINOPHILS (%) BY TREATMENT GROUP – ITT 53

TABLE 14A.14A. SUMMARY OF CHANGE FROM BASELINE IN SPUTUM LYMPHOCYTES (%) BY TREATMENT GROUP - ITT 53

TABLE 14A.15A. SUMMARY OF CHANGE FROM BASELINE IN SPUTUM IL-8 (NG/ML) BY TREATMENT GROUP - ITT53

TABLE 14.16A. SUMMARY OF CHANGE FROM BASELINE IN PULMONARY FUNCTION TEST SVC BY TREATMENT GROUP – PP 54

TABLE 14A.16A. SUMMARY OF CHANGE FROM BASELINE IN PULMONARY FUNCTION TEST SVC BY TREATMENT GROUP – ITT 54

TABLE 14.01B. DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL CD68+ (MACROPHAGES)/MM^2 BY TREATMENT GROUP - PP 55

TABLE 14.01G. DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL CD68+ MACROPHAGES/MM^2 TISSUE BY TREATMENT GROUP – PP (SMOKERS) 55

TABLE 14.01H. DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL CD68+ MACROPHAGES/MM^2 TISSUE BY TREATMENT GROUP – PP (NON-SMOKERS) 55

TABLE 14.02B. DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL CD8+ T-LYMPHOCYTES/MM^2 TISSUE BY TREATMENT GROUP - PP 55

TABLE 14.02G. DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL CD8+ T-LYMPHOCYTES/MM^2 TISSUE BY TREATMENT GROUP – PP (SMOKERS) 55

TABLE 14.02H. DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL CD8+ T-LYMPHOCYTES/MM^2 TISSUE BY TREATMENT GROUP – PP (NON-SMOKERS) 55

TABLE 14.03B. DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL NEUTROPHILS (NE+)/MM^2 TISSUE BY TREATMENT GROUP – PP 55

TABLE 14.04B. DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL CD4 + LYMPHOCYTES/MM^2 TISSUE BY TREATMENT GROUP – PP 55

TABLE 14.05B. DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL IL-8+MRNA CELLS/MM^2 TISSUE BY TREATMENT GROUP – PP 55

TABLE 14.06B. DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL TNF-ALPHA+MRNA CELLS/MM^2 TISSUE BY TREATMENT GROUP - PP 56

TABLE 14.07B. DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL CD45 POSITIVE CELLS/MM^2 TISSUE BY TREATMENT GROUP – PP 56

TABLE 14.08B1. DESCRIPTIVE STATISTICS FOR EPITHELIAL MUCIN EXPRESSION /MM^2 (MUC5AC) TISSUE BY TREATMENT GROUP – PP 56

TABLE 14.08B2. DESCRIPTIVE STATISTICS FOR SUB-MUCOSA MUCIN EXPRESSION /MM^2 (MUC5AC) TISSUE BY TREATMENT GROUP – PP 56

TABLE 14.08B3. DESCRIPTIVE STATISTICS FOR EPITHELIAL MUCIN EXPRESSION /MM^2 (MUC5B) TISSUE BY TREATMENT GROUP – PP 56

TABLE 14.08B4. DESCRIPTIVE STATISTICS FOR SUB-MUCOSA MUCIN EXPRESSION /MM^2 (MUC5B) TISSUE BY TREATMENT GROUP – PP 56

TABLE 14A.01B. DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL CD68+ MACROPHAGES/MM^2 TISSUE BY TREATMENT GROUP - ITT 56

TABLE 14A.02B. DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL CD8+ T-LYMPHOCYTES/MM^2 TISSUE BY TREATMENT GROUP - ITT 56

TABLE 14A.03B. DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL NEUTROPHILS (NE+)/MM^2 TISSUE BY TREATMENT GROUP – ITT 56

TABLE 14A.04B. DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL CD4 + LYMPHOCYTES/MM^2 TISSUE BY TREATMENT GROUP – ITT 56

TABLE 14A.05B. DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL IL-8+MRNA CELLS/MM^2 TISSUE BY TREATMENT GROUP – ITT 56

TABLE 14A.06B. DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL TNF-ALPHA+MRNA CELLS/MM^2 TISSUE BY TREATMENT GROUP - ITT 56

TABLE 14A.07B. DESCRIPTIVE STATISTICS FOR SUB-EPITHELIAL CD45 POSITIVE CELLS/MM^2 TISSUE BY TREATMENT GROUP – ITT 56

TABLE 14A.08B1. DESCRIPTIVE STATISTICS FOR EPITHELIAL MUCIN EXPRESSION /MM^2 (MUC5AC) TISSUE BY TREATMENT GROUP – ITT 56

TABLE 14A.08B2. DESCRIPTIVE STATISTICS FOR SUB-MUCOSA MUCIN EXPRESSION /MM^2 (MUC5AC) TISSUE BY TREATMENT GROUP – ITT 56

TABLE 14A.08B3. DESCRIPTIVE STATISTICS FOR EPITHELIAL MUCIN EXPRESSION /MM^2 (MUC5B) TISSUE BY TREATMENT GROUP – ITT 56

TABLE 14A.08B4. DESCRIPTIVE STATISTICS FOR SUB-MUCOSA MUCIN EXPRESSION /MM^2 (MUC5B) TISSUE BY TREATMENT GROUP – ITT....56

TABLE 14.10B. DESCRIPTIVE STATISTICS FOR SPUTUM TOTAL CELL COUNTS (10^6/ML) BY TREATMENT GROUP - PP 57

TABLE 14.11B. DESCRIPTIVE STATISTICS FOR SPUTUM MACROPHAGES AS A PERCENTAGE OF TOTAL CELLS BY TREATMENT GROUP - PP....57

TABLE 14.12B. DESCRIPTIVE STATISTICS FOR SPUTUM ELASTASE (NG/ML) BY TREATMENT GROUP – PP....57

TABLE 14.13B. DESCRIPTIVE STATISTICS FOR SPUTUM EOSINOPHILS (%) BY TREATMENT GROUP – PP....57

TABLE 14.14B. DESCRIPTIVE STATISTICS FOR SPUTUM LYMPHOCYTES (%) BY TREATMENT GROUP - PP....57

TABLE 14.15B. DESCRIPTIVE STATISTICS FOR SPUTUM IL-8 (NG/ML) BY TREATMENT GROUP - PP....57

TABLE 14A.10B. DESCRIPTIVE STATISTICS FOR SPUTUM TOTAL CELL COUNTS (10^6/ML) BY TREATMENT GROUP - ITT 57

TABLE 14A.11B. DESCRIPTIVE STATISTICS FOR SPUTUM MACROPHAGES AS A PERCENTAGE OF TOTAL CELLS BY TREATMENT GROUP - III....57

TABLE 14A.12B. DESCRIPTIVE STATISTICS FOR SPUTUM ELASTASE (NG/ML) BY TREATMENT GROUP – ITT....57

TABLE 14A.13B. DESCRIPTIVE STATISTICS FOR SPUTUM EOSINOPHILS (%) BY TREATMENT GROUP – ITT....57

TABLE 14A.14B. DESCRIPTIVE STATISTICS FOR SPUTUM LYMPHOCYTES (%) BY TREATMENT GROUP - ITT....57

TABLE 14A.15B. DESCRIPTIVE STATISTICS FOR SPUTUM IL-8 (NG/ML) BY TREATMENT GROUP - ITT....57

TABLE 14.16B. DESCRIPTIVE STATISTICS FOR PULMONARY FUNCTION TEST SVC BY TREATMENT GROUP - PP....58

TABLE 14A.16B. DESCRIPTIVE STATISTICS FOR PULMONARY FUNCTION TEST SVC BY TREATMENT GROUP – ITT58

TABLE 14.01C. SUMMARY OF TESTS OF SIGNIFICANCE FOR INTERACTION TERMS AND COVARIATES FOR CHANGE FROM BASELINE IN SUB-EPITHELIAL CD68+ (MACROPAGES) /MM^2 - PP....59

TABLE 14.02C. SUMMARY OF TESTS OF SIGNIFICANCE FOR INTERACTION TERMS AND COVARIATES FOR CHANGE FROM BASELINE IN SUB-EPITHELIAL CD8+ (MACROPAGES) /MM^2 - PP....59

TABLE 14A.01C. SUMMARY OF TESTS OF SIGNIFICANCE FOR INTERACTION TERMS AND COVARIATES FOR CHANGE FROM BASELINE IN SUB-EPITHELIAL CD68+ (MACROPAGES) /MM^2 – ITT....59

TABLE 14A.02C. SUMMARY OF TESTS OF SIGNIFICANCE FOR INTERACTION TERMS AND COVARIATES FOR CHANGE FROM BASELINE IN SUB-EPITHELIAL CD8+ (MACROPAGES) /MM^2 – ITT....59

TABLE 14.01D. SUMMARY OF POISSON REGRESSION MODEL USING GEE FOR CHANGE IN CD68-PP....60

TABLE 14.02D. SUMMARY OF POISSON REGRESSION MODEL USING GEE FOR CHANGE IN CD8 - PP....60

TABLE 14A.01D. SUMMARY OF POISSON REGRESSION MODEL USING GEE FOR CHANGE IN CD64 - ITT....60

TABLE 14A.02D. SUMMARY OF POISSON REGRESSION MODEL USING GEE FOR CHANGE IN CD8 - ITT....60

SAFETY....61

TABLE 15.01A. SUMMARY OF STUDY MEDICATION EXPOSURE (DAYS) BY TREATMENT GROUP....61

TABLE 15.01B. DESCRIPTIVE STATISTICS FOR STUDY MEDICATION EXPOSURE (DAYS) BY TREATMENT GROUP....62

TABLE 15.02A. INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND TREATMENT GROUP....63

TABLE 15.09A. INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES LEADING TO PATIENT WITHDRAWAL BY PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND TREATMENT GROUP....63

TABLE 15.11A. INCIDENCE OF GASTROINTESTINAL ADVERSE EXPERIENCES OF CONCERN BY PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND TREATMENT GROUP 63

TABLE 15.11B. INCIDENCE OF GASTROINTESTINAL ADVERSE EXPERIENCES OF CONCERN LEADING TO PATIENT WITHDRAWAL BY PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND TREATMENT GROUP 63

TABLE 15.02B. INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY BODY SYSTEM, PREFERRED TERM AND TREATMENT GROUP 64

TABLE 15.06. INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES THAT LED TO DOSE INTERRUPTION BY BODY SYSTEM, PREFERRED TERM AND TREATMENT GROUP 64

TABLE 15.07. INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES THAT REQUIRED CORRECTIVE THERAPY BY BODY SYSTEM, PREFERRED TERM AND TREATMENT GROUP 64

TABLE 15.08A. INCIDENCE OF PRE-THERAPY SERIOUS ADVERSE EXPERIENCES BY SOC AND PREFERRED TERM . 64

TABLE 15.08B. INCIDENCE OF ON-THERAPY SERIOUS ADVERSE EXPERIENCES BY SOC, PREFERRED TERM AND TREATMENT GROUP 64

TABLE 15.08C. INCIDENCE OF POST-THERAPY SERIOUS ADVERSE EXPERIENCES BY SOC, PREFERRED TERM AND TREATMENT GROUP 65

TABLE 15.09B. INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES LEADING TO PATIENT WITHDRAWAL BY SOC, PREFERRED TERM AND TREATMENT GROUP 65

TABLE 15.10. INCIDENCE OF ALL POST-THERAPY ADVERSE EXPERIENCES BY SOC, PREFERRED TERM AND TREATMENT GROUP 65

TABLE 15.03. INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT, BODY SYSTEM, PREFERRED TERM AND TREATMENT GROUP 66

TABLE 15.04A. INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY, BODY SYSTEM, AND PREFERRED TERM - PLACEBO 67

TABLE 15.04B. INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY, BODY SYSTEM, AND PREFERRED TERM – SB207499 68

TABLE 15.05. INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY TREATMENT DAY OF ONSET, BODY SYSTEM, PREFERRED TERM AND TREATMENT GROUP 69

TABLE 15.12A. NUMBER AND PERCENT OF PATIENTS WITH GASTROINTESTINAL ADVERSE EXPERIENCES OF CONCERN AND ON-THERAPY POSITIVE FECAL OCCULT BLOOD BY TREATMENT GROUP AND BASELINE RESULT .. 71

TABLE 15.12B. NUMBER AND PERCENT OF PATIENTS WITH ON-THERAPY POSITIVE FECAL OCCULT BLOOD BY TREATMENT GROUP AND BASELINE RESULT 71

TABLE 15.14. DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND TREATMENT GROUP 72

TABLE 15.16. DESCRIPTIVE STATISTICS FOR STANDARD VITAL SIGNS BY VISIT/WEEK AND TREATMENT GROUP . 72

TABLE 15.17. TRANSITIONS FROM BASELINE IN SITTING VITAL SIGNS 73

TABLE 15.20 SUMMARY OF COPD EXACERBATIONS DURING THE DOUBLE-BLIND PERIOD BY LEVEL - ALL RANDOMISED PATIENTS 74

FIGURES 75

FIGURE 19.02A. MEAN (SEM) CHANGE FROM BASELINE IN SUB-EPITHELIAL CD8+ LYMPHOCYTES (BY WEEK) – PP 75

FIGURE 19.01A. MEAN (SEM) CHANGE FROM BASELINE IN SUB-EPITHELIAL CD68+ MACROPHAGES (BY WEEK) – PP 76

FIGURE 19A.01A. MEAN (SEM) CHANGE FROM BASELINE IN SUB-EPITHELIAL CD68+ MACROPHAGES (BY WEEK) – ITT 76

FIGURE 19A.02A. MEAN (SEM) CHANGE FROM BASELINE IN SUB-EPITHELIAL CD8+ LYMPHOCYTES (BY WEEK) – ITT 76

FIGURE 19.10A. MEAN (SEM) CHANGE FROM BASELINE IN SPUTUM TOTAL COUNT (BY WEEK) – PP 76

FIGURE 19A.10A. MEAN (SEM) CHANGE FROM BASELINE IN SPUTUM TOTAL COUNT (BY WEEK) – ITT 76

FIGURE 19.11A. MEAN (SEM) CHANGE FROM BASELINE IN SPUTUM MACROPHAGES (BY WEEK) – PP 76

FIGURE 19A.11A. MEAN (SEM) CHANGE FROM BASELINE IN SPUTUM MACROPHAGES (BY WEEK) – ITT 76

FIGURE 19.16A. MEAN (SEM) CHANGE FROM BASELINE IN SVC (BY WEEK) – PP 77

FIGURE 19.02B. MEAN (SEM) CHANGE FROM BASELINE IN SUB-EPITHELIAL CD8+ LYMPHOCYTES AT ENDPOINT – PP **ERROR! BOOKMARK NOT DEFINED.**

FIGURE 19.01B. MEAN (SEM) CHANGE FROM BASELINE IN SUB-EPITHELIAL CD68+ (MACROPHAGES) AT ENDPOINT – PP ..... **ERROR! BOOKMARK NOT DEFINED.**

FIGURE 19.03A. MEAN (SEM) CHANGE FROM BASELINE IN SUB-EPITHELIAL NEUTROPHIL COUNTS AT ENDPOINT – PP **ERROR! BOOKMARK NOT DEFINED.**

FIGURE 19A.01B. MEAN (SEM) CHANGE FROM BASELINE IN SUB-EPITHELIAL CD68+ (MACROPHAGES) AT ENDPOINT – ITT ..... **ERROR! BOOKMARK NOT DEFINED.**

FIGURE 19A.02B. MEAN (SEM) CHANGE FROM BASELINE IN SUB-EPITHELIAL CD8+ LYMPHOCYTES AT ENDPOINT – ITT ..... **ERROR! BOOKMARK NOT DEFINED.**

FIGURE 19A.03A. MEAN (SEM) CHANGE FROM BASELINE IN SUB-EPITHELIAL NEUTROPHIL COUNTS AT ENDPOINT – ITT ..... **ERROR! BOOKMARK NOT DEFINED.**

FIGURE 19.01D. MEAN (95% CI) DIFFERENCE OVER PLACEBO FOR SUB-EPITHELIAL CD68+ (MACROPHAGES) BY ANALYSIS POPULATION 78

FIGURE 19.01E. MEAN (95% CI) DIFFERENCE OVER PLACEBO FOR SUB-EPITHELIAL CD8+ LYMPHOCYTES BY ANALYSIS POPULATION 78

APPENDIX 79

APPENDIX A.01. TREATMENT RANDOMISATION WITH PATIENT NUMBER 79

APPENDIX B.01. REASON FOR STUDY CONCLUSION, DAYS OF PARTICIPATING IN THE STUDY AND DEMOGRAPHICS BY PATIENT NUMBER 80

APPENDIX B.02A. EXCLUSIONARY MEDICATIONS AND VISIT SPECIFIC PROTOCOL VIOLATIONS BY PATIENT NUMBER 81

APPENDIX B.02B. VIOLATIONS OF ELIGIBILITY CRITERIA BY PATIENT NUMBER 82

APPENDIX B.02C. CONDUCT OF STUDY DEVIATIONS BY PATIENT NUMBER 83

APPENDIX B.04. CIGARETTE SMOKING HISTORY AT SCREENING BY PATIENT NUMBER 84

APPENDIX B.06. CURRENT MEDICAL CONDITIONS BY PATIENT NUMBER AND DISEASE CLASSIFICATION 85

APPENDIX B.07. PRIOR MEDICATIONS BY PATIENT NUMBER 86

APPENDIX B.08A. CONCOMITANT MEDICATIONS BY PATIENT NUMBER 86

APPENDIX B.10. BASELINE SIGNS AND SYMPTOMS BY PATIENT NUMBER, BODY SYSTEM, PREFERRED TERM AND VERBATIM TERM 87

APPENDIX B.11. STUDY MEDICATION COMPLIANCE BY PATIENT NUMBER 88

APPENDIX B.12. STUDY MEDICATION RECORD BY PATIENT NUMBER 89

APPENDIX C.01. SPUTUM ANALYSIS BY PATIENT NUMBER 90

APPENDIX C.02. PULMONARY FUNCTION PARAMETERS BY PATIENT NUMBER 91

APPENDIX C.03. BRONCHIAL BIOPSY ANALYSIS BY PATIENT NUMBER 92

APPENDIX C.04. COPD EXACERBATIONS BY PATIENT NUMBER 93

APPENDIX C.05. MUCIN EXPRESSION ANALYSIS BY PATIENT NUMBER 94

APPENDIX D.01. ON-THERAPY ADVERSE EXPERIENCES BY TREATMENT GROUP, PATIENT NUMBER, BODY SYSTEM, PREFERRED TERM AND VERBATIM TERM 95

APPENDIX D.02A. ON-THERAPY ADVERSE EXPERIENCES RELATED TO TREATMENT BY TREATMENT GROUP, PATIENT NUMBER, BODY SYSTEM, PREFERRED TERM AND VERBATIM TERM 95

APPENDIX D.02B. ON-THERAPY ADVERSE EXPERIENCES NOT RELATED TO TREATMENT BY TREATMENT GROUP, PATIENT NUMBER, BODY SYSTEM, PREFERRED TERM AND VERBATIM TERM 95

APPENDIX D.03. ON-THERAPY ADVERSE EXPERIENCES THAT LED TO DOSE INTERRUPTION BY TREATMENT GROUP, PATIENT NUMBER, BODY SYSTEM, PREFERRED TERM AND VERBATIM TERM 95

APPENDIX D.05A. RUN-IN SERIOUS ADVERSE EXPERIENCES BY PATIENT NUMBER, BODY SYSTEM, PREFERRED TERM AND VERBATIM TERM 95

APPENDIX D.05B. ON-THERAPY SERIOUS ADVERSE EXPERIENCES BY TREATMENT GROUP, PATIENT NUMBER, BODY SYSTEM, PREFERRED TERM AND VERBATIM TERM 96

APPENDIX D.05C. POST-THERAPY SERIOUS ADVERSE EXPERIENCES BY TREATMENT GROUP, PATIENT NUMBER, BODY SYSTEM, PREFERRED TERM AND VERBATIM TERM 96

APPENDIX D.05D PATIENT FATALITIES BY PATIENT NUMBER 96

APPENDIX D.06A. ON-THERAPY ADVERSE EXPERIENCES THAT LED TO WITHDRAWAL BY TREATMENT GROUP, PATIENT NUMBER, BODY SYSTEM, PREFERRED TERM AND VERBATIM TERM 96

APPENDIX D.06B. RUN-IN ADVERSE EXPERIENCES THAT LED TO WITHDRAWAL BY TREATMENT GROUP, PATIENT NUMBER, BODY SYSTEM, PREFERRED TERM AND VERBATIM TERM 96

APPENDIX D.07. POST-THERAPY ADVERSE EXPERIENCES BY TREATMENT GROUP, PATIENT NUMBER, BODY SYSTEM, PREFERRED TERM AND VERBATIM TERM 96

APPENDIX D.08. GASTROINTESTINAL ADVERSE EXPERIENCES OF CONCERN BY TREATMENT GROUP, PATIENT NUMBER, BODY SYSTEM, PREFERRED TERM AND VERBATIM TERM 96

APPENDIX D.10. ABDOMINAL PAIN ASSESSMENT BY PATIENT NUMBER 97

APPENDIX D.11. STOOL ASSESSMENT BY PATIENT NUMBER 98

APPENDIX D.12. PHYSICAL EXAMINATIONS FOR PATIENTS WITH GASTROINTESTINAL SYMPTOMS OF CONCERN BY PATIENT NUMBER 99

APPENDIX D.13. FOB TEST RESULTS BY PATIENT NUMBER 100

APPENDIX E.01A. STANDARD VITAL SIGNS BY PATIENT NUMBER 101

APPENDIX F.02. CLINICAL LABORATORY VALUES BY TREATMENT GROUP AND PATIENT NUMBER 102

APPENDIX I.01A. ANALYSIS OF VARIANCE TEST FOR TREATMENT-BY CENTRE INTERACTION FOR SUB-EPITHELIAL CD68+ (MACROPHAGE) - PP ..... **ERROR! BOOKMARK NOT DEFINED.**

APPENDIX I.02A. ANALYSIS OF VARIANCE TEST FOR TREATMENT-BY-CENTRE INTERACTION FOR SUB-EPITHELIAL CD8+ (LYMPHOCYTES) - PP ..... **ERROR! BOOKMARK NOT DEFINED.**

APPENDIX I.01B. ANALYSIS OF VARIANCE TEST FOR TREATMENT DIFFERENCE FOR SUB-EPITHELIAL CD68+ (MACROPHAGE) - PP ..... **ERROR! BOOKMARK NOT DEFINED.**

APPENDIX I.02B. ANALYSIS OF VARIANCE TEST FOR TREATMENT DIFFERENCE FOR SUB-EPITHELIAL CD8+ (LYMPHOCYTES) - PP ..... **ERROR! BOOKMARK NOT DEFINED.**

APPENDIX I.01E. WILCOXON SIGN TEST FOR TREATMENT DIFFERENCE FOR SUB-EPITHELIAL CD68+ (MACROPHAGE) – PP 104

APPENDIX I.02E. WILCOXON SIGN TEST FOR TREATMENT DIFFERENCE FOR SUB-EPITHELIAL CD8+ (LYMPHOCYTES) – PP 104

APPENDIX I.12A. WILCOXON SIGN TEST FOR TREATMENT DIFFERENCE IN CHANGE FROM BASELINE IN NEUTROPHILS ELASTASE (NG/ML) BY TREATMENT GROUP – PP 104

APPENDIX I.15A. WILCOXON SIGN TEST FOR TREATMENT DIFFERENCE IN CHANGE FROM BASELINE IN SPUTUM IL-8 (NG/ML) BY TREATMENT GROUP – PP 104

APPENDIX I.05. NORMAL PROBABILITY PLOT OF RESIDUALS FOR SUB-EPITHELIAL CD68+ (MACROPHAGE) AT ENDPOINT - PP 105

APPENDIX I.06. NORMAL PROBABILITY PLOT OF RESIDUALS FOR SUB-EPITHELIAL CD8+ (LYMPHOCYTES)) AT ENDPOINT - PP 105

19.2. Data Display Specifications

Demographic

Table 13.01B. Summary of Patient Disposition by Country, Centre and Treatment Group

			Treatment Group			
Country	Centre	Disposition	Placebo	SB 207499	Non-Rand.	Total
Cccccccc	xxx	Entered Single-blind	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Randomised	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		PP efficacy	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		ITT Efficacy	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Completed DB	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xxx	Entered Single-blind	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		⋮	⋮	⋮	⋮	⋮
	Total	Entered Single-blind	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		⋮	⋮	⋮	⋮	⋮
Cccccccc	xxx	Entered Single-blind	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		⋮	⋮	⋮	⋮	⋮
	Total	Entered Single-blind	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		⋮	⋮	⋮	⋮	⋮
Total		Entered Single-blind	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		⋮	⋮	⋮	⋮	⋮

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED WITHIN EACH CENTRE OR COUNTRY.

2. TOTAL ROWS UNDER CENTRE REPRESENT THE TOTAL ACROSS ALL CENTRES WITH THE COUNTRY, TOTAL ROW UNDER COUNTRY REPRESENTS THE TOTAL ACROSS ALL COUNTRIES..

Table 13.02. Distribution of Randomised Patients in Study by Visit/Week and Treatment Group

	Treatment Group		
	Placebo	SB 207499	Total
Visit/Week	(n = xxx)	(n = xxx)	(n = xxx)
Visit 2/2A/Week –1(Baseline)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Visit 3/Week 0	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Visit 4/Week 4	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Visit 5/Week 8	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Visit 6/6a/Week 12	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Visit 7/Week 13	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Follow-up	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED

Table 13.03. Reasons for Concluding the Run-in Period

Reason	Placebo (n = xxx)
Total Withdrawn	xx (xx.x%)
Adverse Experience	xx (xx.x%)
COPD Exacerbation	
Protocol Violation	
Lack of Efficacy of Study Medication	
Lost-to-follow-up	
Consent Withdrawn	
Did not Fulfil Entry Criterion	
Other	xx (xx.x%)

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS WHO ENTERED SINGLE-BLIND RUN-IN

Table 13.04. Reasons for Concluding the Double-blind Period by Treatment Group

	Treatment Group	
	Placebo	SB 207499
Reason	(n = xxx)	(n = xxx)
Total Withdrawn	xx (xx.x%)	xx (xx.x%)
Adverse Experience	xx (xx.x%)	xx (xx.x%)
COPD Exacerbation	xx (xx.x%)	xx (xx.x%)
Protocol Violation	xx (xx.x%)	xx (xx.x%)
Lack of Efficacy of Study Medication	xx (xx.x%)	xx (xx.x%)
Lost-to-follow-up	xx (xx.x%)	xx (xx.x%)
Consent Withdrawn	xx (xx.x%)	xx (xx.x%)
Other	xx (xx.x%)	xx (xx.x%)
Completed Study	xx (xx.x%)	xx (xx.x%)

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED

2. ADVERSE EXPERIENCE ROW INCLUDES PATIENTS WITHDRAWN DUE TO COPD EXACERBATIONS

Table 13.06A. Summary of Protocol Violations Resulting in Exclusion from Per-Protocol Analysis by Treatment Group

		Treatment Group	
		Placebo	SB 207499
Type of Violation	Violation	(n = xxx)	(n = xxx)
Eligibility Criteria	ccc ccccc cc ccccccc	xx (xx.x%)	xx (xx.x%)
	⋮	xx (xx.x%)	xx (xx.x%)
Exclusionary Medication	⋮	xx (xx.x%)	xx (xx.x%)
	⋮	xx (xx.x%)	xx (xx.x%)
Visit Specific Violations	⋮	xx (xx.x%)	xx (xx.x%)
	⋮	xx (xx.x%)	xx (xx.x%)
All violations		xx (xx.x%)	xx (xx.x%)

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS WITH EFFICACY DATA WITHIN EACH TREATMENT GROUP

Table 13.06B. Summary of Protocol Violations Resulting in Exclusion from Per-Protocol Analysis by Treatment Group and Visit/Week

		Treatment Group	
Visit/Week	Violation	Placebo	SB 207499
Visit 2/2A//Week –1(Baseline)	ccc ccccc cc ccccccc	xx/xx (xx.x%)	xx/xx (xx.x%)
Visit 3/Week 0	⋮	xx/xx (xx.x%)	xx/xx (xx.x%)
Visit 4/Week 4	⋮	xx/xx (xx.x%)	xx/xx (xx.x%)
Visit 5/Week 8	⋮	xx/xx (xx.x%)	xx/xx (xx.x%)
Visit 6/6A/Week 12	⋮	xx/xx (xx.x%)	xx/xx (xx.x%)
Visit 7/Week 13	⋮	xx/xx (xx.x%)	xx/xx (xx.x%)

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS WITH EFFICACY DATA WITHIN EACH TREATMENT GROUP

2. TOTAL ROW REPRESENTS THE TOTAL NUMBER OF PATIENTS EXCLUDED FOR A PROTOCOL VIOLATION AT A GIVEN VISIT

Table 13.06C. Summary of Conduct of Study Deviations by Treatment Group

	Treatment Group	
	Placebo	SB 207499
Conduct of Study Deviation	(n = xxx)	(n = xxx)
ccc ccccc cc ccccccc	xx (xx.x%)	xx (xx.x%)
⋮	xx (xx.x%)	xx (xx.x%)
⋮	xx (xx.x%)	xx (xx.x%)
⋮	xx (xx.x%)	xx (xx.x%)
⋮	xx (xx.x%)	xx (xx.x%)
⋮	xx (xx.x%)	xx (xx.x%)

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS WITH EFFICACY DATA WITHIN EACH TREATMENT GROUP

Table 13.07A. Summary of Demographic Characteristics at Screening by Treatment Group – All Randomised Patients

		Treatment Group		
		Placebo	SB 207499	Total
Characteristic		(n = xxx)	(n = xxx)	(n = xxx)
Sex	Male	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Female	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Race	Caucasian	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Black	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Oriental	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Other	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Age Category	<50	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	50-65	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	>65	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Age (yrs)	N	xx	xx	xx
	Mean	xx.xx	xx.xx	xx.xx
	SD	xx.xx	xx.xx	xx.xx
	Median	xx.xx	xx.xx	xx.xx
	Min	xx.xx	xx.xx	xx.xx
	Max	xx.xx	xx.xx	xx.xx
Height (cm)	N	xx	xx	xx
	Mean	xx.xx	xx.xx	xx.xx
	SD	xx.xx	xx.xx	xx.xx
	Median	xx.xx	xx.xx	xx.xx
	Min	xx.xx	xx.xx	xx.xx
	Max	xx.xx	xx.xx	xx.xx
Weight (kg)	N	xx	xx	xx
	Mean	xx.xx	xx.xx	xx.xx
	SD	xx.xx	xx.xx	xx.xx
	Median	xx.xx	xx.xx	xx.xx
	Min	xx.xx	xx.xx	xx.xx
	Max	xx.xx	xx.xx	xx.xx

1. Percentages are based on the total number of subjects randomised within each treatment group

Additional Tables With Same Format As 13.06A

Table 13.07B. Summary of Demographic Characteristics at Screening by Treatment Group - PP

Table 13.08A. Descriptive Statistics for Pulmonary Function Parameters at Screening by Treatment Group – All Randomised Patients

		Treatment Group		
Parameter		Placebo (N=XXX)	SB 207499 (N=XXX)	Total (N=XXX)
FEV1 (L)	N	xx	xx	xx
	Mean	xx.xx	xx.xx	xx.xx
	SD	xx.xx	xx.xx	xx.xx
	Median	xx.xx	xx.xx	xx.xx
	Min	xx.xx	xx.xx	xx.xx
	Max	xx.xx	xx.xx	xx.xx
FVC (L)	N	xx	xx	xx
	⋮	⋮	⋮	⋮
SVC(L)	N	xx	xx	xx
	⋮	⋮	⋮	⋮
%PREDICTED FEV1	N	xx	xx	xx
	⋮	⋮	⋮	⋮
%PREDICTED FVC	N	xx	xx	xx
	⋮	⋮	⋮	⋮
%PREDICTED SVC	N	xx	xx	xx
	⋮	⋮	⋮	⋮
REVERSIBILITY (%)	N	xx	xx	xx
	⋮	⋮	⋮	⋮
FEV1/FVC (%)	N	xx	xx	xx
	⋮	⋮	⋮	⋮

1. FEV1/FVC RATIO FEV1, FVC ARE REPORTED PRE-SALBUTAMOL INHALATION

2. %PREDICTED FEV1 IS REPORTED POST-SALBUTAMOL INHALATION

Note: Predicted FEV1/FVC is found on the CRF but should not be. Thus, it should not be included in this table. Also, the predicted values for FVC and SVC should not be calculated but instead should be taken from the CRF.

Additional Tables With Same Format As 13.07A

Table 13.08B. Descriptive Statistics for Pulmonary Function Parameters at Screening by Treatment Group - PP

Table 13.09A. Descriptive Statistics for Smoking History at Screening by Treatment Group – All Randomised Patients

		Treatment Group		
Characteristic		Placebo	SB 207499	Total
Smoking Status	Past Smoker	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Current Smoker	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Pack years	N	xx	xx	xx
	Mean	xx.xx	xx.xx	xx.xx
	SD	xx.xx	xx.xx	xx.xx
	Median	xx.xx	xx.xx	xx.xx
	Min	xx.xx	xx.xx	xx.xx
	Max	xx.xx	xx.xx	xx.xx
Cigarettes/Day	N	xx	xx	xx
	Mean	xx.xx	xx.xx	xx.xx
	SD	xx.xx	xx.xx	xx.xx
	Median	xx.xx	xx.xx	xx.xx
	Min	xx.xx	xx.xx	xx.xx
	Max	xx.xx	xx.xx	xx.xx

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED

Additional Tables With Same Format As 13.09A

Table 13.09B. Descriptive Statistics for Smoking History at Screening by Treatment Group - PP

Table 13.10A Summary of Pulmonary History by Treatment Group – All Randomised Patients

		Treatment Group		
Characteristic		Placebo	SB 207499	Total
Duration COPD (years)	<5 years	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	≥ 5 years to <10 years	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	≥ 10 years to >15 years	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	≥15 years to <20 years	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	≥ 20 years to <25 years	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	≥25 years	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Exacerbations in the Last 12 Months that were Self-Managed	N	xx	xx	xx
	Mean	xx.xx	xx.xx	xx.xx
	SD	xx.xx	xx.xx	xx.xx
	Median	xx.xx	xx.xx	xx.xx
	Min	xx.xx	xx.xx	xx.xx
	Max	xx.xx	xx.xx	xx.xx
Exacerbations in the Last 12 Months that Required Oral Corticosteroids and/or Antibiotics	N	xx	xx	xx
	⋮	⋮	⋮	⋮
Exacerbations in the Last 12 Months that Required Hospitalisation	N	xx	xx	xx
	⋮	⋮	⋮	⋮
Type of COPD	Chronic bronchitis	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Emphysema	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED

Additional Tables With Same Format As 13.10A

Table 13.10B Summary of Pulmonary History by Treatment Group-PP

Table 13.12. Summary of Baseline Signs and Symptoms by Medra SOC and Verbatim Term

System Organ Class	Verbatim Term	Placebo (N=XXX)	SB 207499 (N=XXX)	Non-Rand. (N=XXX)	Total (N=XXX)
Total	Total	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Respiratory System Disorders	Total	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Dyspnea	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Upper Respiratory Infection	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Hypoxia	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Bronchitis	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Body as a Whole	Total	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Headache	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER SOC/VERBATIM TERM

2. TOTAL ROWS REPRESENT TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/AT LEAST ONE AE WITHIN SOC

3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED FOR PLACEBO AND SB 207499 COLUMNS AND ON TOTAL NUMBER OF PATIENTS ENTERING RUN-IN FOR TOTAL COLUMN

Table 13.13A. Summary of Prior Medications by Generic Term and Treatment Group

	Treatment Group		
Generic term	Placebo (n = xxx)	SB 207499 (n = xxx)	Total (n = xxx)
Total	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Aerobid	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Salbutamol	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Aminophylline	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Cromolyn sodium	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION

2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED AND ASSESSED FOR PRIOR MEDICATION USE

3. SUMMARY INCLUDES MEDICATIONS CONTINUED POST-RANDOMISATION AND MEDICATIONS DISCONTINUED PRIOR TO RANDOMISATION

4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

Additional Tables With Same Format As 13.13A

Table 13.13B. Summary of Concomitant Medications by Generic Term and Treatment Group

2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMISED PATIENTS ASSESSED FOR CONCOMITANT MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMISATION AND MEDICATIONS INITIATED POST-RANDOMISATION

Table 13.13C. Summary of Post-Therapy Medications by Generic Term and Treatment Group

2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMISED PATIENTS ASSESSED FOR POST-THERAPY MEDICATION USE
3. SUMMARY INCLUDES MEDICATIONS INITIATED ON OR AFTER DATE OF LAST DOSE OF DOUBLE-BLIND TREATMENT

Table 13.13D. Summary of Medications Given For COPD Exacerbations by Generic Term and Treatment Group

2. SAMPLE SIZE IS BASED ON NUMBER OF RANDOMISED PATIENTS ASSESSED FOR COPD EXACERBATIONS MEDICATION USE DURING THE 12 WEEK DOUBLE BLIND PERIOD
3. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE SB 207499 GROUP

Table 13.14A. Summary of Study Medication Compliance (%) by Treatment Group and Visit/Week

		Treatment Group	
Visit/Week	Compliance	Placebo	SB 207499
Run-in period	< 80%	xx (xx.x%)	xx (xx.x%)
	80-120%	xx (xx.x%)	xx (xx.x%)
	> 120%	xx (xx.x%)	xx (xx.x%)
Visit 3 - Visit 4	< 80%	xx (xx.x%)	xx (xx.x%)
	80-120%	xx (xx.x%)	xx (xx.x%)
	> 120%	xx (xx.x%)	xx (xx.x%)
Visit 4 - Visit 5	< 80%	xx (xx.x%)	xx (xx.x%)
	80-120%	xx (xx.x%)	xx (xx.x%)
	> 120%	xx (xx.x%)	xx (xx.x%)
Visit 5-Visit 6/6A	< 80%	xx (xx.x%)	xx (xx.x%)
	80-120%	xx (xx.x%)	xx (xx.x%)
	> 120%	xx (xx.x%)	xx (xx.x%)
Visit 6/6A – Visit 7	< 80%	xx (xx.x%)	xx (xx.x%)
	80-120%	xx (xx.x%)	xx (xx.x%)
	> 120%	xx (xx.x%)	xx (xx.x%)
Overall	< 80%	xx (xx.x%)	xx (xx.x%)
	80-120%	xx (xx.x%)	xx (xx.x%)
	> 120%	xx (xx.x%)	xx (xx.x%)

1. SINGLE-BLIND RUN-IN REPRESENTS COMPLIANCE DURING THE PLACEBO RUN-IN PERIOD

2. OVERALL REPRESENTS COMPLIANCE OVER 13 WEEK DOUBLE-BLIND PERIOD

3. TABLE INCLUDES RANDOMISED PATIENTS WITH NON-MISSING COMPLIANCE DATA

NOTE: NOT ALL VISITS ARE DISPLAYED ON MOCK-UP

Table 13.14B. Descriptive Statistics for Study Medication Compliance (%) by Treatment Group and Visit/Week

		Treatment Group	
Visit/Week	Statistic	Placebo	SB 207499
Single-blind run-in	N	xx	xx
	Mean	xx.xx	xx.xx
	SD	xx.xx	xx.xx
	Median	xx.xx	xx.xx
	Min	xx.xx	xx.xx
	Max	xx.xx	xx.xx
Visit 4/Week 4	N	xx	xx
	Mean	xx.xx	xx.xx
	SD	xx.xx	xx.xx
	Median	xx.xx	xx.xx
	Min	xx.xx	xx.xx
	Max	xx.xx	xx.xx
Visit 7/Week 13	N	xx	xx
	Mean	xx.xx	xx.xx
	SD	xx.xx	xx.xx
	Median	xx.xx	xx.xx
	Min	xx.xx	xx.xx
	Max	xx.xx	xx.xx
Overall	N	xx	xx
	Mean	xx.xx	xx.xx
	SD	xx.xx	xx.xx
	Median	xx.xx	xx.xx
	Min	xx.xx	xx.xx
	Max	xx.xx	xx.xx

1. SINGLE-BLIND RUN-IN REPRESENTS COMPLIANCE DURING THE PLACEBO RUN-IN PERIOD

2. OVERALL REPRESENTS COMPLIANCE OVER 13 WEEK DOUBLE-BLIND PERIOD

3. TABLE INCLUDES RANDOMISED PATIENTS WITH NON-MISSING COMPLIANCE DATA

NOTE: NOT ALL VISITS ARE DISPLAYED ON MOCK-UP

Table 13.15. Summary of Patient Smoking Status by Baseline Status and Treatment Group at Visit 7

Treatment Group	Number Assessed	Baseline Status	Smoking Status at Visit 7	Not Smoking at Visit 7
Placebo	xx	Smoking	xx (xx.xx%)	xx (xx.xx%)
	xx	Not Smoking	xx (xx.xx%)	xx (xx.xx%)
	xx	Total	xx (xx.xx%)	xx (xx.xx%)
SB 207499	xx	Smoking	xx (xx.xx%)	xx (xx.xx%)
	xx	Not Smoking	xx (xx.xx%)	xx (xx.xx%)
	xx	Total	xx (xx.xx%)	xx (xx.xx%)

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ASSESSED AT BASELINE AND VISIT 7

Efficacy

Table 14.01A. Summary of Change from Baseline in Sub-Epithelial CD68+ (Macropages) (Cell/MM^2) by Treatment Group - PP

			Weekly Assessment		Change from Baseline				Comparison to Placebo			
Week	Treatment Group	N	Adjusted Mean	SEM	Adjusted Mean	SEM	Lower 95% C.I. Limit	Upper 95% C.I. Limit	Mean Difference	Lower 95% C.I. Limit	Upper 95% C.I. Limit	P-value (diff $\geq$ 0)
Baseline	Placebo	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	0.xxxx
	SB 207499	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx				
Week 12	Placebo	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	0.xxxx
	SB 207499	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx				
Endpoint	Placebo	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	0.xxxx
	SB 207499	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx				

1. MEAN VALUES ARE ADJUSTED FOR CENTRE

2. BASELINE=VISIT 2/2A, WEEK 12=VISIT 6/6A, ENDPOINT=VISIT 6 AND EWA

3.N REPRESENTS NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

Additional Tables With Same Format As 14.01A

Table 14.01E. Summary of Change from Baseline in Sub-epithelial CD68+ (Macrophages) (Cell/MM^2) by Treatment Group – PP (Smokers)

Table 14.01F. Summary of Change from Baseline in Sub-epithelial CD68+ (Macrophages) (Cell/MM^2) by Treatment Group – PP (Non-Smokers)

Table 14.02A. Summary of Change from Baseline in Sub-epithelial CD8+ T-lymphocytes (Cells/MM^2) Tissue by Treatment Group – PP

Table 14.02E. Summary of Change from Baseline in Sub-epithelial CD8+ T-lymphocytes (Cells/MM^2) Tissue by Treatment Group – PP (Smokers)

Table 14.02F. Summary of Change from Baseline in Sub-epithelial CD8+ T-lymphocytes (Cells/MM^2) Tissue by Treatment Group – PP (Non-Smokers)

Table 14.03A. Summary of Change from Baseline in Sub-epithelial Neutrophils (ne+) (Cells/MM^2) Tissue by Treatment Group – PP

Table 14.04A. Summary of Change from Baseline in Sub-epithelial CD4 + Lymphocytes (Cells/MM^2)Tissue by Treatment Group – PP

Table 14.05A. Summary of Change from Baseline in Sub-epithelial IL-8+mRNA (Cells/MM^2) Tissue by Treatment Group – PP

Table 14.06A. Summary of Change from Baseline in Sub-epithelial TNF-alpha+mRNA (Cells/MM^2) Tissue by Treatment Group - PP

Table 14.07A. Summary of Change from Baseline in Sub-epithelial CD45 Positive (Cells/MM^2) Tissue by Treatment Group – PP

Table 14.08A1. Summary of Change from Baseline in Epithelial Mucin Expression (MUC5AC) (Cells/MM^2) Tissue by Treatment Group – PP

Table 14.08A2. Summary of Change from Baseline in Sub-mucosa Mucin Expression (MUC5AC) (Cells/MM^2) Tissue by Treatment Group – PP

Table 14.08A3. Summary of Change from Baseline in Epithelial Mucin Expression (MUC5B) (Cells/MM^2) Tissue by Treatment Group – PP

Table 14.08A4. Summary of Change from Baseline in Sub-mucosa Mucin Expression (MUC5B) (Cells/MM^2) Tissue by Treatment Group – PP

Table 14A.01A. Summary of Change from Baseline in Sub-epithelial CD68+ Macrophages (Cells/MM^2) Tissue by Treatment Group - ITT

Table 14A.02A. Summary of Change from Baseline in Sub-epithelial CD8+ T-lymphocytes (Cells/MM^2) Tissue by Treatment Group - ITT

Table 14A.03A. Summary of Change from Baseline in Sub-epithelial Neutrophils (ne+) (Cells/MM^2) Tissue by Treatment Group – ITT

Table 14A.04A. Summary of Change from Baseline in Sub-epithelial CD4 + Lymphocytes (Cells/MM^2) Tissue by Treatment Group – ITT

Table 14A.05A. Summary of Change from Baseline in Sub-epithelial IL-8+mRNA (Cells/MM^2)Tissue by Treatment Group – ITT

Table 14A.06A. Summary of Change from Baseline in Sub-epithelial TNF-alpha+mRNA (Cells/MM^2) Tissue by Treatment Group - ITT

Table 14A.07A. Summary of Change from Baseline in Sub-epithelial CD45 Positive (Cells/MM^2) Tissue by Treatment Group – ITT

Table 14A.08A1. Summary of Change from Baseline in Epithelial Mucin Expression (MUC5AC) (Cells/MM^2) Tissue by Treatment Group – ITT

Table 14A.08A2. Summary of Change from Baseline in Sub-mucosa Mucin Expression (MUC5AC) (Cells/MM^2) Tissue by Treatment Group – ITT

Table 14A.08A3. Summary of Change from Baseline in Epithelial Mucin Expression (MUC5B) (Cells/MM^2) Tissue by Treatment Group – ITT

Table 14A.08A4. Summary of Change from Baseline in Sub-mucosa Mucin Expression (MUC5B) (Cells/MM^2) Tissue by Treatment Group – ITT

Table 14.10A. Summary of Change from Baseline in Sputum Total Cell Counts (10^6/ML) by Treatment Group – PP

			Weekly Assessment		Change from Baseline				Comparison to Placebo			
Week	Treatment Group	N	Adjusted Mean	SEM	Adjusted Mean	SEM	Lower 95% C.I. Limit	Upper 95% C.I. Limit	Mean Difference	Lower 95% C.I. Limit	Upper 95% C.I. Limit	P-value (diff ≥ 0)
Baseline	Placebo	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	0.xxxx
	SB 207499	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx				
Week 13	Placebo	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	0.xxxx
	SB 207499	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx				
Endpoint	Placebo	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	0.xxxx
	SB 207499	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx				

1. MEAN VALUES ARE ADJUSTED FOR CENTRE

2. BASELINE=VISIT 2/2A, WEEK 13=VISIT 7/7A, ENDPOINT=VISIT 7 AND EWA

3.N REPRESENTS NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

Additional Tables With Same Format As 14.10A

Table 14.11A. Summary of Change from Baseline in Sputum Macrophages as a Percentage of Total Cells by Treatment Group - PP

Table 14.12A. Summary of Change from Baseline in Neutrophils Elastase (NG/ML) by Treatment Group – PP

Table 14.13A. Summary of Change from Baseline in Sputum Eosinophils (%) by Treatment Group – PP

Table 14.14A. Summary of Change from Baseline in Sputum Lymphocytes (%) by Treatment Group – PP

Table 14.15A. Summary of Change from Baseline in Sputum IL-8 (NG/ML) by Treatment Group – PP

Table 14A.10A. Summary of Change from Baseline in Sputum Total Cell Counts (10^6/ML) by Treatment Group - ITT

Table 14A.11A. Summary of Change from Baseline in Sputum Macrophages as a Percentage of Total Cells by Treatment Group - ITT

Table 14A.12A. Summary of Change from Baseline in Neutrophils Elastase (NG/ML) by Treatment Group – ITT

Table 14A.13A. Summary of Change from Baseline in Sputum Eosinophils (%) by Treatment Group – ITT

Table 14A.14A. Summary of Change from Baseline in Sputum Lymphocytes (%) by Treatment Group - ITT

Table 14A.15A. Summary of Change from Baseline in Sputum IL-8 (NG/ML) by Treatment Group - ITT

Table 14.16A. Summary of Change from Baseline in Pulmonary Function Test SVC by Treatment Group – PP

			Weekly Assessment		Change from Baseline				Comparison to Placebo			
Week	Treatment Group	N	Adjusted Mean	SEM	Adjusted Mean	SEM	Lower 95% C.I. Limit	Upper 95% C.I. Limit	Mean Difference	Lower 95% C.I. Limit	Upper 95% C.I. Limit	P-value
Baseline	Placebo	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	0.xxxx
	SB 207499	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx				
Week 4	Placebo	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	0.xxxx
	SB 207499	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx				
Week 8	Placebo	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	0.xxxx
	SB 207499	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx				
Week 12	Placebo	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	0.xxxx
	SB 207499	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx				
Week 13	Placebo	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	0.xxxx
	SB 207499	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx				
Endpoint	Placebo	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	0.xxxx
	SB 207499	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx				

1. MEAN VALUES ARE ADJUSTED FOR CENTRE

2. BASELINE=VISIT 3, WEEK 4 = VISIT 4, WEEK 8 = VISIT 5, WEEK 12 = VISIT 6/6A, WEEK 13=VISIT 7, ENDPOINT=VISIT 7 AND EWA

3.N REPRESENTS NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

Additional Tables With Same Format As 14.16A

Table 14A.16A. Summary of Change from Baseline in Pulmonary Function Test SVC by Treatment Group – ITT

Table 14.01B. Descriptive Statistics for Sub-Epithelial CD68+ (Macrophages)/MM^2 by Treatment Group - PP

		Baseline			Weekly Assessment						Change from Baseline					
Week	Treatment Group	N	Mean	SD	N	Mean	SD	Median	Min	Max	N	Mean	SD	Median	Min	Max
Week 12	Placebo	xx	xx.xx	xx.xx	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	SB 207499	xx	xx.xx	xx.xx	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Endpoint	Placebo	xx	xx.xx	xx.xx	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	SB 207499	xx	xx.xx	xx.xx	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx

1. MEAN VALUES ARE THE SAMPLE MEAN

2. BASELINE=VISIT 2/2A, WEEK 12=VISIT 6/6A, ENDPOINT=VISIT 6 AND EWA

3.N REPRESENTS NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

Additional Tables With Same Format As 14.01B

Table 14.01G. Descriptive Statistics for Sub-epithelial CD68+ Macrophages/MM^2 Tissue by Treatment Group – PP (Smokers)

Table 14.01H. Descriptive Statistics for Sub-epithelial CD68+ Macrophages/MM^2 Tissue by Treatment Group – PP (Non-Smokers)

Table 14.02B. Descriptive Statistics for Sub-epithelial CD8+ T-lymphocytes/MM^2 Tissue by Treatment Group - PP

Table 14.02G. Descriptive Statistics for Sub-epithelial CD8+ T-lymphocytes/MM^2 Tissue by Treatment Group – PP (Smokers)

Table 14.02H. Descriptive Statistics for Sub-epithelial CD8+ T-lymphocytes/MM^2 Tissue by Treatment Group – PP (Non-Smokers)

Table 14.03B. Descriptive Statistics for Sub-epithelial Neutrophils (ne+)/MM^2 Tissue by Treatment Group – PP

Table 14.04B. Descriptive Statistics for Sub-epithelial CD4 + Lymphocytes/MM^2 Tissue by Treatment Group – PP

Table 14.05B. Descriptive Statistics for Sub-epithelial IL-8+mRNA Cells/MM^2 Tissue by Treatment Group – PP

Table 14.06B. Descriptive Statistics for Sub-epithelial TNF-alpha+mRNA Cells/MM^2 Tissue by Treatment Group - PP

Table 14.07B. Descriptive Statistics for Sub-epithelial CD45 Positive Cells/MM^2 Tissue by Treatment Group – PP

Table 14.08B1. Descriptive Statistics for Epithelial Mucin Expression /MM^2 (MUC5AC) Tissue by Treatment Group – PP

Table 14.08B2. Descriptive Statistics for Sub-mucosa Mucin Expression /MM^2 (MUC5AC) Tissue by Treatment Group – PP

Table 14.08B3. Descriptive Statistics for Epithelial Mucin Expression /MM^2 (MUC5B) Tissue by Treatment Group – PP

Table 14.08B4. Descriptive Statistics for Sub-mucosa Mucin Expression /MM^2 (MUC5B) Tissue by Treatment Group – PP

Table 14A.01B. Descriptive Statistics for Sub-epithelial CD68+ Macrophages/MM^2 Tissue by Treatment Group - ITT

Table 14A.02B. Descriptive Statistics for Sub-epithelial CD8+ T-lymphocytes/MM^2 Tissue by Treatment Group - ITT

Table 14A.03B. Descriptive Statistics for Sub-epithelial Neutrophils (ne+)/MM^2 Tissue by Treatment Group – ITT

Table 14A.04B. Descriptive Statistics for Sub-epithelial CD4 + Lymphocytes/MM^2 Tissue by Treatment Group – ITT

Table 14A.05B. Descriptive Statistics for Sub-epithelial IL-8+mRNA Cells/MM^2 Tissue by Treatment Group – ITT

Table 14A.06B. Descriptive Statistics for Sub-epithelial TNF-alpha+mRNA Cells/MM^2 Tissue by Treatment Group - ITT

Table 14A.07B. Descriptive Statistics for Sub-epithelial CD45 Positive Cells/MM^2 Tissue by Treatment Group – ITT

Table 14A.08B1. Descriptive Statistics for Epithelial Mucin Expression /MM^2 (MUC5AC) Tissue by Treatment Group – ITT

Table 14A.08B2. Descriptive Statistics for Sub-mucosa Mucin Expression /MM^2 (MUC5AC) Tissue by Treatment Group – ITT

Table 14A.08B3. Descriptive Statistics for Epithelial Mucin Expression /MM^2 (MUC5B) Tissue by Treatment Group – ITT

Table 14A.08B4. Descriptive Statistics for Sub-mucosa Mucin Expression /MM^2 (MUC5B) Tissue by Treatment Group – ITT

Table 14.10B. Descriptive Statistics for Sputum Total Cell Counts (10^6/ML) by Treatment Group - PP

		Baseline			Weekly Assessment						Change from Baseline					
Week	Treatment Group	N	Mean	SD	N	Mean	SD	Median	Min	Max	N	Mean	SD	Median	Min	Max
Week 13	Placebo	xx	xx.xx	xx.xx	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	SB 207499	xx	xx.xx	xx.xx	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Endpoint	Placebo	xx	xx.xx	xx.xx	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	SB 207499	xx	xx.xx	xx.xx	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx

1. MEAN VALUES ARE THE SAMPLE MEAN

2. BASELINE=VISIT 2/2A, WEEK 13=VISIT 7/7A, ENDPOINT=VISIT 7 AND EWA

3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

Additional Tables With Same Format As 14.10B

Table 14.11B. Descriptive Statistics for Sputum Macrophages as a Percentage of Total Cells by Treatment Group - PP

Table 14.12B. Descriptive Statistics for Sputum Elastase (NG/ML) by Treatment Group – PP

Table 14.13B. Descriptive Statistics for Sputum Eosinophils (%) by Treatment Group – PP

Table 14.14B. Descriptive Statistics for Sputum Lymphocytes (%) by Treatment Group - PP

Table 14.15B. Descriptive Statistics for Sputum IL-8 (NG/ML) by Treatment Group - PP

Table 14A.10B. Descriptive Statistics for Sputum Total Cell Counts (10^6/ML) by Treatment Group - ITT

Table 14A.11B. Descriptive Statistics for Sputum Macrophages as a Percentage of Total Cells by Treatment Group - III

Table 14A.12B. Descriptive Statistics for Sputum Elastase (NG/ML) by Treatment Group – ITT

Table 14A.13B. Descriptive Statistics for Sputum Eosinophils (%) by Treatment Group – ITT

Table 14A.14B. Descriptive Statistics for Sputum Lymphocytes (%) by Treatment Group - ITT

Table 14A.15B. Descriptive Statistics for Sputum IL-8 (NG/ML) by Treatment Group - ITT

Table 14.16B. Descriptive Statistics for Pulmonary Function Test SVC by Treatment Group - PP

		Baseline			Weekly Assessment						Change from Baseline					
Week	Treatment Group	N	Mean	SD	N	Mean	SD	Median	Min	Max	N	Mean	SD	Median	Min	Max
Week 4	Placebo	xx	xx.xx	xx.xx	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	SB 207499	xx	xx.xx	xx.xx	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Week 8	Placebo	xx	xx.xx	xx.xx	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	SB 207499	xx	xx.xx	xx.xx	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Week 12	Placebo	xx	xx.xx	xx.xx	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	SB 207499	xx	xx.xx	xx.xx	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Week 13	Placebo	xx	xx.xx	xx.xx	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	SB 207499	xx	xx.xx	xx.xx	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Endpoint	Placebo	xx	xx.xx	xx.xx	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	SB 207499	xx	xx.xx	xx.xx	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx

1. MEAN VALUES ARE THE SAMPLE MEAN

2. BASELINE=VISIT 3, WEEK 4=VISIT 4, WEEK 8=VISIT 5, WEEK 12=VISIT 6, WEEK 13=VISIT 7, ENDPOINT=LOCF

3. N REPRESENTS THE NUMBER OF PATIENTS WITH EVALUATION AT BASELINE AND THE SPECIFIED WEEK

Additional Tables With Same Format As 14.16B

Table 14A.16B. Descriptive Statistics for Pulmonary Function Test SVC by Treatment Group – ITT

Table 14.01C. Summary of Tests of Significance for Interaction Terms and Covariates for Change From Baseline In Sub-Epithelial CD68+ (Macropages) /MM^2 - PP

Factor	F-Statistic	P-value
Age	xxx.xx	0.xxxx
Sex	xxx.xx	0.xxxx
Smoking Status	xxx.xx	0.xxxx
ATS Severity	xxx.xx	0.xxxx
Treatment-by-Centre	xxx.xx	0.xxxx

1. STATISTICAL TESTING FOR COVARIATES WAS BASED ON MODEL WITH EFFECTS TREATMENT, CENTRE AND EACH OF THE COVARIATES
2. STATISTICAL TESTING FOR TREATMENT-BY-CENTRE INTERACTION WAS BASED ON MODEL WITH EFFECTS FOR TREATMENT, CENTRE AND THE INTERACTION OF THE TWO

Additional Tables With Same Format As 14.01C

Table 14.02C. Summary of Tests of Significance for Interaction Terms and Covariates for Change From Baseline In Sub-Epithelial CD8+ (Macropages) /MM^2 - PP

Table 14A.01C. Summary of Tests of Significance for Interaction Terms and Covariates for Change From Baseline In Sub-Epithelial CD68+ (Macropages) /MM^2 – ITT

Table 14A.02C. Summary of Tests of Significance for Interaction Terms and Covariates for Change From Baseline In Sub-Epithelial CD8+ (Macropages) /MM^2 – ITT

Table 14.01D. Summary of Poisson Regression Model Using GEE For Change in CD68-PP

Factor	Cells per unit area	%95 CI	Incidence Ratio	95% CI	P-Value
Placebo	xxx.xx	(xx.xx, xx.xx)			
SB 207499	xxx.xx	(xx.xx, xx.xx)	xxx.xx	(xx.xx, xx.xx)	0.xxxx

1. Model adjusts for centre, baseline smoking status and baseline value.

Additional Tables With Same Format As 14.01D

Table 14.02D. Summary of Poisson Regression Model Using GEE for Change in CD8 - PP

Table 14A.01D. Summary of Poisson Regression Model Using GEE for Change in CD64 - ITT

Table 14A.02D. Summary of Poisson Regression Model Using GEE for Change in CD8 - ITT

Safety

Table 15.01A. Summary of Study Medication Exposure (Days) by Treatment Group

	Treatment Group	
	Placebo	SB 207499
Exposure	(n = xxx)	(n = xxx)
≤13 days	xx (xx.x%)	xx (xx.x%)
14-27	xx (xx.x%)	xx (xx.x%)
28-55	xx (xx.x%)	xx (xx.x%)
56-83	xx (xx.x%)	xx (xx.x%)
84-90	xx (xx.x%)	xx (xx.x%)
91-Max	xx (xx.x%)	xx (xx.x%)

1. EXPOSURE = (DATE OF LAST DOUBLE BLIND STUDY MEDICATION-DATE OF FIRST DOUBLE BLIND STUDY MEDICATION)+1.

2. NO ADJUSTMENTS ARE MADE FOR DOSE INTERRUPTIONS

Table 15.01B. Descriptive Statistics for Study Medication Exposure (Days) by Treatment Group

	Treatment Group	
	Placebo	SB 207499
N	xx	xx
Mean	xx.xx	xx.xx
SD	xx.xx	xx.xx
Median	xx.xx	xx.xx
Min	xx.xx	xx.xx
Max	xx.xx	xx.xx

1. EXPOSURE = (DATE OF LAST DOUBLE BLIND STUDY MEDICATION-DATE OF FIRST DOUBLE BLIND STUDY MEDICATION)+1.

2. NO ADJUSTMENTS ARE MADE FOR DOSE INTERRUPTIONS

Table 15.02A. Incidence of On-therapy Adverse Experiences by Preferred Term, Descending Frequency of Occurrence and Treatment Group

	Treatment Group	
	Placebo	SB 207499
Preferred term	(n = xxx)	(n = xxx)
Total	xx (xx.x%)	xx (xx.x%)
Headache	xx (xx.x%)	xx (xx.x%)
Nausea	xx (xx.x%)	xx (xx.x%)
Abdominal pain	xx (xx.x%)	xx (xx.x%)
Vomiting	xx (xx.x%)	xx (xx.x%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER PREFERRED TERM

2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AN ADVERSE EXPERIENCE

3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED

4. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO THE SB 207499 TREATMENT GROUP

Additional tables with same format as 15.02a:

Table 15.09A. Incidence of On-Therapy Adverse Experiences Leading to Patient Withdrawal by Preferred Term, Descending Frequency of Occurrence and Treatment Group

Table 15.11A. Incidence of Gastrointestinal Adverse Experiences of Concern by Preferred Term, Descending Frequency of Occurrence and Treatment Group

Table 15.11B. Incidence of Gastrointestinal Adverse Experiences of Concern Leading To Patient Withdrawal by Preferred Term, Descending Frequency of Occurrence and Treatment Group

Table 15.02B. Incidence of On-therapy Adverse Experiences by Body System, Preferred Term and Treatment Group

		Treatment Group	
		Placebo	SB 207499
Body system	Preferred Term	(n = xxx)	(n = xxx)
Total	Total	xx (xx.x%)	xx (xx.x%)
Respiratory System Disorders	Total	xx (xx.x%)	xx (xx.x%)
	Dyspnea	xx (xx.x%)	xx (xx.x%)
	Upper Respiratory Infection	xx (xx.x%)	xx (xx.x%)
	Hypoxia	xx (xx.x%)	xx (xx.x%)
	Bronchitis	xx (xx.x%)	xx (xx.x%)
Body as a Whole	Total	xx (xx.x%)	xx (xx.x%)
	Headache	xx (xx.x%)	xx (xx.x%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER BODY SYSTEM/PREFERRED TERM

2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS REPORTING AT LEAST ONE AE/AT LEAST ONE AE WITHIN THE BODY SYSTEM

3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED

Additional tables with same format as Table 15.02B

Table 15.06. Incidence of On-Therapy Adverse Experiences That Led to Dose Interruption by Body System, Preferred Term and Treatment Group

Table 15.07. Incidence of On-Therapy Adverse Experiences That Required Corrective Therapy by Body System, Preferred Term and Treatment Group

Table 15.08A. Incidence of Pre-Therapy Serious Adverse Experiences by SOC and Preferred Term

Table 15.08B. Incidence of On-Therapy Serious Adverse Experiences by SOC, Preferred Term and Treatment Group

Table 15.08C. Incidence of Post-Therapy Serious Adverse Experiences by SOC, Preferred Term and Treatment Group

Table 15.09B. Incidence of On-Therapy Adverse Experiences Leading to Patient Withdrawal by SOC, Preferred Term and Treatment Group

Table 15.10. Incidence of All Post-Therapy Adverse Experiences by SOC, Preferred Term and Treatment Group

Table 15.03. Incidence of On-therapy Adverse Experiences by Investigator-determined Relationship to Treatment, Body System, Preferred Term and Treatment Group

		Placebo (N=XXX)				SB 207499 (N=XXX)			
Body system	Preferred Term	Missing	Not Related	Related	Total	Missing	Not Related	Related	Total
Total	Total	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Respiratory System Disorders	Total	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Dyspnea	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Upper Respiratory Infection	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Hypoxia	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Bronchitis	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Body as a Whole	Total	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Headache	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER BODY SYSTEM, PREFERRED TERM AND RELATIONSHIP

2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED

3. WORST-CASE RELATIONSHIP IS USED FOR EACH ADVERSE EVENT FOR EACH PATIENT

4. TOTAL ROW REPRESENTS TOTAL NUMBERS OF PATIENTS REPORTING AT LEAST ONE AE/AT LEAST ONE AE WITHIN THE BODY SYSTEM

Table 15.04A. Incidence of On-therapy Adverse Experiences by Investigator-determined Intensity, Body System, and Preferred Term - Placebo

		Placebo (N=XXX)			
Body system	Preferred Term	Mild	Moderate	Severe	Missing / Not Applicable
Total	Total	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Respiratory System Disorders	Total	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Dyspnea	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Upper Respiratory Infection	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Hypoxia	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Bronchitis	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Body as a Whole	Total	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Headache	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER BODY SYSTEM, PREFERRED TERM AND INTENSITY
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED
3. MAXIMUM INTENSITY IS USED FOR EACH ADVERSE EVENT FOR EACH PATIENT
4. TOTAL ROW REPRESENTS TOTAL NUMBERS OF PATIENTS REPORTING AT LEAST ONE AE/AT LEAST ONE AE WITHIN THE BODY SYSTEM

Table 15.04B. Incidence of On-therapy Adverse Experiences by Investigator-determined Intensity, Body System, and Preferred Term – SB207499

		SB207499 (N=XXX)			
Body system	Preferred Term	Mild	Moderate	Severe	Missing / Not Applicable
Total	Total	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Respiratory System Disorders	Total	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Dyspnea	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Upper Respiratory Infection	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Hypoxia	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Bronchitis	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Body as a Whole	Total	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Headache	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER BODY SYSTEM, PREFERRED TERM AND INTENSITY
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS RANDOMISED
3. MAXIMUM INTENSITY IS USED FOR EACH ADVERSE EVENT FOR EACH PATIENT
4. TOTAL ROW REPRESENTS TOTAL NUMBERS OF PATIENTS REPORTING AT LEAST ONE AE/AT LEAST ONE AE WITHIN THE BODY SYSTEM

Table 15.05. Incidence of On-therapy Adverse Experiences by Treatment Day of Onset, Body System, Preferred Term and Treatment Group

Body system	Preferred Term	1 (N=XXX)	2-7 (N=XXX)	8-14 (N=XXX)	15-28 (N=XXX)	29-42 (N=XXX)	43-56 (N=XXX)	57-70 (N=XXX)	>70 (N=XXX)	Total (N=XXX)
		Placebo								
Total	Total	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Respiratory System Disorders	Total	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Dyspnea	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Upper Respiratory Infection	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Hypoxia	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Bronchitis	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Body as a Whole	Total	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Table 15.05. Incidence of On-therapy Adverse Experiences by Treatment Day of Onset, Body System, Preferred Term and Treatment Group

Body system	Preferred Term	1 (N=XXX)	2-7 (N=XXX)	8-14 (N=XXX)	15-28 (N=XXX)	29-42 (N=XXX)	43-56 (N=XXX)	57-70 (N=XXX)	>70 (N=XXX)	Total (N=XXX)
		SB 207499								
Total	Total	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Respiratory System Disorders	Total	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Dyspnea	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Upper Respiratory Infection	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Hypoxia	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Bronchitis	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Body as a Whole	Total	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER BODY SYSTEM AND PREFERRED TERM

2. TOTAL ROW REPRESENTS TOTAL NUMBERS OF PATIENTS REPORTING AT LEAST ONE AE

3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS EXPOSED TO STUDY MEDICATION WITHIN EACH TIME INTERVAL

4. ONLY EVENTS OCCURRING IN AT LEAST 2% OF PATIENTS RANDOMISED TO SB 207499 ARE INCLUDED

Table 15.12A. Number and Percent of Patients with Gastrointestinal Adverse Experiences of Concern and On-therapy Positive Fecal Occult Blood By Treatment Group and Baseline Result

		On-therapy		
Treatment Group	Baseline	Negative	Positive	Total
Placebo	Negative	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Positive	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Total	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
SB 207499	Negative	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Positive	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Total	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

1. ONLY PATIENTS WITH GASTROINTESTINAL ADVERSE EXPERIENCES ARE INCLUDES IN THE SUMMARY

Additional tables with same format as 15.12A

Table 15.12B. Number and Percent of Patients with On-Therapy Positive Fecal Occult Blood by Treatment Group and Baseline Result

Note: No footnotes.

Table 15.14. Descriptive Statistics for Clinical Laboratories by Visit/Week and Treatment Group

			Result					Change from Baseline				
Parameter	Visit/Week	Treatment Group	N	Mean	STD	Min	Max	N	Mean	STD	Min	Max
Alkaline Phosphatase	Visit1/Screening	Placebo	xx	xx.xx	xx.xx	xx.xx	xx.xx					
		SB 207499	xx	xx.xx	xx.xx	xx.xx	xx.xx					
	Visit7/Week 13	Placebo	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx	xx.xx	xx.xx	xx.xx	xx.xx
		SB 207499	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx	xx.xx	xx.xx	xx.xx	xx.xx

1.BASELINE VALUE IS VALUE AT VISIT 1.

Additional tables with same format as 15.14

Table 15.16. Descriptive Statistics for Standard Vital Signs by Visit/Week and Treatment Group

Table 15.17. Transitions from Baseline in Sitting Vital Signs

Parameter: Systolic BP

Timepoint: Total On-therapy

Treatment Group	Baseline	Number of Patients Tested	Double-blind				
			Low Concern	Low	Normal	High	High Concern
Placebo	Low concern (< 75 mm Hg)	xxx	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
	Low (75 mm Hg – 89 mm Hg)	xxx	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
	Normal (90 mm Hg – 139 mm Hg)	xxx	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
	High (140 mm Hg –180 mm Hg)	xxx	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
	High concern (> 180 mm Hg)	xxx	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
	Missing	xxx	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
	Total	xxx	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
SB 207499	Low concern (< 75 mm Hg)	xxx	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
	Low (75 mm Hg – 89 mm Hg)	xxx	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
	Normal (90 mm Hg – 139 mm Hg)	xxx	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
	High (140 mm Hg –180 mm Hg)	xxx	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
	High concern (> 180 mm Hg)	xxx	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
	Missing	xxx	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
	Total	xxx	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE

2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE

3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY

4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

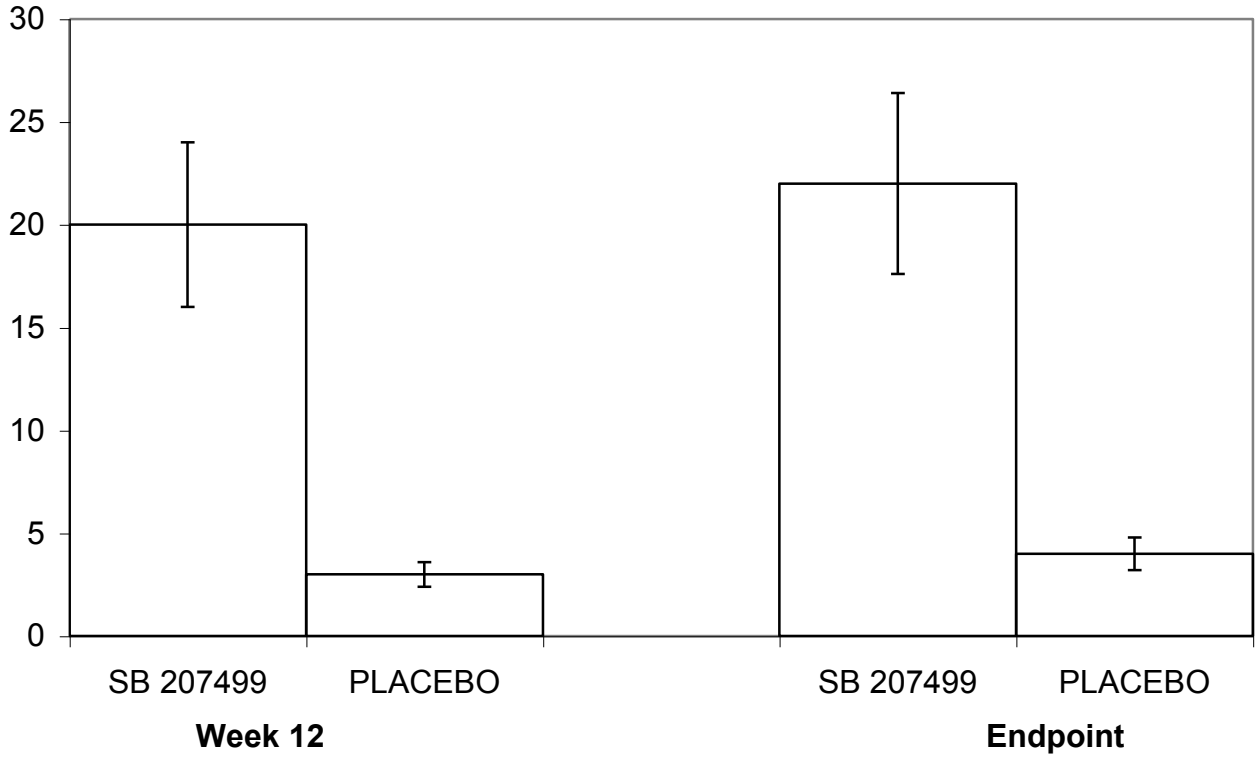
^Other parameters to be applied: Diastolic BP, Heart rate

Table 15.20 Summary of COPD Exacerbations During the Double-Blind Period by Level - All Randomised Patients

Treatment Group	Level	Number of Patients	Number of Exacerbations
Placebo (N=XXX)	Mild	xx	xx
	Moderate	xx	xx
	Severe	xx	xx
	Total	xx	xx
SB 207499 (N=XXX)	Mild	xx	xx
	Moderate	xx	xx
	Severe	xx	xx
	Total	xx	xx

Figures

Figure 19.02A. Mean (SEM) Change from Baseline in Sub-epithelial CD8+ Lymphocytes (by Week) – PP



Additional figures with same format as 19.02A

Figure 19.01A. Mean (SEM) Change from Baseline in Sub-epithelial CD68+ Macrophages (by Week) – PP

Figure 19A.01A. Mean (SEM) Change from Baseline in Sub-epithelial CD68+ Macrophages (by Week) – ITT

Figure 19A.02A. Mean (SEM) Change from Baseline in Sub-epithelial CD8+ Lymphocytes (by Week) – ITT

Figure 19.10A. Mean (SEM) Change from Baseline in Sputum Total Count (by Week) – PP

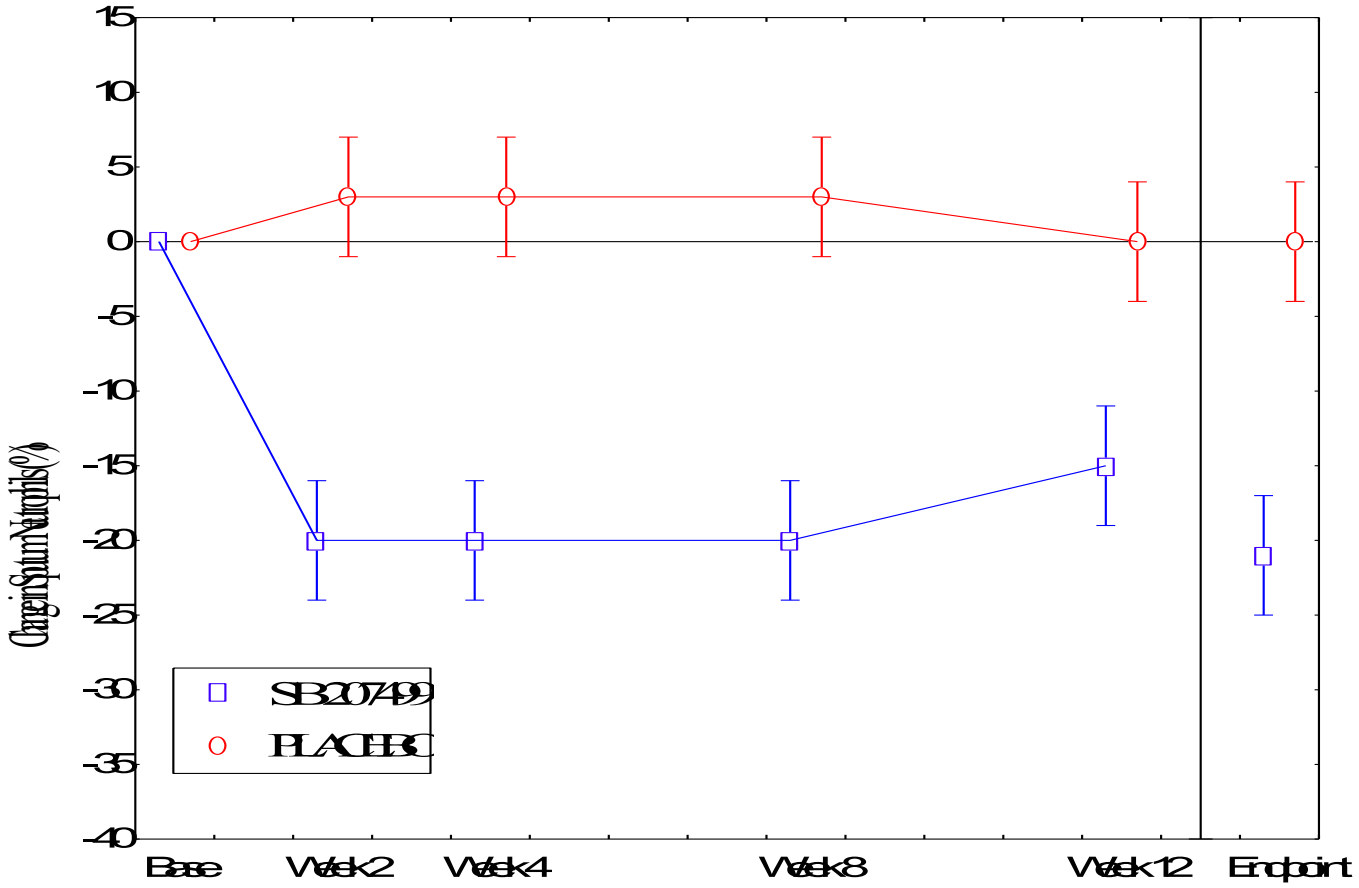
Figure 19A.10A. Mean (SEM) Change from Baseline in Sputum Total Count (by Week) – ITT

Figure 19.11A. Mean (SEM) Change from Baseline in Sputum Macrophages (by Week) – PP

Figure 19A.11A. Mean (SEM) Change from Baseline in Sputum Macrophages (by Week) – ITT

The sputum figures are measured at week 13 instead of week 12.

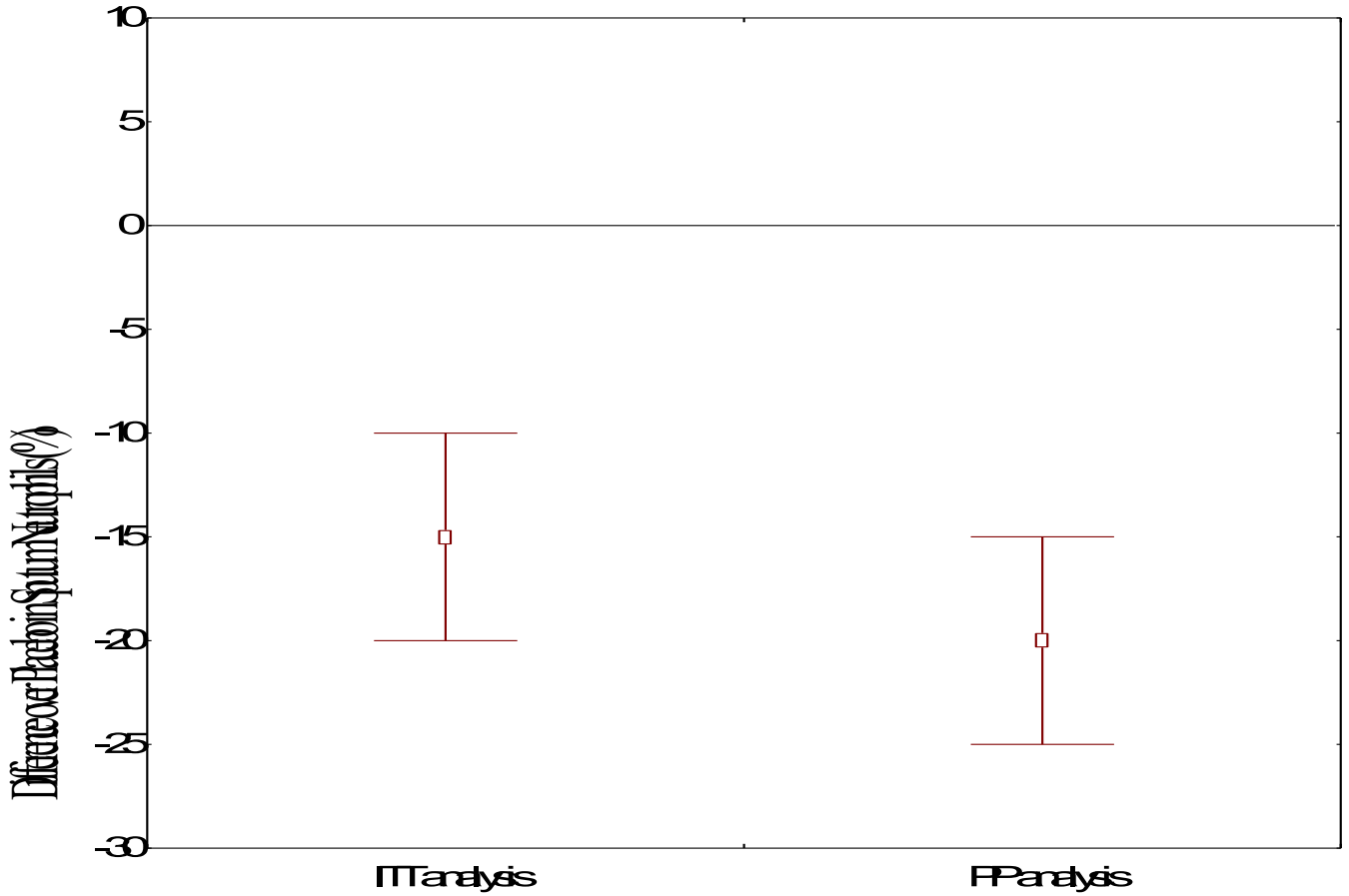
Figure 19.16A. Mean (SEM) Change from Baseline in SVC (by Week) – PP



Additional figures with same format as 19.16A

Figure 19A.16A. Mean (SEM) Change from Baseline in SVC (by Week) – ITT

Figure 19.01D. Mean (95% CI) Difference over Placebo for Sub-epithelial CD68+ (Macrophages) by Analysis Population



Additional figures with same format as 19.01D

Figure 19.01E. Mean (95% CI) Difference over Placebo for Sub-epithelial CD8+ Lymphocytes by Analysis Population

Appendix

Appendix A.01. Treatment Randomisation with Patient Number

Patient Number	Treatment Group	Randomisation Number

1. LISTING INCLUDES ONLY RANDOMISED PATIENTS

Appendix B.01. Reason for Study Conclusion, Days of Participating in the Study and Demographics by Patient Number

Patient Number	Sex	Race	Age	Treatment Group	Study Conclusion	Days in DB	Relative Day at Visit													
							1	2	2A	3	4	5	6	6A	7	8	EW	ITT	PP	Safety

1. LISTING INCLUDES ONLY RANDOMISED PATIENTS

Appendix B.02A. Exclusionary Medications and Visit Specific Protocol Violations by Patient Number

Patient Number	Treatment Group	Visit Excluded	Protocol Violation

1. LISTING INCLUDES ONLY PATIENTS WITH EFFICACY DATA

Appendix B.02B. Violations of Eligibility Criteria by Patient Number

Patient Number	Treatment Group	Protocol Violation

1. LISTING INCLUDES ONLY PATIENTS WITH EFFICACY DATA

Appendix B.02C. Conduct of Study Deviations by Patient Number

Patient Number	Treatment Group	Deviation	Visit

1. Listing includes only patients with efficacy data

Appendix B.04. Cigarette Smoking History at Screening by Patient Number

Patient Number	Treatment Group	Sex	Has Patient Previously Smoked Cigarettes	Current Smoker	Average Number of Cigarettes	Pack Years	X-ray Results

1. LISTING INCLUDES ONLY RANDOMISED PATIENTS

Appendix B.06. Current Medical Conditions by Patient Number and Disease Classification

Patient Number	Treatment Group	System Organ Class

1. LISTING INCLUDES ONLY RANDOMISED PATIENTS

Appendix B.07. Prior Medications by Patient Number

Patient Number	Treatment Group	Generic Term	ATC Classification (Level 1)	Route	Indication	Start Day	End Day	Duration	Cont. trt

1. LISTING INCLUDES ONLY RANDOMISED PATIENTS

2. LISTING INCLUDES MEDICATIONS CONTINUED POST-RANDOMISATION AND MEDICATIONS DISCONTINUED PRIOR TO RANDOMISATION

CONT TRT =CONTINUING TREATMENT

ROUTE: PO = BY MOUTH, IV = INTROVENOUS, IM= INTRAMUSCULAR, IAR = INTRA-ARTERIAL, TO= TOPICAL
SL= SUBLINGUAL, IT = INTRATHECAL, A = VAGINAL, NA = NASAL, IA = INTRA-ARTICULAR INEJECTION
TD = TRANSDERMAL, IH = INHALED, SC= SUBCUTANEOUS, PR=RECTAL, ID = INTRADERMAL

Other Tables with the same format as Appendix B.07

Appendix B.08A. Concomitant Medications by Patient Number

2. LISTING INCLUDES MEDICATIONS CONTINUED FROM PRE-RANDOMISATION AND MEDICATIONS INITIATED POST-RANDOMISATION

Appendix B.10. Baseline Signs and Symptoms by Patient Number, Body System, Preferred Term and Verbatim Term

Patient Number	Body System	Who Preferred Term	Verbatim (Modified) Term	Onset (Days)	Dur	Outcome	Inv. Act.	Inv. Int	Inv. Rel	With.	SAE

1. LISTING INCLUDES RANDOMISED AND NON-RANDOMISED PATIENTS

* NUMBER OF DAYS RELATIVE TO START OF STUDY MEDICATION (NUMBER OF DAYS RELATIVE TO STOP OF STUDY MEDICATION)

[OUTCOME] OUTCOME : RESO = RESOLVED, ONGO = ONGOING, DIED = DIED

[COURSE] EXPERIENCE COURSE : INTE = INTERMITTENT, CONS = CONSTANT; [NO. EPI] NUMBER OF EPISODES :

[INV INT] INVESTIGATOR INTENSITY : MIL = MILD, MOD = MODERATE, SEV = SEVERE

[INV REL] INVESTIGATOR RELATIONSHIP : NOT = NOT RELATED, PRB = PROBABLE, SUS = SUSPECTED, UNL = UNLIKELY

[CORR THER] CORRECTIVE THERAPY; [WITHAE] PATIENT WITHDRAWN DUE TO AE : Y= YES N = NO

[SAE] SERIOUS AE AS JUDGED BY SB CRITERIA (INVESTIGATOR) : Y = YES, N = NO, - = UNAVAILABLE

[AE TERM] P: AE PREFERRED TERM, C: AE COMMON TERM, M: AE ENHANCED/MODIFIED TERM, V: AE VERBATIM TERM

Appendix B.11. Study Medication Compliance by Patient Number

Patient Number	Treatment Group	Visit/Week	Date	Tablets/Capsules				Days Since Last Visit	Compliance (%)
				Dispensed	Taken	Lost	Returned		

1. LISTING INCLUDES ONLY RANDOMISED PATIENTS

2. VALUE OF COLUMN 'DAYS SINCE LAST VISIT' FOR 'OVERALL' ROW REPRESENTS THE TOTAL

Appendix B.12. Study Medication Record by Patient Number

Patient Number	Treatment Group	Dose	Freq	Visit	Visit Date

1. LISTING INCLUDES RANDOMISED PATIENTS ONLY

* Days relative to start of study medication (days relative to stop of study medication)

Appendix C.01. Sputum Analysis by Patient Number

								Differential Cell Counts (% of 400 cells)			
Patient	Treatment	Baseline Smoking Status	Visit	Volume of Sample (micro-litre/mg)	Total Cell Count (10^6/ml)	IL-8 (NG/ML)	Neutrophil Elastase (NG/ML)	Eos	Macro	Lympho	Epithelial

1. LISTING INCLUDES ONLY RANDOMISED PATIENTS

Appendix C.02. Pulmonary Function Parameters by Patient Number

Patient Number	Treatment Group	Visit/Week	Time	FEV1 (L)	SVC (L)	FVC (L)

1. PRE-BD=PRE BRONCHODILATOR, POST-BD=POST BRONCHODILATOR

2. MAXIMUM OF THE THREE MEASUREMENTS FOR EACH PULMONARY FUNCTION TEST IS DISPLAYED

3. LISTING INCLUDES ONLY RANDOMISED PATIENTS

Appendix C.03. Bronchial Biopsy Analysis by Patient Number

Patient	Treatment	Baseline Smoking Status	Visit	Rel. Day	SUB-EPITHELIAL CELLS/MM^2 TISSUE CD8+	CD68+	Mass Cells	CD45	CD4	IL-8	TNF - alpha

1. LISTING INCLUDES ONLY RANDOMISED PATIENTS

Appendix C.04. COPD Exacerbations by Patient Number

Patient Number	Treatment Group	Onset Date	Relative Day	Duration (days)	Severity	Withdrawn?	Corticosteroids?	Antibiotics?	SAE?

1. LISTING INCLUDES ONLY RANDOMISED PATIENTS

Appendix C.05. Mucin Expression Analysis by Patient Number

Patient Number	Treatment Group	Baseline Smoking Status	Visit	Mucin Expression	Level	% Positive Staining in Epithelium			% Positive Staining in Sub-mucosa		
						Biopsy 1	Biopsy 2	Mean	Biopsy 1	Biopsy 2	Mean
xxx.xxx.xxxx	ccccccccc	C	CC	MUC5AC	C	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
			CC	MUC5B	C	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
xxx.xxx.xxxx	ccccccccc	C	CC	MUC5AC	C	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
			CC	MUC5B	C	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x

1. LISTING INCLUDES ONLY RANDOMISED PATIENTS

Appendix D.01. On-Therapy Adverse Experiences by Treatment Group, Patient Number, Body System, Preferred Term and Verbatim Term

Patient Number	Treatment Group	Medra System Organ Class	Adverse Experience Term	Onset* ST/END	Dur	Out-come	INV INT	Act ion	With.	INV REL	SAE

1. LISTING INCLUDES ONLY RANDOMISED PATIENTS

* NUMBER OF DAYS RELATIVE TO START OF STUDY MEDICATION (NUMBER OF DAYS RELATIVE TO STOP OF STUDY MEDICATION)

OUTCOME: R = RESOLVED, S = RESOLVED WITH SEQUELAE, N = NOT RESOLVED

ACTION TAKEN: DOSE ADJ = DOSE ADJUSTED, TEMP INT = TEMPORARIY INTERRUPTED, PER DISC = PERMANENTLY DISCONTINUED, NOT APP = NOT APPLICABLE

Note: Use text for maximum intensity

Other Listings with the Same Format as Appendix D.01

Appendix D.02A. On-Therapy Adverse Experiences Related to Treatment by Treatment Group, Patient Number, Body System, Preferred Term and Verbatim Term

Appendix D.02B. On-Therapy Adverse Experiences Not Related to Treatment by Treatment Group, Patient Number, Body System, Preferred Term and Verbatim Term

Appendix D.03. On-Therapy Adverse Experiences That Led to Dose Interruption by Treatment Group, Patient Number, Body System, Preferred Term and Verbatim Term

Appendix D.05A. Run-in Serious Adverse Experiences by Patient Number, Body System, Preferred Term and Verbatim Term

Remove footnote 1.

Appendix D.05B. On-Therapy Serious Adverse Experiences by Treatment Group, Patient Number, Body System, Preferred Term and Verbatim Term

Appendix D.05C. Post-Therapy Serious Adverse Experiences by Treatment Group, Patient Number, Body System, Preferred Term and Verbatim Term

Appendix D.05D Patient Fatalities by Patient Number

Appendix D.06A. On-Therapy Adverse Experiences That Led to Withdrawal by Treatment Group, Patient Number, Body System, Preferred Term and Verbatim Term

Appendix D.06B. Run-In Adverse Experiences That Led to Withdrawal by Treatment Group, Patient Number, Body System, Preferred Term and Verbatim Term

Remove footnote 1.

Appendix D.07. Post-Therapy Adverse Experiences by Treatment Group, Patient Number, Body System, Preferred Term and Verbatim Term

Appendix D.08. Gastrointestinal Adverse Experiences of Concern by Treatment Group, Patient Number, Body System, Preferred Term and Verbatim Term

Appendix D.10. Abdominal Pain Assessment by Patient Number

Patient Number	Treatment Group	Relative Day	Location of Pain	Pain Onset	Pain Quality	Pain Radiation	Radiation Location of Pain

1. RELATIVE DAY IS RELATIVE TO START OF STUDY MEDICATION (LAST DOSE OF STUDY MEDICATION)
2. LISTING INCLUDES ONLY RANDOMISED PATIENTS WITH GI AE OF CONCERN

Appendix D.11. Stool Assessment by Patient Number

Patient Number	Treatment Group	Relative Day	First Time Noticed	Number of Bowel Movements	Nosebleed/Gumbleed	Menstrual Origin	Hemmorhoids	NSAIDS/ ASA	Stool Appearance	Fecal Occult Blood

1. RELATIVE DAY IS RELATIVE TO START OF STUDY MEDICATION (LAST DOSE OF STUDY MEDICATION)

2. LISTING INCLUDES ONLY RANDOMISED PATIENTS WITH GI AE OF CONCERN

Appendix D.12. Physical Examinations for Patients with Gastrointestinal Symptoms of Concern by Patient Number

Patient Number	Treatment Group	Relative Days	Weight (KG)	Abdominal Tenderness	Abdominal Masses	Peritoneal Signs	Other Findings

1. LISTING INCLUDES ONLY RANDOMISED PATIENTS

* DAYS RELATIVE TO START OF STUDY MEDICATION (DAYS RELATIVE TO STOP OF STUDY MEDICATION)

Appendix D.13. FOB Test Results by Patient Number

Patient Number	Treatment Group	Visit/Week Recorded	Relative(*) Days	Test Result

(*) DAYS RELATIVE TO START OF STUDY MEDICATION (DAYS RELATIVE TO STOP OF STUDY MEDICATION)

1. LISTING INCLUDES ONLY RANDOMISED PATIENTS

Appendix E.01A. Standard Vital Signs by Patient Number

Patient Number	Treatment Group	Visit/Week	Relative Day	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Heart Rate (bpm)	HT (cm)	WT (kg)	Temp. (C)

1. LISTING INCLUDES ONLY RANDOMISED PATIENTS

* DAYS RELATIVE TO START OF STUDY MEDICATION (DAYS RELATIVE TO STOP OF STUDY MEDICATION)

[ ] (CLINICAL CONCERN FLAG) : +/- VALUE ABOVE/BELOW LEVELS OF CLINICAL CONCERN

Appendix F.02. Clinical Laboratory Values by Treatment Group and Patient Number

Treatment Group: PID:

Patient Number	Age	Sex	Visit/Week	Relative Days	Lab Value	RRF	BF	CCF	Reference Range	Lab Units

1. LISTING INCLUDES ONLY RANDOMISED PATIENTS

* DAYS RELATIVE TO START OF STUDY MEDICATION (DAYS RELATIVE TO STOP OF STUDY MEDICATION)

RRF (REFERENCE RANGE FLAG) : H/L= VALUE ABOVE/BELOW REFERENCE RANGE, U= UNFLAGGABLE

BF (BASELINE FLAG) : I/D= INCREASE/DECREASE FROM BASELINE BY A PRE-DEFINED AMOUNT, B= BASELINE, U= UNFLAGGABLE

CCF (CLINICAL CONCERN FLAG) : +/-= VALUE ABOVE/BELOW LEVELS OF CLINICAL CONCERN, U= UNFLAGGABLE

APPENDIX H

CASE REPORT FORM TABULATIONS

MOCKUPS NOT DISPLAYED

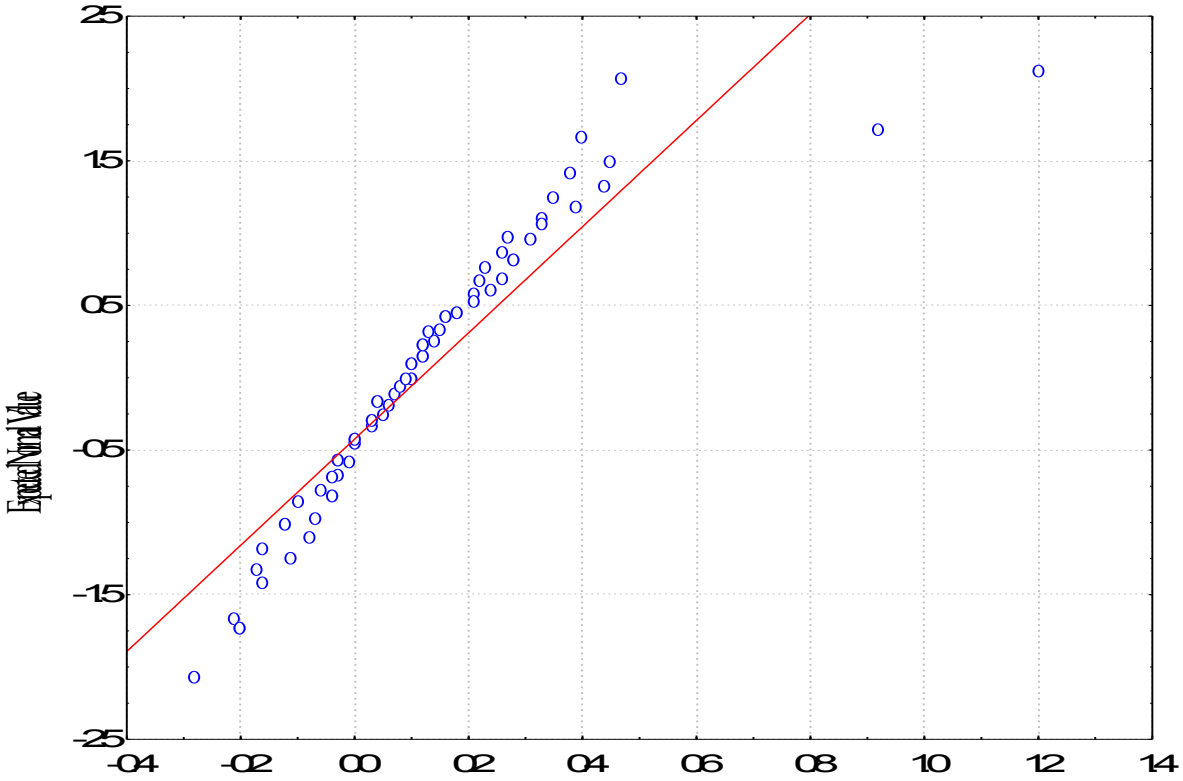
Appendix I.01E. Wilcoxon Sign Test for Treatment Difference for sub-epithelial CD68+ (Macrophage) – PP

Appendix I.02E. Wilcoxon Sign Test for Treatment Difference for sub-epithelial CD8+ (Lymphocytes) – PP

Appendix I.12A. Wilcoxon Sign Test for Treatment Difference in Change from Baseline in Neutrophils Elastase (NG/ML) by Treatment Group – PP

Appendix I.15A. Wilcoxon Sign Test for Treatment Difference in Change from Baseline in Sputum IL-8 (NG/ML) by Treatment Group – PP

Appendix I.05. Normal Probability Plot of Residuals for sub-epithelial CD68+ (Macrophage) at Endpoint - PP



Additional figures with the same format

Appendix I.06. Normal Probability Plot of Residuals for sub-epithelial CD8+ (Lymphocytes)) at Endpoint - PP

GlaxoSmithKline

Subject number

CONFIDENTIAL

CASE REPORT FORM

207499/181

A 13-week Randomised, Double-blind, Parallel Group, Multicentre Study to Compare The Bronchial Anti-inflammatory Activity of Oral Cilomilast (15 mg bd) with Placebo Twice Daily in Subjects with Chronic Obstructive Pulmonary Disease (COPD)

Treatment number	Investigator/Centre number

GlaxoSmithKline Research and Development
Greenford Road
Greenford, Middlesex, UB6 0HE, UK
Telephone: [redacted]

Standard Completion Guidelines For Case Report Forms (CRFs)

In studies where a study reference manual is used, additional guidelines for completion of specific CRF pages (laboratory data, concomitant medications, etc.) may be available.

General Rules for CRF Completion

- Complete CRFs in English.
- Print neatly and legibly.
- Make all entries on the CRF with black ink and press firmly so that all copies are legible.
- Do not write in shaded areas unless requested.
- Avoid use of abbreviations and acronyms whenever possible. Use only abbreviations that are clear and in standard medical use.
- Enter subject number when not preprinted in the space provided at the top of each CRF page.
- Use only subject number to identify subject. Do not use the subject's name or initials.
- The treatment number is entered only on the cover page and for pages which are sent in for prompt reporting (e.g., Serious Adverse Event).
- Record all values in the units indicated on the CRF.
- Boxes must be completed from right to left e.g., 12 written as | 0 | 0 | 1 | 2 |.
- Check that information classified as *Other* does not fit in one of the listed categories. If a ✔ is present for *Other*, *specify*, provide text in the specified field.

Missing Data

- Use the following abbreviations for missing information:
  - NA not available/not applicable
  - ND not done
  - UNK unknown (e.g., for dates, if the month is unknown record as *UNK/01*)

Text Entries

- Comments must be clear, concise and in English.
- Do not write data on page margins or outside of allocated spaces.

Dates and Times

- Record dates in DD MMM YY | 0 | 6 | | J | A | N | | 0 | 2 | format.
  day month year
- Watch for obvious year errors, especially for the months of December, January, and February.
- Record time in 24-hour clock format (range 00:00-23:59) with midnight = 00:00.
- If the CRF is not completed at time of assessment, record date of assessment, not date of CRF completion.
- If a full date is not available, enter the partial date and use *UNK* for missing data.
- Check that all visit dates are in chronological order.

CRF Collation

- Ensure that all appropriate pages are present in the CRF and are in the proper sequence.
- Number extra pages using the .01 numbering convention, e.g., the first page inserted between pages 5 and 6 is numbered 5.01, with subsequent pages numbered as 5.02, 5.03 etc.

Correction Process

- Draw a single line through the incorrect entry.
- Do not "write over" or erase an incorrect entry or re-copy the original page.
- Do not use correction materials (e.g., correction fluid or tape) on the CRF.
- Write the correct data nearby.
- Date and initial the correction.
- If a correction results in data being located outside the designated space, circle the data and draw an arrow to the correct space.

Time and Events Table

Visit	1	2/2A[l]	3	4	5	6/6A[l]	7	8	EWV[a]
Period	Screen	Baseline	Start of double-blind Treatment	Treatment				Follow-Up	
Duration (Weeks ± days)	-4 ±3 days	-1 ±3 days	0 ±3 days	4 ±3 days	8 ±3 days	12 ±3 days	13 ±3 days	14 ±3 days	
Signed written informed consent	X								
Inclusion/Exclusion criteria	X		X						
Demography	X								
Medical & surgical history	X								
Postero-anterior chest radiograph [b]	X								
Pulmonary history & symptoms	X								
Concurrent Medication history	X								
Current Medical Conditions	X								
Compliance of Study Medication	X	X	X	X	X	X	X	X	X
Concomitant medication/medical procedures	X	X	X	X	X	X	X	X	X
Adverse Events	X*	X	X	X	X	X	X	X	X
Smoking history	X						X		X
Exacerbation assessment	X	X	X	X	X	X	X	X	X
Physical examination [c]	X							X	X[d]
Vital signs (BP,HR)		X	X			X	X	X	X
Resting SaO_2[e]	X								
Salbutamol reversibility [f]	X								
Post bronchodilator PFTs[g]	X	X	X	X	X	X	X	X	X
Sputum induction and sample preparation			X				X		X[h]
Blood clotting tests	X				X				X
Bronchial biopsy and sample preparation		X				X			X[h]
Clinical Laboratory and pregnancy testing	X							X	
Faecal Occult Blood test (FOB)	X	X[j]					X	X	X
Dispense double-blind medication			X						
Collect study medication				X	X	X	X	X	X

continued...

Time and Events Table *Continued*

[a] *Subjects who withdraw between clinic visits will attend the clinic within 24 hours for an early withdrawal visit (EWV)*

[b] *Postero-anterior chest X-ray must be is available to the Investigator by Visit 2 prior to taking the biopsy.*

[c] *To include a respiratory examination*

[d] *If abnormalities are present at previous visit for subjects who complete Week 13 or withdraw from the study*

[e] *Resting SaO 2 will be measured by pulse oximetry.*

[f] *Before and 30 minutes after administration of 400mcg salbutamol via MDI and spacer to determine % predicted normal FEV_1, and FVC*

[g] *Includes FEV_1, FVC, and SVC measured by the same person at each visit (please note only SVC at all other visits except visit 1)*

[h] *Sputum should be performed, if possible 7 days after Bronchial biopsies which is done 1 week after the Early Withdrawal visit*

[i] *The baseline and end of treatment bronchial biopsies will only be performed, if the safety criteria are met, otherwise the biopsy procedure should be rescheduled within 1 to 7 days (Visit 2A and Visit 6A respectively).*

[j] *Assessment of FOB kit (which was given to subject at previous visit)*

** Only SAEs related to study participation will be collected and reported from screening, all AEs should be collected.*

Protocol code

207499/181

Inclusion Criteria Worksheet
Visit 1 (Screening)

Instructions to Investigator

- Review the worksheet first.
- Answer each question on the worksheet.
- ✔ appropriate box for each Inclusion criterion question.
- Ensure that you maintain the source documents that validate the Inclusion criteria.

Formula for Calculating Smoking History

$$\text{Total number pack years} = \frac{\text{Number of cigarettes a day}}{20} \times \text{Number of years of smoking}$$

NOTE: Subjects should not be entered if they have a smoking history of <10 pack years.

Monitor Data Validation Checks

- Check that either a YES or NO box is ✔ for each Inclusion criterion.

Protocol code

207499/181

Subject number

Inclusion Criteria Worksheet
Visit 1 (Screening)

Inclusion Criteria ✔ *one box for each question:*

		Yes	No
1.	Is the subject a male or female adult 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.	Does the subject have a clinical diagnosis of COPD, as defined by GOLD guidelines? *NOTE: A diagnosis of COPD should be considered in any subject who has symptoms of cough, sputum production, or dyspnoea, and/or a history of exposure to risk factors for the disease. The diagnosis is confirmed by spirometry. The presence of a post-bronchodilator FEV_1 < 80% of the predicted normal value in combination with an FEV_1/FVC <70% confirms the presence of airflow limitation that is not fully reversible)*	☐	☐
3.	Does the subject have a smoking history (current or ex-smoker) of ≥10 pack years (1 pack year = 20 cigarettes smoked per day for 1 year or equivalent). *NOTE: (Ex-smokers are defined as those who have stopped smoking for at least 6 months prior to Visit 1. Ex-smokers are eligible to enter the study provided they have at least 10 pack years smoking history).*	☐	☐
4.	Did the subject have a pre-bronchodilator FEV_1 to FVC ratio (FEV_1:FVC) ≤0.7 at Visit 1.	☐	☐
5.	Does the subject have poor reversibility of airflow obstruction, defined by ≤10% increase in FEV_1 as % of predicted normal value OR ≤200ml (or both) increase in FEV_1 after the administration of salbutamol 400 mcg via MDI at Visit 1 (Screening visit)?	☐	☐
6.	Does the subject have a post-salbutamol FEV_1 of ≥40 and ≤80% of predicted normal for height, age and gender at Visit 1? *NOTE: Subjects will be assessed 30 minutes after the administration of 400mcg salbutamol via MDI and spacer?*	☐	☐
7.	Is the subject without hypoxaemia? *NOTE: All subjects must have an O_2 saturation ≥88% on room air.*	☐	☐
8.	Did the subject give their signed and dated written informed consent to participate in the study?	☐	☐

*If any INCLUSION CRITERIA question is answered **NO**, this subject must **NOT** enter this study.*

GlaxoSmithKline

Protocol code

207499/181

Exclusion Criteria Worksheet
Visit 1 (Screening)

Instructions to Investigator

- Review the worksheet first.
- Answer each question on the worksheet.
- ✔ appropriate box for each Exclusion criterion question.
- Ensure that you maintain the source documents that validate the Exclusion criteria.

Monitor Data Validation Checks

- Check that either a YES or NO box is ✔ for each Exclusion criterion.

Protocol code

207499/181

Subject number

Exclusion Criteria Worksheet
Visit 1 (Screening)

Exclusion Criteria ✔ *one box for each question:*	Yes	No
1. Is the subject pregnant or lactating?	☐	☐
2. Does the subject have asthma and/or atopy as the main component of their obstructive airways disease?	☐	☐
3. Does the subject have poorly controlled COPD, defined as the occurrence of any of the following in the 4 weeks prior to Visit 1 (Screening): acute worsening of COPD that is managed by the subject at home by self-treatment with corticosteroids or antibiotics, or that requires treatment prescribed by a physician, or for which the subject is hospitalised?	☐	☐
4. Does the subject have known active tuberculosis, lung cancer, clinically overt bronchiectasis, or other known specific pulmonary disease, any other condition known to be associated with inflammation (sarcoidosis and arthritis)?	☐	☐
5. Did the subject have a chest X-ray indicating diagnosis other than COPD that might interfere with the study (chest X-ray to be taken at entry to the run-in period or in the 3 months prior to entry to the run-in period)?	☐	☐
6. Does the subject have clinically significant cardiovascular, neurological, renal, endocrine, or haematological abnormalities that are uncontrolled on permitted therapy?	☐	☐
7. Does the subject have clinically significant gastrointestinal or hepatic abnormalities?	☐	☐
8. Does the subject have a history of bleeding diathesis?	☐	☐
9. Does the subject have a history of hypersensitivity to PDE4 inhibitors?	☐	☐
10. Does the subject have a suspected abuse of alcohol or any other recreational substance?	☐	☐
11. Is the subject receiving treatment with inhaled cromolyn sodium or nedocromil, inhaled long-acting beta$_2$-agonists, and/or oral beta$_2$-agonists, long acting anticolinergic (e.g. tiotropium bromide) xanthines, leukotriene modifiers, mucolytics, oral/inhaled corticosteroids, or NACs N-Acetyl Cysteine.?	☐	☐

NOTE: All COPD medications except short- acting anticholinergic medication or salbutamol should be withdrawn prior to or at Visit 1 (Screening). All oral/inhaled corticosteroids, long-acting anticolinergic (e.g. tiotropium bromide), xanthines must be withdrawn at least four weeks prior to Visit 1.

*If any EXCLUSION CRITERIA question is answered **YES**, this subject must **NOT** enter this study.*

continued...

Protocol code

207499/181

Subject number

Exclusion Criteria Worksheet *Continued*
Visit 1 (Screening)

Exclusion Criteria ✔ *one box for each question:*

		Yes	No
12.	Is the subject receiving treatment with long term oxygen therapy (LTOT) or those subjects who require supplemental oxygen more often than on an occasional (prn) basis?	☐	☐
13.	Has the subject 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.	Is the subject unable or unwilling to comply with all protocol specified procedures?	☐	☐

*If any EXCLUSION CRITERIA question is answered **YES**, this subject must **NOT** enter this study.*

Protocol code

207499/181

Inclusion / Exclusion Criteria
Visit 1 (Screening)

Instructions to Investigator

Did the subject meet all the entry criteria?

- If the subject met all the entry criteria (all YES answers to the Inclusion questions and all NO answers to the Exclusion questions), ✔ YES. Otherwise ✔ NO.

Inclusion/Exclusion Criteria

- Only ✔ boxes that represent a violation of the Inclusion/Exclusion criteria.

Monitor Data Validation Checks

- If the question "*Did the subject meet all entry criteria*" is answered YES, check that no ✔ are present in the inclusion or exclusion criteria boxes.
- If the question "*Did the subject meet all entry criteria*" is answered NO, check that a ✔ is present in at least one inclusion and/or exclusion criteria boxes.

Protocol code	Session number	Subject number
207499/181	**1**	

Inclusion / Exclusion Criteria
Visit 1 (Screening)

Did the subject meet all entry criteria (i.e., All "YES" answers for inclusion criteria, all "NO" answers for exclusion criteria)? *See INCLUSION / EXCLUSION CRITERIA WORKSHEET.* Yes ☐ Y No ☐ N

✔ *all boxes that represent a violation of the inclusion / exclusion criteria:*

Inclusion Criteria

1. ☐ 2. ☐ 3. ☐ 4. ☐ 5. ☐ 6. ☐ 7. ☐ 8. ☐

Exclusion Criteria

1. ☐ 2. ☐ 3. ☐ 4. ☐ 5. ☐ 6. ☐ 7. ☐ 8. ☐ 9. ☐

10. ☐ 11. ☐ 12. ☐ 13. ☐ 14. ☐

*NOTE: If any of the boxes above have been ✔ as a violation of the Inclusion or Exclusion criteria, ensure that the END OF STUDY RECORD section is completed and 'did not fulfil entry criteria' is ✔ as the **primary** reason for discontinuation.*

Protocol code

207499/181

Adverse Events
Visit 1 (Screening)

Instructions to Investigator

- *Any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.*

  An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

  NOTE: Evidence of oropharyngeal candidiasis at Visit 1 will NOT be considered an adverse event and should be recorded on the CURRENT MEDICAL CONDITIONS page.

Monitor Data Validation Checks

- Check that any adverse events are recorded in the *ADVERSE EVENT* section of the Case Report Form.
- Check that evidence of oropharyngeal candidiasis at Visit 1 is recorded on the *CURRENT MEDICAL CONDITIONS* page and NOT in the *ADVERSE EVENT* section(s).

Protocol code

207499/181

Subject number

Adverse Events
Visit 1 (Screening)

Adverse Event

Ask the following question:

(a) "Have you had any (other) medical problems within the 4 weeks preceding this visit?" Yes ☐ No ☐

Adverse events should be recorded in the appropriate ADVERSE EVENTS section and related concomitant medication on the CURRENT AND PREVIOUS COPD AND NON-COPD MEDICATION page in this section.

Protocol code

207499/181

Demography
Visit 1 (Screening)

Instructions to Investigator

- **Race**

  Check the single most appropriate category based on physical and genetic characteristics, not socioeconomic or geographic factors. Race is collected to determine if there are any genetic differences that may contribute to differences in study responses.

Monitor Data Validation Checks

- Check that the year in the date of birth is not the current year.

Protocol code	Session number	Subject number
207499/181	1	

Demography
Visit 1 (Screening)

Date of assessment ☐☐ day ☐☐☐ month ☐☐ year

Date of birth ☐☐ day ☐☐☐ month ☐☐☐☐ year

Sex

Male ☐ M

Female ☐ F

Race, ✔ *one:*

White ☐ 1 *Origins in the original peoples of Europe, the Middle East, Western Russia, Afghanistan, or the white racial groups of Africa.*

Black ☐ 2 *Origins in any of the black racial groups of Africa.*

Oriental ☐ 3 *Origins in the original peoples of the Indian subcontinent, the Far East, Southeast Asia, or the Pacific islands.*

Other ☐ 4 *People whose racial group is not represented above, or whose predominant origin cannot be determined.*

Height ☐☐☐ cm

Weight ☐☐☐.☐ kg

Protocol code

207499/181

Demography for Females
Visit 1 (Screening)

Monitor Data Validation Checks

- Check that the *DEMOGRAPHY FOR FEMALES* page has not been completed if this is a male subject.
- Check that information on contraceptive drugs (i.e., oral or depot contraceptives) has been recorded In the *NON-COPD CONCOMITANT MEDICATIONS* section of the CRF for subject taking contraceptives.

Protocol code	Session number	Subject number
207499/181	**1**	

Demography for Females
Visit 1 (Screening)

Pregnancy test result, ✔*one:*

Positive ☐ P

Negative ☐ N

Not applicable ☐ X (Not of childbearing potential)

Protocol code

207499/181

Current and Previous COPD and Non-COPD Medication

Instructions to Investigator

Current and Previous COPD Medication

- Record all COPD medication in the last 12 weeks.

The dose and frequency should be recorded as shown by the following example:

If the subject takes 50 μg per puff, 2 puffs bid (i.e., 100 μg bid)

The **dose** column should be recorded as 100.
The μg should be circled in the **units** column.
The **frequency** column should be recorded as bid.

Route Key for Concomitant Medication

PO	=	By mouth	SL	=	Sublingual	TD	=	Transdermal
IV	=	Intravenous	IT	=	Intrathecal	IH	=	Inhaled
IM	=	Intramuscular	A	=	Vaginal	SC	=	Subcutaneous
IAR	=	Intra-arterial	NA	=	Nasal	PR	=	Rectal
TO	=	Topical	IA	=	Intra-articular injection	ID	=	Intradermal

Concomitant Medications

- All Inhaled, oral and systemic corticosteroids, all long-acting anticholinergics e.g. tiotropium bromide and all Xanthines, must have been stopped at least 4 weeks **before** the start of Visit 1.
- All inhaled, long acting β_2-agonists must have been stopped 2 weeks **before** the start of Visit 1.
- Stop subjects relief VENTOLIN at Visit 1 and provide them with salbutamol and/or ipratropium bromide as relief medication for use during the Run-in and Treatment period.

*NOTE: The use of salbutamol and/or ipratropium bromide medication **during** the study must be recorded in the CONCOMITANT MEDICATION section of the CRF.*

*NOTE: **During** the study, details of all COPD and all Non-COPD concomitant medications, should be recorded in the appropriate CONCOMITANT MEDICATIONS section(s) of this CRF.*

Protocol code	Session number	Subject number
207499/181	1	

Current and Previous COPD and Non-COPD Medication

Current and Previous COPD and Non-COPD Medication

*Record below, all **COPD medication** taken during the **12 weeks** preceding this visit together with all **other medication** taken during **4 weeks** preceding this visit.*

Drug Trade name preferred	Dose	Units	Fre-quency	Route	Date started day month year	✔ If drug con-tinued	Date stopped day month year	Medical illness/diagnosis *(or symptoms in absence of diagnosis)*
Example 1 ***Flixotide***	***100***	(µg)/mg	***BID***	(IH)/PO	***01 AUG 98***	✔		
Example 2 ***DUOVENT (100 / 40 µg)***	***1***	µg/mg PUFF	***BID***	(IH)/PO	***01 AUG 98***	✔		
1.		µg/mg		IH/PO				
2.		µg/mg		IH/PO				
3.		µg/mg		IH/PO				
4.		µg/mg		IH/PO				
5.		µg/mg		IH/PO				
6.		µg/mg		IH/PO				
7.		µg/mg		IH/PO				
8.		µg/mg		IH/PO				

Protocol code

207499/181

Medical / Surgical History Worksheet
Visit 1 (Screening)

Instructions to Investigator

- For each body system listed, place a ✔ in the appropriate YES or NO box.
- If YES is ✔ specify all conditions concisely, separating multiple conditions with a slash (/).
- Do not record dates or detailed descriptions of signs and symptoms.
- Past medical conditions **include**:
  - Acute conditions (e.g., flu, upper respiratory tract infection)
  - Intermittent conditions (e.g., migraine, seasonal rhinitis)
  - Conditions from which subject is recovering (e.g., myocardial infarction)
  - Chronic conditions (e.g., hypertension, asthma)
- Past medical conditions **do not include**:
  - Acute events that have resolved without sequelae (e.g., transient ischemic attack)
  - Previous surgery without sequelae (e.g., hysterectomy)
  - Fractures that have healed (e.g., broken collar bone)

Monitor Data Validation Checks

- Check that YES or NO is ✔ for each body system.
- If YES is ✔, check that at least one condition is recorded.

Protocol code

207499/181

Subject number

Medical / Surgical History Worksheet
Visit 1 (Screening)

*Indicate **past** medical and surgical conditions **(including history of myocardial infarctions)** by ✔ the appropriate boxes. If YES, specify condition(s).*

		Yes	No	*If YES, specify condition(s):*
1.	Ear, nose, and throat	☐	☐	. . . . .
2.	Eyes	☐	☐	. . . . .
3.	Respiratory	☐	☐	. . . . .
4.	Cardiovascular	☐	☐	. . . . .
5.	Gastrointestinal	☐	☐	. . . . .
6.	Hepatobiliary and pancreas	☐	☐	. . . . .
7.	Urinary system	☐	☐	. . . . .
8.	Reproductive system	☐	☐	. . . . .
9.	Neurology	☐	☐	. . . . .
10.	Blood and lymphatic	☐	☐	. . . . .
11.	Endocrine and metabolic	☐	☐	. . . . .
12.	Musculoskeletal	☐	☐	. . . . .
13.	Skin	☐	☐	. . . . .
14.	Psychiatry	☐	☐	. . . . .
15.	Allergies	☐	☐	. . . . .

Protocol code

207499/181

Subject number

Physical Examination Worksheet
Visit 1 (Screening)

Indicate current physical findings by ✔ the appropriate box(es) below and if ABNORMAL, describe concisely: [different findings should be separated by either a (;) or a (/)].

	Not Done	Normal	Abnormal	*If Abnormal, specify:*
1. Hair and Skin		☐	☐	. . . . .
2. Lymph nodes		☐	☐	. . . . .
3. Eyes		☐	☐	. . . . .
4. Ears, Nose and Throat		☐	☐	. . . . .
5. Breasts	☐	☐	☐	. . . . .
6. Respiratory		☐	☐	. . . . .
7. Cardiovascular		☐	☐	. . . . .
8. Abdomen		☐	☐	. . . . .
9. Urogenital	☐	☐	☐	. . . . .
10. Pelvic	☐	☐	☐	. . . . .
11. Rectal	☐	☐	☐	. . . . .
12. Musculoskeletal		☐	☐	. . . . .
13. Neurological		☐	☐	. . . . .
14. Mental Status		☐	☐	. . . . .

Protocol code

207499/181

Current Medical Conditions
Visit 1 (Screening)

Instructions to Investigator

- For each body system listed, place a ✔ in the appropriate YES or NO box.
- If YES is ✔ specify all conditions concisely, separating multiple conditions with a slash (/).
- Do not record dates or detailed descriptions of signs and symptoms.
- Current medical conditions **include**:
  - Acute conditions (e.g., flu, upper respiratory tract infection)
  - Intermittent conditions (e.g., migraine, seasonal rhinitis)
  - Conditions from which subject is recovering (e.g., myocardial infarction)
  - Chronic conditions (e.g., hypertension, asthma)
- Current medical conditions **do not include**:
  - Acute events that have resolved without sequelae (e.g., transient ischemic attack)
  - Previous surgery without sequelae (e.g., hysterectomy)
  - Fractures that have healed (e.g., broken collar bone)

Monitor Data Validation Checks

- Check that YES or NO is ✔ for each body system.
- If YES is ✔, check that at least one condition is recorded.

Protocol code	Session number	Subject number
207499/181	1	

Current Medical Conditions
Visit 1 (Screening)

*Indicate **current** medical conditions **(excluding the illness(es) being treated in the study)** by ✔ the appropriate boxes. If YES, specify condition(s).*

		Yes Y	No N	*If YES, specify condition(s):*
1.	Ear, nose, and throat	☐	☐	. . . . .
2.	Eyes	☐	☐	. . . . .
3.	Respiratory	☐	☐	. . . . .
4.	Cardiovascular	☐	☐	. . . . .
5.	Gastrointestinal	☐	☐	. . . . .
6.	Hepatobiliary and pancreas	☐	☐	. . . . .
7.	Urinary system	☐	☐	. . . . .
8.	Reproductive system	☐	☐	. . . . .
9.	Neurology	☐	☐	. . . . .
10.	Blood and lymphatic	☐	☐	. . . . .
11.	Endocrine and metabolic	☐	☐	. . . . .
12.	Musculoskeletal	☐	☐	. . . . .
13.	Skin	☐	☐	. . . . .
14.	Psychiatry	☐	☐	. . . . .
15.	Allergies	☐	☐	. . . . .

Protocol code

207499/181

Smoking Status / Smoking History / Chest X-ray Review
Visit 1 (Screening)

Instructions to Investigator

Smoker Definitions:

Current smoker = Currently smoking or stopped smoking within **6 months** of screening visit.

Former smoker = Previously smoked and stopped smoking at least **6 months** prior to screening visit.

Formula for Calculating Pack Years

$$\text{Total number pack years} = \frac{\text{Number of cigarettes a day}}{20} \times \text{Number of years of smoking}$$

NOTE: One cigar is equivalent to 7 cigarettes and one gram of tobacco is equivalent to one cigarette.

NOTE: Ex-smokers are eligible to enter the study provided they have at least 10 pack years smoking history.

Protocol code	Session number	Subject number
207499/181	1	

Smoking Status / Smoking History / Chest X-ray Review
Visit 1 (Screening)

Smoking Status

Does the subject currently smoke? Yes ☐ Y No ☐ N

If NO, is the subject a former smoker? Yes ☐ Y No ☐ N

*NOTE: If the subject is **not** a current or former smoker, the subject is **not** eligible to participate in the study. Complete the END OF STUDY RECORD section in this CRF.*

If former smoker, date subject stopped smoking ☐☐ ☐☐☐ ☐☐ (day / month / year)

If current or former smoker, number of cigarettes smoked per day ☐☐☐

Smoking History

Number of pack years ☐☐☐.☐
(*see calculation formula on facing page*)

Chest X-ray Review

NOTE: If the results (including film) of a postero-anterior (P-A) chest X-ray taken within 9 weeks of Visit 1, are not available to the Investigator for review, a chest X-ray must be performed at this visit and the results made available prior to the biopsy at Visit 2.

Review a current postero-anterior (PA) chest X-ray (performed within 12 weeks prior to Visit 2).

NOTE: Review of written reports without accompanying films is not acceptable.

Date X-ray performed ☐☐ ☐☐☐ ☐☐ (day / month / year)

Result, ✔ *appropriate box*

Normal ☐ 1 *Within normal limits for COPD subjects*

Abnormal ☐ 2 *Abnormality that may mimic or co-exist with COPD e.g., pneumothorax, bronchial carcinoma or active pulmonary TB*

NOTE: If the chest X-ray indicates diagnosis other than COPD that may interfere with the study, the subject must be excluded from the study and the END OF STUDY RECORD section completed.

Protocol code

207499/181

COPD History
Visit 1 (Screening)

Instructions to Investigator

Type of COPD

Chronic bronchitis is defined as 'had a chronic productive cough for at least three months in each of 2 successive years'. Otherwise it is emphysema.

COPD Exacerbations

Definition of a COPD Exacerbation

For the purpose of this study COPD exacerbations are categorised as follows:

Mild

- Acute worsening of COPD that is self-managed by the subject at home by increasing usual COPD bronchodilators medications, and should not be taking any antibiotics (i.e. the subject does not see a doctor for this episode)

Moderate

- Acute worsening of COPD that requires additional treatment (e.g. a short course of oral steroids, antibiotics, etc.) prescribed by primary care physician or as a result of a hospital out-patient visit (including a visit to the Emergency Room).

Severe

- Acute worsening of COPD that requires the subject to be admitted to hospital for treatment.

Monitor Data Validation Checks

Duration of COPD

- Check that duration is recorded correctly.
- Check that only one box is ✔ for range of duration, and that the bottom of the range is not greater than the subject's age.

COPD Exacerbations

- Check that response boxes for COPD exacerbations have 00 entered if no COPD exacerbations have occurred.

Protocol code	Session number	Subject number
207499/181	1	

COPD History
Visit 1 (Screening)

Type of COPD

✔ ***one*** *box only (most prominent condition):*

Chronic bronchitis ☐ B

Emphysema ☐ E

Duration of COPD

✔ *one box only:*

< 5 years ☐ 9	≥ 5 years to < 10 years ☐ 4	≥ 10 years to < 15 years ☐ 5
≥ 15 years to < 20 years ☐ 13	≥ 20 years to < 25 years ☐ 14	≥ 25 years ☐ 15

COPD Exacerbations

Record subject's previous 12 months history of COPD below:

Number of exacerbations in the last 12 months that were self-managed by the subject ☐☐ *If none, enter '00'.*

Number of exacerbations in the last 12 months that required oral corticosteroids and/or antibiotics (not involving hospitalisation) ☐☐ *If none, enter '00'.*

Number of exacerbations in the last 12 months that required hospitalisation ☐☐ *If none, enter '00'.*

NOTE: Subjects with poorly controlled COPD in the 4 weeks before Visit 1 that required oral corticosteroids and/or antibiotics or any change in COPD medication, are ***not*** *eligible to participate in the study.*

Protocol code

207499/181

SaO_2
Visit 1 (Screening)

Instructions to Investigator

- Ensure the oximetry value has been recorded.
- Ensure that either a YES or NO box has been ✔ for the question.

Protocol code	Session number	Subject number
207499/181	**1**	

SaO_2
Visit 1 (Screening)

Measure the subject's resting oxygen saturation level using pulse oximetry.

Oximetry [ ][ ][ ] %

Is the subject's SaO_2 value at room temperature ≥88%? Yes [ ]Y No [ ]N

*If NO, subject is **not** eligible to participate in the study. Complete the END OF STUDY RECORD section in this CRF.*

Protocol code

207499/181

COPD Pulmonary Function Tests
Visit 1 (Screening)
Pre-salbutamol

Instructions to Investigator

It is preferable that for any individual subject at each study visit, the same pulmonologist, technician or nurse administers pulmonary function tests, in order to ensure consistency of technique.

Where possible, pulmonary function measurements should be performed at the same time of day under Body Temperature and Pressure Standard (BTPS) conditions, using the same spirometer at each visit. The subject should be in the same position (i.e. sitting or standing) at each visit.

It is mandatory to use spirometers that can print out a hard copy of the FEV_1 measurements. The spirometer should be calibrated and maintained to acceptable respiratory function laboratory standards.

- The highest of three technically acceptable FEV_1 measurements **before** inhalation of salbutamol, should be recorded.
- Record FEV_1 to 2 decimal places.
- Record FVC to 2 decimal places.
- Record SVC to 2 decimal places.
- Record FEV_1/FVC ratio to the nearest whole number.
- Lung function printouts must be labelled with the Subject Number, Visit Number, date and time of measurement and signed and dated by the person responsible for the data. All printouts should be kept in the subject's notes.

Monitor Data Validation Checks

- Check that the highest of the 3 technically acceptable measurements has been recorded.
- Check that FEV_1 has been rounded to 2 decimal places.
- Check that FVC has been rounded to 2 decimal places.
- Check that SVC has been rounded to 2 decimal places.
- Check that FEV_1/FVC ratio has been rounded to the nearest whole number.
- Check that all spirometry printouts are signed and dated by the responsible person and clearly indicate the clinic visit, the date of the visit, the time of assessment and the GlaxoSmithKline Subject Number.
  The spirometry printouts must be stored in the subject's notes.

Protocol code	Session number	Subject number
207499/181	1	

COPD Pulmonary Function Tests
Visit 1 (Screening)
Pre-salbutamol

Date of assessment ☐☐ day ☐☐☐ month ☐☐ year

Has the subject smoked in the last 2 hours? Yes ☐ Y No ☐ N

*If YES, 2 hours **must** elapse before the pulmonary function tests are performed.*

Has the subject taken any short-acting β_2-agonist in the last 6 hours? Yes ☐ Y No ☐ N

Has the subject taken any short-acting anticholinergics in the last 6 hours? Yes ☐ Y No ☐ N

If the answer to either of the above is YES, a 6-hour period should elapse before the pulmonary function tests are performed. Remind the subject to refrain from taking any salbutamol and/or ipratropium bromide for 6 hours before the next visit.

Test	Time of assessment pre-salbutamol 00:00-23:59	Actual measurement pre-salbutamol *(highest of 3 measurements)* **A**
e.g. FEV_1 (L)	***08:00***	***1.75***
FEV_1 (L)	**:**	**.**
FVC (L)		**.**
SVC (L)		**.**
FEV_1/FVC ratio		

continued...

Protocol code

207499/181

COPD Pulmonary Function Tests
Visit 1 (Screening)
Post-salbutamol

Instructions to Investigator

It is preferable that for any individual subject at each study visit, the same pulmonologist, technician or nurse administers pulmonary function tests, in order to ensure consistency of technique.

Where possible, pulmonary function measurements should be performed at the same time of day under Body Temperature and Pressure Standard (BTPS) conditions, using the same spirometer at each visit. The subject should be in the same position (i.e. sitting or standing) at each visit.

It is mandatory to use spirometers that can print out a hard copy of the FEV_1 measurements. The spirometer should be calibrated and maintained to acceptable respiratory function laboratory standards.

- The highest of three technically acceptable FEV_1 measurements, 30 minutes **after** inhalation of 400mcg of salbutamol delivered via the MDI inhaler and a Volumatic™ spacer, should be recorded using the spirometer.
- Record FEV_1 to 2 decimal places.
- Record FVC to 2 decimal places.
- Record SVC to 2 decimal places.
- Record FEV_1/FVC ratio to the nearest whole number.
- Record % predicted normal to 1 decimal place.
- Record % reversibility to 1 decimal place.
- Lung function printouts must be labelled with the Subject Number, Visit Number, date and time of measurement and signed and dated by the person responsible for the data. All printouts should be kept in the subject's notes.

Monitor Data Validation Checks

- Check that the highest of the 3 technically acceptable measurements has been recorded.
- Check that predicted normal is correct.
- Check that FEV_1 has been rounded to 2 decimal places.
- Check that FVC has been rounded to 2 decimal places.
- Check that SVC has been rounded to 2 decimal places.
- Check that % predicted normal has been rounded to 1 decimal place.
- Check that % reversibility has been rounded to 1 decimal place.
- Check that FEV_1/FVC ratio has been rounded to the nearest whole number.
- Check that all spirometry printouts are signed and dated by the responsible person and clearly indicate the clinic visit, the date of the visit, the time of assessment and the GlaxoSmithKline Subject Number. The spirometry printouts must be stored in the subject's notes.

Protocol code	Session number	Subject number
207499/181	**1**	

COPD Pulmonary Function Tests *Continued*
Visit 1 (Screening)
Post-salbutamol

Test	Time salbutamol 400 mcg administered	Time of assessment 30 minutes post-salbutamol	Predicted normal	% Predicted normal	Actual measurement 30 minutes post-salbutamol *(highest of 3 measurements)*	% Reversibility
	00:00-23:59	00:00-23:59	**B**	**$\frac{A}{B}$ x100**	**C**	**$\frac{C-A}{B}$ x100**
e.g. FEV_1 (L)	***08:05***	***08:35***	***3.25***	***53.8***	***1.82***	***17.6***
FEV_1 (L)	**:**	**:**	**.**	**.**	**.**	**.**
FVC (L)			**.**	**.**	**.**	
SVC (L)			**.**	**.**	**.**	
FEV_1/FVC ratio			**.**	**.**		

*NOTE: A reversibility defined as <10% increase in FEV_1 as a percentage of the predicted normal value **OR** <200mls absolute improvement, 30 minutes following inhalation of 400mcg salbutamol via the MDI and a Volumatic spacer, must be demonstrated at Visit 1.*

Reversibility Calculation:

$$\text{Reversibility} = \frac{[\text{ Highest post-bronchodilator } FEV_1 \text{ (C) - Highest Pre-bronchodilator } FEV_1 \text{ (A) }]}{\text{Predicted normal } FEV_1 \text{ (B)}} \times 100$$

Protocol code	Session number	Subject number
207499/181	1	

Laboratory Tests / Faecal Occult Blood
Visit 1 (Screening)

Laboratory Tests

Take blood samples for hematology and blood chemistry and a urine sample for urinalysis.

Date sample taken ☐☐ ☐☐☐ ☐☐ (day / month / year)

Are there any **clinically significant abnormal** laboratory values? Yes ☐ Y No ☐ N

NOTE: All clinically significant abnormal laboratory findings are to be repeated until the values return to normal. Record all clinically significant abnormalities in the appropriate ADVERSE EVENT section.

Faecal Occult Blood

Three tests will be collected on consecutive bowel movements, (if possible). The tests are to be performed according to the instructions provided with the faecal occult blood kits. Faecal occult blood will also be tested in subjects who report gastrointestinal symptoms which are of concern to them or interfere with daily activities.

Sample	Date of collection day month year	Result	
		Positive (Pos)	Negative (Neg)
e.g., 1	***06 JAN 02***		✔
1			
2			
3			

NOTE: If the faecal occult blood test is positive, 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.

Record all clinically significant abnormalities in the appropriate ADVERSE EVENT section.

Has the faecal occult blood kit been issued for the Visit 2 analysis? Yes ☐ Y No ☐ N

Protocol code

207499/181

Subject number

Investigator's Checklist
Visit 1 (Screening)

- Ensure written informed consent has been obtained.
- Perform a full physical examination. Concurrent conditions should be recorded on the *CURRENT MEDICAL CONDITIONS* page of this CRF.
- Review a current postero-anterior (P-A) chest radiograph (performed within the 12 weeks prior to Visit 2). If a prior film is not available for review, a new film should be obtained and results must be available at Visit 2. **Review of written reports without the accompanying films is not acceptable**.
- Issue single-blind Run-in medication.
- Issue salbutamol and/or ipratropium bromide for use as a relief medication on an 'as required' basis. *(NOTE: The use of this medication must be recorded in the COPD CONCOMITANT MEDICATION section of this CRF).*
- Issue the Run-in Daily Record Card (DRC) and inform the subject of the importance of completing the DRC correctly and explain how to record the use of relief medication and any exacerbations.
- Ensure a urine or serum pregnancy test has been performed (*for females of childbearing potential only*).
- Ensure a blood sample has been taken and clinical laboratory test performed.
- Ensure Faecal Occult Blood test has been performed.
- Review inclusion/exclusion criteria and ensure all Visit 1 sections have been completed.
- Telephone GlaxoSmithKline's Registration and Medication Ordering System (RAMOS) to register the subject into the study.
- Record Run-in medication start date in the *INVESTIGATIONAL PRODUCT* section.
- Make an appointment for the subject to return for Visit 2 (week -1) in 21 (± 3) days, at the same time of day.

Remind the subject of the following:

- To stop taking *Ventolin* and take their salbutamol and/or ipratropium bromide as prescribed and to contact the investigator if they experience symptoms that do not react adequately to salbutamol and/or ipratropium bromide.
- **Not** to use asprin/NSAIDs in the **5-day** period before Visit 2.
- **Not** to eat or drink anything for **8 hours** before the bronchial biopsy at Visit 2
- To refrain from using their salbutamol and/or ipratropium bromide medication for at least **6 hours** immediately before Visit 2.
- To refrain from smoking for **2 hours** immediately before Visit 2.
- To attend the clinic for Visit 2 at the same time of day (± 2 hours).
- To arrange for a responsible companion to collect them following the bronchial biopsy at Visit 2.
- To bring the Run-In Daily Record Card, Run-in medication and any remaining salbutamol and/or ipratropium bromide medication to the clinic for Visit 2.

NOTE: If the subject discontinues the study during the run-in period, complete the END OF STUDY RECORD section in the Case Report Form.

Protocol code	Session number	Subject number
207499/181	**2**	

Visit Date / Chest X-ray Review
Visit 2 (Baseline)

Visit Date [ ][ ] [ ][ ][ ] [ ][ ]
day month year

Record the date and time of the subject's last dose of salbutamol and/or ipratropium bromide medication immediately before Visit 2.

Date [ ][ ] [ ][ ][ ] [ ][ ] Time [ ][ ] : [ ][ ]
day month year 00:00-23:59

If the subject is a **current smoker**, has the subject smoked during the 2 hours before Visit 2? Yes [ ]Y No [ ]N

Chest X-ray Review (*ONLY if not reviewed at Visit 1*)

Was a chest X-ray reviewed at Visit 1? Yes [ ]Y No [ ]N

If NO, review a current postero-anterior (P-A) chest X-ray (performed within 12 weeks prior to Visit 2).

NOTE: Review of written reports without accompanying films is not acceptable.

Date X-ray performed [ ][ ] [ ][ ][ ] [ ][ ]
day month year

Result, ✔ *appropriate box*

Normal [ ]1 *Within normal limits for COPD patients*

Abnormal [ ]2 *Abnormality that may mimic or co-exist with COPD e.g., pneumothorax, bronchial carcinoma or active pulmonary TB*

NOTE: If the chest X-ray indicates diagnosis other than COPD that may interfere with the study, the subject must be excluded from the study and the END OF STUDY RECORD section completed.

Protocol code

207499/181

Adverse Event / Concomitant Medication / Exacerbation of COPD
Visit 2 (Baseline)

Instructions to Investigator

Adverse Event

- Any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

  An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

Exacerbation of COPD

Definition of a COPD Exacerbation

For the purpose of this study COPD exacerbations are categorised as follows:

Mild

- Acute worsening of COPD that is self-managed by the subject at home by increasing usual COPD bronchodilators medications, and should not be taking any antibiotics (i.e. the subject does not see a doctor for this episode)

Moderate

- Acute worsening of COPD that requires additional treatment (e.g. a short course of oral steroids, antibiotics, etc.) prescribed by primary care physician or as a result of a hospital out-patient visit (including a visit to the Emergency Room)

Severe

- Acute worsening of COPD that requires the subject to be admitted to hospital for treatment

Monitor Data Validation Checks

Adverse Event / Concomitant Medication

- Check that any adverse events are recorded in the *ADVERSE EVENT* section and any changes/new medications are recorded in the *CONCOMITANT MEDICATION* section(s) of the Case Report Form.

  NOTE: ✔ if done box should always be completed to confirm these questions have been asked, regardless of whether an adverse event has occurred or new medicine has been taken.

Exacerbation of COPD

- If the subject has experienced an exacerbation since their last visit, check that the *COPD EXACERBATION and if appropriate, the COPD CONCOMITANT MEDICATION and the ADVERSE EVENT* section(s) have been completed.

  NOTE: ✔ if done box should always be completed to confirm DRC has been checked, regardless of whether the subject has experienced an exacerbation.

Protocol code

207499/181

Subject number

Adverse Event / Concomitant Medication / Exacerbation of COPD
Visit 2 (Baseline)

Adverse Event / Concomitant Medication

Check the subject's Daily Record Card to determine whether they have experienced an adverse event.

Ask the following questions:

(a) "Have you had any (other) medical problems since your last visit/assessment?"

(b) "Have you taken any new medicines, other than those provided in this study, since your last visit/ assessment?"

Adverse events should be recorded in the appropriate ADVERSE EVENTS section.

Concomitant medications should be recorded in the appropriate CONCOMITANT MEDICATIONS section.

Confirm these adverse event and concomitant medication questions have been asked. ☐ ✔ *if done*

Exacerbation of COPD

Check the subject's Daily Record Card to determine whether they have experienced an exacerbation of COPD (according to the definition on the facing page).

Ask the following question:

Have you experienced an exacerbation of your COPD since the last visit?

If necessary, complete the COPD EXACERBATION section and if appropriate, the COPD CONCOMITANT MEDICATION section and ADVERSE EVENTS section in this Case Report Form.

Confirm this exacerbation question has been asked. ☐ ✔ *if done*

NOTE: Subjects who experience a moderate or severe exacerbation during the Run-In period are not eligible to be randomised to the double-blind Treatment Period and must be ***withdrawn*** *from the study and the END OF STUDY RECORD section completed.*

Protocol code

207499/181

Daily Record Card / Vital Signs
Visit 2 (Baseline)

Instructions to Investigator

Daily Record Card

- Check DRC for exacerbations.
- Transcribe any medications from the medication section into the appropriate *CONCOMITANT MEDICATION* section in this Case Report Form.
- Transcribe any Adverse Events that have been reported into the appropriate *ADVERSE EVENT* section of this CRF.
- Any changes, corrections or explanations that you have made regarding dates must be initialled and dated in the presence of the subject.

Vital Signs

- Salbutamol and/or ipratropium bromide must not be taken for 6 hours prior to vital signs being measured.

Monitor Data Validation Checks

Daily Record Card

- Check the Run-In Daily Record Card for the period between Visit 1 and Visit 2. Ensure that any adverse events and changes in medication reported in the Run-In Daily Record Card have been transcribed to the appropriate *ADVERSE EVENT*, *and CONCOMITANT MEDICATION* section(s) of the Case Report Form.
- If any corrections are made, the investigator must initial and date them.

Vital Signs

- Check that blood pressure values are within reasonable limits and systolic blood pressure is greater than diastolic blood pressure.
- Check that heart rate value is within reasonable limits for beats per minute.

Protocol code	Session number	Subject number
207499/181	**2**	

Daily Record Card / Vital Signs
Visit 2 (Baseline)

Daily Record Card

Has the Daily Record Card been collected and reviewed? Yes ☐ Y No ☐ N

Vital Signs

Vital signs must be measured at least 6 hours after the subject's last salbutamol and/or ipratropium bromide administration after the subject has been sitting for 5 minutes.

Date	Blood pressure mmHg		Heart rate	Temperature
day month year	systolic	diastolic	beats/min	°C
e.g., 06 JAN 02	***110***	***80***	***75***	***36.5***
				.

Record all clinically significant abnormalities in the appropriate ADVERSE EVENT section(s).

Protocol code

207499/181

COPD Pulmonary Function Tests / Faecal Occult Blood
Visit 2 (Baseline)

Instructions to Investigator

It is preferable that for any individual subject at each study visit, the same pulmonologist, technician or nurse administers pulmonary function tests, in order to ensure consistency of technique.

Where possible, pulmonary function measurements should be performed at the same time of day under Body Temperature and Pressure Standard (BTPS) conditions, using the same spirometer at each visit. The subject should be in the same position (i.e. sitting or standing) at each visit.

- The highest of three technically acceptable SVC measurements should be recorded **before and after** inhalation of salbutamol.
- Record SVC to 2 decimal places.
- Lung function printouts must be labelled with the Subject Number, Visit Number, date and time of measurement and signed and dated by the person responsible for the data. All printouts should be kept in the subject's notes.

Monitor Data Validation Checks

- Check that the highest of the 3 technically acceptable measurements has been recorded.
- Check that SVC has been rounded to 2 decimal places.
- Check that all spirometry printouts are signed and dated by the responsible person and clearly indicate the clinic visit, the date of the visit, the time of assessment and the GlaxoSmithKline Subject Number. The spirometry printouts must be stored in the subject's notes.

Protocol code	Session number	Subject number
207499/181	**2**	

COPD Pulmonary Function Tests / Faecal Occult Blood
Visit 2 (Baseline)

Date of assessment ☐☐ ☐☐☐ ☐☐ (day / month / year)

*NOTE: Subjects must refrain from smoking for **2 hours** immediately before pulmonary function tests.*

Has the subject taken any salbutamol and/or ipratropium bromide in the last 6 hours? Yes ☐ Y No ☐ N

If YES, a 6 hour period should elapse before the pulmonary function tests are performed. Remind the subject to refrain from taking any for 6 hours before the next visit.

Test	Time of assessment pre-salbutamol 00:00-23:59	Actual measurement pre-salbutamol *(highest of 3 measurements)*	Time of assessment 30 minutes post-salbutamol 00:00-23:59	Actual measurement 30 minutes post-salbutamol *(highest of 3 measurements)*
e.g. SVC	***08:00***	***1.75***	***08:30***	***1.80***
SVC (L)	**:**	**.**	**:**	**.**

Faecal Occult Blood

Three tests will be collected on consecutive bowel movements, (if possible). The tests are to be performed according to the instructions provided with the faecal occult blood kits. Faecal occult blood will also be tested in subjects who report gastrointestinal symptoms which are of concern to them or interfere with daily activities.

Sample	Date of collection day month year	Result	
		Positive (Pos)	Negative (Neg)
e.g., 1	***06 JAN 02***		✔
1			
2			
3			

NOTE: If the faecal occult blood test is positive, 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.

Record all clinically significant abnormalities in the appropriate ADVERSE EVENT section.

Protocol code

207499/181

Subject number

Pre Bronchial Biopsy Checklist
Visit 2 (Baseline)

Has the subject consumed any food or drink since midnight? Yes ☐ No ☐

Has the subject used asprin or NSAIDS in the 5 days preceding the biopsy? Yes ☐ No ☐

NOTE: If either of the above is answered YES, the procedure must be rescheduled for within 1-7 days.

The subject must meet the following safety criteria on the scheduled day of the biopsy procedure:

	Criteria met? Yes	No
Pre-salbutamol FEV_1 40-80% predicted normal value.	☐	☐
No history of bleeding diathesis. Normal blood clotting parameters.	☐	☐
Ability to be collected by a friend/relative at the end of the biopsy procedure	☐	☐

*NOTE: If any of the safety criteria questions are answered **NO**, the subject is unsuitable for the bronchoscopy on the scheduled day and the procedure must be rescheduled for within 1-7 days. If the procedure is rescheduled, **do not** complete the remaining Visit 2 assessments.*

All safety criteria must be re-checked on the day of the rescheduled procedure.

Protocol code

207499/181

Bronchial Biopsy
Visit 2 (Baseline)

Instructions to Investigator

NOTE: Refer to the Bronchial Biopsy Procedure (BBP) document prior to starting the biopsy.

- The subject must meet specific safety criteria on the day of the bronchoscopy, before the procedure can proceed.
- A **Biopsy Safety Form must** be completed and stored in the subject's notes prior to performing the bronchoscopy.
- The procedure should be performed using the methodology described in the Bronchial Biopsy Procedure (BBP).
- Bronchoscopies should be performed using an Olympus BF fibreoptic bronchoscope (type IT40, 2.8 mm channel or similar) or equivalent. Use of any other type of bronchoscope must be pre-agreed with GSK.
- Cup forceps [FB-35C-1, 2.8 mm (fenestrated forceps)] or equivalent should be used for all subjects and each set should be replaced after every 5-biopsy occasions. Use of any other type of forceps must be pre-agreed with GSK.
- Six biopsies of adequate size (2mm) should be performed on the right side beginning at the subcarinae in the right lower lobe (2 biopsies), then the right middle lobe (2 biopsies) and finally the right upper lobe (2 biopsies).
- Report any serious complications relating to the bronchoscopy, e.g. severe bleeding or pneumothorax, to the study monitor as soon as possible (within 24 hours).
- The **Biopsy Sample Worksheet** and the **Processing of Biopsy Sample Worksheet** must be sent with the samples via QUEST to Dr Q. Hamid's laboratory.

Protocol code	Session number	Subject number
207499/181	**2**	

Bronchial Biopsy
Visit 2 (Baseline)

Confirm all safety criteria have been met. ☐ ✔ *if met*

Complete a Biopsy Safety Form prior to the biopsy.

Date of biopsy ☐☐ (day) ☐☐☐ (month) ☐☐ (year) Time of biopsy ☐☐ : ☐☐ (00:00-23:59)

Record below, all medication administered at the time of the bronchoscopy:

Drug name	Medication administered		Time administered 00:00-23:59
	Yes (Y)	No (N)	
e.g., Atropine	✔		***10:30***
Atropine			:
Midazolam			:
Salbutamol			:
Intravenous flumazenil			:
Topical lignocaine			:
Lignocaine gel			:

Record number of mucosal biopsies taken.

Biopsy site	Number of biopsies taken	Biopsy lung ✔ *one*	
		Left	Right
Lower lobe (Level A)			
Middle lobe (Level B)			
Upper lobe (Level C)			

continued...

Protocol code

207499/181

Investigator's Checklist
Visit 2 (Baseline)

- Check the Run-in single-blind medication bottles and complete the *COMPLIANCE* section of this CRF.
- Issue new salbutamol and/or ipratropium bromide medication as appropriate.
- Instruct the subject to continue recording any exacerbations in their Run-in DRC.
- Ensure all Visit 2 sections have been completed.
- Ensure any adverse events which have occurred, have been recorded in the *ADVERSE EVENTS* section(s) of the CRF.
- Ensure any changes or additions to the subjects concomitant medications has been recorded in the appropriate *CONCOMITANT MEDICATIONS* section(s) of the CRF.
- Ensure subject's use of salbutamol and/or ipratropium bromide is recorded in the *COPD CONCOMITANT MEDICATION* section of this CRF).
- Give the subject a printed information sheet detailing a contact telephone number in case of post-biopsy difficulties.
- Telephone the subject the day after the procedure to confirm that they have recovered well. Any subject not fully recovered at 6 hours from their bronchoscopy should be admitted to overnight observation under medical supervision.
- Make an appointment for the subject to return for Visit 3 (Week 0) in 7 (± 3) days, at the same time of day.

Remind the subject of the following:

- Not to drive or operate complex machinery for the remainder of the day.
- To take their salbutamol and/or ipratropium bromide medication as prescribed and to contact the investigator if they experience symptoms that do not react adequately to salbutamol and/or ipratropium bromide.
- To refrain from using their salbutamol and/or ipratropium bromide medication for at least **6 hours** immediately before Visit 3.
- To refrain from smoking for **2 hours** immediately before Visit 3.
- To attend the clinic for Visit 3 at the same time of day (± 2 hours).
- To bring the Run-in Daily Record Card and their salbutamol and/or ipratropium bromide medication to the clinic for Visit 3.

If the Biopsy is rescheduled for Visit 2A:

- Ask subject to return to the clinic for Visit 2A in 7 (±3) days, at the same time of day.
- To take their salbutamol and/or ipratropium bromide medication as prescribed and to contact the investigator if they experience symptoms that do not react adequately to salbutamol and/or ipratropium bromide
- To refrain from using their salbutamol and/or ipratropium bromide medication for at least **6 hours** immediately before Visit 3.
- To refrain from smoking for **2 hours** immediately before Visit 2A.
- **Not** to eat or drink anything for **8 hours** before the bronchial biopsy at Visit 2A.
- **Not** to use asprin/NSAIDs in the **5-day** period before Visit 2A.
- To bring their Run-In Daily Record Card, Run-in medication and their salbutamol and/or ipratropium bromide medication to the clinic for Visit 2A.

NOTE: If the subject discontinues the study during the run-in period, complete the END OF STUDY RECORD section in the Case Report Form.

Protocol code	Session number	Subject number
207499/181	**2.5**	

Visit Date / Chest X-ray Review
Visit 2A (Baseline)

Visit Date [ ][ ] [ ][ ][ ] [ ][ ]
day month year

Record the date and time of the subject's last dose of salbutamol and/or ipratropium bromide medication immediately before Visit 2A.

Date [ ][ ] [ ][ ][ ] [ ][ ]
day month year

Time [ ][ ] : [ ][ ]
00:00-23:59

If the subject is a **current smoker**, has the subject smoked during the 2 hours before Visit 2A? Yes [ ]Y No [ ]N

Chest X-ray Review (*ONLY if not reviewed at Visit 2*)

Was a chest X-ray reviewed at Visit 1? Yes [ ]Y No [ ]N

If NO, review a current postero-anterior (P-A) chest X-ray (performed within 12 weeks prior to Visit 2).

NOTE: Review of written reports without accompanying films is not acceptable.

Date X-ray performed [ ][ ] [ ][ ][ ] [ ][ ]
day month year

Result, ✔ *appropriate box*

Normal [ ]1 *Within normal limits for COPD patients*

Abnormal [ ]2 *Abnormality* that may mimic or co-exist with COPD e.g., pneumothorax, bronchial carcinoma or active pulmonary TB

Protocol code

207499/181

Adverse Event / Concomitant Medication / Exacerbation of COPD
Visit 2A (Baseline)

Instructions to Investigator

Adverse Event

- Any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

  An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

Exacerbation of COPD

Definition of a COPD Exacerbation

For the purpose of this study COPD exacerbations are categorised as follows:

Mild

- Acute worsening of COPD that is self-managed by the subject at home by increasing usual COPD bronchdilators medications, and should not be taking any antibiotics (i.e. the subject does not see a doctor for this episode)

Moderate

- Acute worsening of COPD that requires additional treatment (e.g. a short course of oral steroids, antibiotics, etc) prescribed by primary care physician or as a result of a hospital out-patient visit (including a visit to the Emergency Room)

Severe

- Acute worsening of COPD that requires the subject to be admitted to hospital for treatment

Monitor Data Validation Checks

Adverse Event / Concomitant Medication

- Check that any adverse events are recorded in the *ADVERSE EVENT* section and any changes/new medications are recorded in the *CONCOMITANT MEDICATION* section(s) of the Case Report Form.

  NOTE: ✔ if done box should always be completed to confirm these questions have been asked, regardless of whether an adverse event has occurred or new medicine has been taken.

Exacerbation of COPD

- If the subject has experienced an exacerbation since their last visit, check that the *COPD EXACERBATION and if appropriate, the COPD CONCOMITANT MEDICATION and the ADVERSE EVENT* section(s) have been completed.

  NOTE: ✔ if done box should always be completed to confirm DRC has been checked, regardless of whether the subject has experienced an exacerbation.

Protocol code

207499/181

Subject number

Adverse Event / Concomitant Medication / Exacerbation of COPD
Visit 2A (Baseline)

Adverse Event / Concomitant Medication

Check the subject's Daily Record Card to determine whether they have experienced an adverse event.

Ask the following questions:

(a) "Have you had any (other) medical problems since your last visit/assessment?"

(b) "Have you taken any new medicines, other than those provided in this study, since your last visit/ assessment?"

Adverse events should be recorded in the appropriate ADVERSE EVENTS section(s).

Concomitant medications should be recorded in the CONCOMITANT MEDICATIONS section(s).

Confirm these adverse event and concomitant medication questions have been asked. ☐ ✔ *if done*

Exacerbation of COPD

Check the subject's Daily Record Card to determine whether they have experienced an exacerbation of COPD (according to the definition on the facing page).

Ask the following question:

Have you experienced an exacerbation of your COPD since the last visit?

If necessary, complete the COPD EXACERBATION section and if appropriate, the COPD CONCOMITANT MEDICATION section and ADVERSE EVENTS section in this Case Report Form.

Confirm this exacerbation question has been asked. ☐ ✔ *if done*

NOTE: Subjects who experience a moderate or severe exacerbation during the Run-In period are not eligible to be randomised to the double-blind Treatment Period and must be ***withdrawn*** *from the study and the END OF STUDY RECORD section completed.*

Protocol code

207499/181

Daily Record Card / Vital Signs
Visit 2A (Baseline)

Instructions to Investigator

Daily Record Card

- Check DRC for exacerbations.
- Transcribe any medications from the medication section into the appropriate *CONCOMITANT MEDICATION* section in this Case Report Form.
- Transcribe any Adverse Events that have been reported into the appropriate *ADVERSE EVENT* section of this CRF.
- Any changes, corrections or explanations that you have made regarding dates must be initialled and dated in the presence of the subject.

Vital Signs

- Salbutamol and/or ipratropium bromide must not be taken for 6 hours prior to vital signs being measured.

Monitor Data Validation Checks

Daily Record Card

- Check the Run-In Daily Record Card for the period between Visit 2 and Visit 2A. Ensure that any adverse events and changes in medication reported in the Run-In Daily Record Card have been transcribed to the appropriate *ADVERSE EVENT*, *and CONCOMITANT MEDICATION* section(s) of the Case Report Form.
- If any corrections are made, the investigator must initial and date them.

Vital Signs

- Check that blood pressure values are within reasonable limits and systolic blood pressure is greater than diastolic blood pressure.
- Check that heart rate value is within reasonable limits for beats per minute.

Protocol code	Session number	Subject number
207499/181	**2.5**	

Daily Record Card / Vital Signs
Visit 2A (Baseline)

Daily Record Card

Has the Daily Record Card been collected and reviewed? Yes ☐ Y No ☐ N

Vital Signs

Vital signs must be measured at least 6 hours after the subject's last salbutamol and/or ipratropium bromide administration after the subject has been sitting for 5 minutes.

Date	Blood pressure mmHg		Heart rate	Temperature
day month year	systolic	diastolic	beats/min	°C
e.g., 06 JAN 02	***110***	***80***	***75***	***36.5***
				.

Record all clinically significant abnormalities in the appropriate ADVERSE EVENT section(s).

Protocol code

207499/181

COPD Pulmonary Function Tests / Faecal Occult Blood
Visit 2A (Baseline)

Instructions to Investigator

It is preferable that for any individual subject at each study visit, the same pulmonologist, technician or nurse administers pulmonary function tests, in order to ensure consistency of technique.

Where possible, pulmonary function measurements should be performed at the same time of day under Body Temperature and Pressure Standard (BTPS) conditions, using the same spirometer at each visit. The subject should be in the same position (i.e. sitting or standing) at each visit.

- The highest of three technically acceptable SVC measurements should be recorded **before and after** inhalation of salbutamol.
- Record SVC to 2 decimal places.
- Lung function printouts must be labelled with the Subject Number, Visit Number, date and time of measurement and signed and dated by the person responsible for the data. All printouts should be kept in the subject's notes.

Monitor Data Validation Checks

- Check that the highest of the 3 technically acceptable measurements has been recorded.
- Check that SVC has been rounded to 2 decimal places.
- Check that all spirometry printouts are signed and dated by the responsible person and clearly indicate the clinic visit, the date of the visit, the time of assessment and the GlaxoSmithKline Subject Number. The spirometry printouts must be stored in the subject's notes.

Protocol code	Session number	Subject number
207499/181	**2.5**	

COPD Pulmonary Function Tests / Faecal Occult Blood
Visit 2A (Baseline)

Date of assessment ☐☐ ☐☐☐ ☐☐ (day / month / year)

*NOTE: Subjects must refrain from smoking for **2 hours** immediately before pulmonary function tests.*

Has the subject taken any salbutamol and/or ipratropium bromide in the last 6 hours? Yes ☐ Y No ☐ N

If YES, a 6 hour period should elapse before the pulmonary function tests are performed. Remind the subject to refrain from taking any for 6 hours before the next visit.

Test	Time of assessment pre-salbutamol 00:00-23:59	Actual measurement pre-salbutamol *(highest of 3 measurements)*	Time of assessment 30 minutes post-salbutamol 00:00-23:59	Actual measurement 30 minutes post-salbutamol *(highest of 3 measurements)*
e.g. SVC	***08:00***	***1.75***	***08:30***	***1.80***
SVC (L)	**:**	**.**	**:**	**.**

Faecal Occult Blood

Three tests will be collected on consecutive bowel movements, (if possible). The tests are to be performed according to the instructions provided with the faecal occult blood kits. Faecal occult blood will also be tested in subjects who report gastrointestinal symptoms which are of concern to them or interfere with daily activities.

Sample	Date of collection day month year	Result	
		Positive (Pos)	Negative (Neg)
e.g., 1	***06 JAN 02***		✔
1			
2			
3			

NOTE: If the faecal occult blood test is positive, 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.

Record all clinically significant abnormalities in the appropriate ADVERSE EVENT section.

Protocol code

207499/181

Subject number

Pre Bronchial Biopsy Checklist
Visit 2A (Baseline)

Has the subject consumed any food or drink since midnight? Yes ☐ No ☐

Has the subject used asprin or NSAIDS in the 5 days preceding the biopsy? Yes ☐ No ☐

NOTE: If either of the above is answered YES, the procedure must be rescheduled for within 1-7 days.

The subject must meet the following safety criteria on the scheduled day of the biopsy procedure:

	Criteria met? Yes	No
Pre-salbutamol FEV_1 40-80% predicted normal value.	☐	☐
No history of bleeding diathesis. Normal blood clotting parameters.	☐	☐
Ability to be collected by a friend/relative at the end of the biopsy procedure	☐	☐

*NOTE: If any of the safety criteria questions are answered **NO**, the subject is unsuitable for the bronchoscopy and must be **withdrawn** from the study and the END OF STUDY RECORD section completed.*

Protocol code

207499/181

Bronchial Biopsy
Visit 2A (Baseline)

Instructions to Investigator

NOTE: Refer to the Bronchial Biopsy Procedure (BBP) document prior to starting the biopsy.

- The subject must meet specific safety criteria on the day of the bronchoscopy, before the procedure can proceed.
- A **Biopsy Safety Form must** be completed and stored in the subject's notes prior to performing the bronchoscopy.
- The procedure should be performed using the methodology described in the Bronchial Biopsy Procedure (BBP).
- Bronchoscopies should be performed using an Olympus BF fibreoptic bronchoscope (type IT40, 2.8 mm channel or similar) or equivalent. Use of any other type of bronchoscope must be pre-agreed with GSK.
- Cup forceps [FB-35C-1, 2.8 mm (fenestrated forceps)] or equivalent should be used for all subjects and each set should be replaced after every 5-biopsy occasions. Use of any other type of forceps must be pre-agreed with GSK.
- Six biopsies of adequate size (2mm) should be performed on the right side beginning at the subcarinae in the right lower lobe (2 biopsies), then the right middle lobe (2 biopsies) and finally the right upper lobe (2 biopsies).
- Report any serious complications relating to the bronchoscopy, e.g. severe bleeding or pneumothorax, to the study monitor as soon as possible (within 24 hours).
- The **Biopsy Sample Worksheet** and the **Processing of Biopsy Sample Worksheet** must be sent with the samples via QUEST to Dr Q. Hamid's laboratory.

Protocol code	Session number	Subject number
207499/181	**2.5**	

Bronchial Biopsy
Visit 2A (Baseline)

Confirm all safety criteria have been met. ☐ ✔ *if met*

Complete a Biopsy Safety Form prior to the biopsy.

Date of biopsy ☐☐ (day) ☐☐☐ (month) ☐☐ (year) Time of biopsy ☐☐ : ☐☐ (00:00-23:59)

Record below, all medication administered at the time of the bronchoscopy:

Drug name	Medication administered		Time administered 00:00-23:59
	Yes (Y)	No (N)	
e.g., Atropine	✔		***10:30***
Atropine			:
Midazolam			:
Salbutamol			:
Intravenous flumazenil			:
Topical lignocaine			:
Lignocaine gel			:

Record number of mucosal biopsies taken.

Biopsy site	Number of biopsies taken	Biopsy lung ✔ *one*	
		Left	Right
Lower lobe (Level A)			
Middle lobe (Level B)			
Upper lobe (Level C)			

continued...

Protocol code

207499/181

Investigator's Checklist
Visit 2A (Baseline)

NOTE: ***If results of any assessment made at Baseline (Visit 2/2A) are not available at the time of assessment and subsequently preclude continuation in the study, the subject must be withdrawn immediately.***

- Check the Run-in single-blind medication bottles and complete the *COMPLIANCE* section of this CRF.
- Issue new salbutamol and/or ipratropium bromide medication as appropriate.
- Instruct the subject to continue recording any exacerbations in their Run-in DRC.
- Ensure any adverse events which have occurred, have been recorded in the *ADVERSE EVENTS* section(s) of the CRF.
- Ensure any changes or additions to the subjects concomitant medications has been recorded in the appropriate *CONCOMITANT MEDICATIONS* section(s) of the CRF.
- Ensure subject's use of salbutamol and/or ipratropium bromide is recorded in the *COPD CONCOMITANT MEDICATION* section of this CRF).
- Ensure all Visit 2 sections have been completed.
- Give the subject a printed information sheet detailing a contact telephone number in case of post-biopsy difficulties.
- Telephone the subject the day after the procedure to confirm that they have recovered well. Any subject not fully recovered at 6 hours from their bronchoscopy should be admitted to overnight observation under medical supervision.
- Make an appointment for the subject to return for Visit 3 in 7 days (± 3) days, at the same time of day.

Remind the subject of the following:

- Not to drive or operate complex machinery for the remainder of the day.
- To take their salbutamol and/or ipratropium bromide medication as prescribed and to contact the investigator if they experience symptoms that do not react adequately to salbutamol and/or ipratropium bromide.
- To refrain from using their salbutamol and/or ipratropium bromide medication for at least **6 hours** immediately before Visit 3.
- To refrain from smoking for **2 hours** immediately before Visit 3.
- To attend the clinic for Visit 3 at the same time of day (± 2 hours).
- To bring the Run-in Daily Record Card, Run-in medication and their salbutamol and/or ipratropium bromide medication to the clinic for Visit 3.

NOTE: ***If the subject discontinues the study during the run-in period, complete the END OF STUDY RECORD section in the Case Report Form.***

Protocol code	Session number	Subject number
207499/181	**3**	

Visit Date
Visit 3 (Start of Double-blind Treatment Period)

Visit Date ☐☐ ☐☐☐ ☐☐
day month year

Record the date and time of the subject's last dose of salbutamol and/or ipratropium bromide medication immediately before Visit 3.

Date ☐☐ ☐☐☐ ☐☐
day month year

Time ☐☐ : ☐☐
00:00-23:59

If the subject is a **current smoker**, has the subject smoked during the 2 hours before Visit 3? Yes ☐ Y No ☐ N

Protocol code

207499/181

Adverse Event / Concomitant Medication / Exacerbation of COPD
Visit 3 (Start of Double-blind Treatment Period)

Instructions to Investigator

Adverse Event

- Any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

  An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

Exacerbation of COPD

Definition of a COPD Exacerbation

For the purpose of this study COPD exacerbations are categorised as follows:

Mild

- Acute worsening of COPD that is self-managed by the subject at home by increasing usual COPD bronchodilators medications, and should not be taking any antibiotics (i.e. the subject does not see a doctor for this episode)

Moderate

- Acute worsening of COPD that requires additional treatment (e.g. a short course of oral steroids, antibiotics, etc.) prescribed by primary care physician or as a result of a hospital out-patient visit (including a visit to the Emergency Room)

Severe

- Acute worsening of COPD that requires the subject to be admitted to hospital for treatment

Monitor Data Validation Checks

Adverse Event / Concomitant Medication

- Check that any adverse events are recorded in the *ADVERSE EVENT* section and any changes/new medications are recorded in the *CONCOMITANT MEDICATION* section(s) of the Case Report Form.

  NOTE: ✔ if done box should always be completed to confirm these questions have been asked, regardless of whether an adverse event has occurred or new medicine has been taken.

Exacerbation of COPD

- If the subject has experienced an exacerbation since their last visit, check that the *COPD EXACERBATION and if appropriate, the COPD CONCOMITANT MEDICATION and the ADVERSE EVENT* section(s) have been completed.

  NOTE: ✔ if done box should always be completed to confirm DRC has been checked, regardless of whether the subject has experienced an exacerbation.

Protocol code

207499/181

Subject number

Adverse Event / Concomitant Medication / Exacerbation of COPD
Visit 3 (Start of Double-blind Treatment Period)

Adverse Event / Concomitant Medication

Check the subject's Daily Record Card to determine whether they have experienced an adverse event.

Ask the following questions:

(a) "Have you had any (other) medical problems since your last visit/assessment?"

(b) "Have you taken any new medicines, other than those provided in this study, since your last visit/ assessment?"

Adverse events should be recorded in the appropriate ADVERSE EVENTS section(s).

Concomitant medications should be recorded in the CONCOMITANT MEDICATIONS section(s).

Confirm these adverse event and concomitant medication questions have been asked. ☐ ✔ *if done*

Exacerbation of COPD

Check the subject's Daily Record Card to determine whether they have experienced an exacerbation of COPD (according to the definition on the facing page).

Ask the following question:

Have you experienced an exacerbation of your COPD since the last visit?

If necessary, complete the COPD EXACERBATION section and if appropriate, the COPD CONCOMITANT MEDICATION section and ADVERSE EVENTS section in this Case Report Form.

Confirm this exacerbation question has been asked. ☐ ✔ *if done*

NOTE: Subjects who experience a moderate or severe exacerbation during the Run-In period are not eligible to be randomised to the double-blind Treatment Period and must be ***withdrawn*** *from the study and the END OF STUDY RECORD section completed.*

Protocol code

207499/181

Daily Record Card / Vital Signs
Visit 3 (Start of Double-blind Treatment Period)

Instructions to Investigator

Daily Record Card

- Check DRC for exacerbations.
- Transcribe any medications from the medication section into the appropriate *CONCOMITANT MEDICATION* section in this Case Report Form.
- Transcribe any Adverse Events that have been reported into the appropriate *ADVERSE EVENT* section(s) of this CRF.
- Any changes, corrections or explanations that you have made regarding dates must be initialled and dated in the presence of the subject.

Vital Signs

- Salbutamol and/or ipratropium bromide must not be taken for 6 hours prior to vital signs being measured.

Monitor Data Validation Checks

Daily Record Card

- Check the Run-In Daily Record Card for the period between Visit 2/2A and Visit 3. Ensure that any adverse events and changes in medication reported in the Run-In Daily Record Card have been transcribed to the appropriate *ADVERSE EVENT*, *and CONCOMITANT MEDICATION* section(s) of the Case Report Form.
- If any corrections are made, the investigator must initial and date them.

Vital Signs

- Check that blood pressure values are within reasonable limits and systolic blood pressure is greater than diastolic blood pressure.
- Check that heart rate value is within reasonable limits for beats per minute.

Protocol code	Session number	Subject number
207499/181	**3**	

Daily Record Card / Vital Signs
Visit 3 (Start of Double-blind Treatment Period)

Daily Record Card

Has the Daily Record Card been collected and reviewed? Yes ☐ Y No ☐ N

Vital Signs

*Vital signs must be measured at least **6 hours after** the subject's last salbutamol and/or ipratropium bromide administration after the subject has been sitting for 5 minutes.*

Date	Blood pressure mmHg		Heart rate	Temperature
day month year	systolic	diastolic	beats/min	°C
e.g., 06 JAN 02	***110***	***80***	***75***	***36.5***
				.

Record all clinically significant abnormalities in the appropriate ADVERSE EVENT section(s).

Protocol code

207499/181

Subject number

COPD Pulmonary Function Tests
Visit 3 (Start of Double-blind Treatment Period)

Instructions to Investigator

It is preferable that for any individual subject at each study visit, the same pulmonologist, technician or nurse administers pulmonary function tests, in order to ensure consistency of technique.

Where possible, pulmonary function measurements should be performed at the same time of day under Body Temperature and Pressure Standard (BTPS) conditions, using the same spirometer at each visit. The subject should be in the same position (i.e. sitting or standing) at each visit.

- The highest of three technically acceptable SVC measurements should be recorded **before and after** inhalation of salbutamol.
- Record SVC to 2 decimal places.
- Lung function printouts must be labelled with the Subject Number, Visit Number, date and time of measurement and signed and dated by the person responsible for the data. All printouts should be kept in the subject's notes.

Monitor Data Validation Checks

- Check that SVC has been rounded to 2 decimal places.
- Check that all spirometry printouts are signed and dated by the responsible person and clearly indicate the clinic visit, the date of the visit, the time of assessment and the GlaxoSmithKline Subject Number. The spirometry printouts must be stored in the subject's notes.

Protocol code	Session number	Subject number
207499/181	**3**	

COPD Pulmonary Function Tests
Visit 3 (Start of Double-blind Treatment Period)

Date of assessment ☐☐ ☐☐☐ ☐☐ (day / month / year)

*NOTE: Subjects must refrain from smoking for **2 hours** immediately before pulmonary function tests.*

Has the subject taken any salbutamol and/or ipratropium bromide in the last 6 hours? Yes ☐ Y No ☐ N

If YES, a 6 hour period should elapse before the pulmonary function tests are performed. Remind the subject to refrain from taking any for 6 hours before the next visit.

Test	Time of assessment pre-salbutamol 00:00-23:59	Actual measurement pre-salbutamol *(highest of 3 measurements)*	Time of assessment 30 minutes post-salbutamol 00:00-23:59	Actual measurement 30 minutes post-salbutamol *(highest of 3 measurements)*
e.g. SVC	***08:00***	***1.75***	***08:30***	***1.80***
SVC (L)	**:**	**.**	**:**	**.**

Protocol code

207499/181

Sputum Induction
Visit 3 (Start of Double-blind Treatment Period)

Instructions to Investigator

NOTE: ***Refer to the Sputum Procedures (SP) document prior to starting the sputum induction.***

NOTE: ***All subjects must have post bronchodilator spirometry prior to the sputum induction (within 60 minutes). If the FEV_1 after β_2 agonist is $\leq$0.8 L, or less than 40% predicted, DO NOT proceed with the test.***

- A doctor must be nearby during each procedure.
- Sputum induction must only be undertaken with trained medical personnel within easy access.
- The usual laboratory resuscitation apparatus plus nebulised salbutamol must be readily available.
- Collect and process sputum according to the methodology described in the Sputum Procedures (SP) document.
- Prior to commencing the induction it is essential that the procedure be explained in full to the subject.
- If at any time that the subject complains of chest discomfort or tightness, the test must be interrupted and the FEV_1 checked.
- All data generated during sputum processing must be recorded on the Sputum Processing Worksheet.
- All subjects that present with a fall in FEV_1 of > 5%, will receive VENTOLIN and must return to within 5% of best post VENTOLIN baseline before discharge.

Monitor Data Validation Checks

- If sputum sample was satisfactory, check that the Sputum Processing Worksheet has been completed.

Protocol code	Session number	Subject number
207499/181	**3**	

Sputum Induction
Visit 3 (Start of Double-blind Treatment Period)

Has a sample of induced sputum been collected? Yes ☐ Y No ☐ N

If Yes,

Date sample collected: ☐☐ ☐☐☐ ☐☐
day month year

Is the induced sputum sample satisfactory? Yes ☐ Y No ☐ N

If YES, providing they meet the randomisation criteria, the subject may be randomised into the double-blind treatment phase. ***Complete the Sputum Processing Worksheet*** *and the* ***Slide Identification Tracking Form****.*

If NO, no further sputum samples should be taken for this subject, but the subject will continue in the study and biopsy procedures should be performed at the scheduled visits.

GlaxoSmithKline

Protocol code

207499/181

Exclusion Criteria Worksheet
Visit 3 (Start of Double-blind Treatment Period)

Instructions to Investigator

- Review the worksheet first.
- Answer each question on the worksheet.
- ✔ appropriate box for each Exclusion criterion question.
- Ensure that you maintain the source documents that validate the Exclusion criteria.

Monitor Data Validation Checks

- Check that either a YES or NO box is ✔ for each Exclusion criterion.

Protocol code

207499/181

Subject number

Exclusion Criteria Worksheet
Visit 3 (Start of Double-blind Treatment Period)

Exclusion Criteria ✔ *one box for each question:*

		Yes	No
1.	Did the subjects have any changes to their COPD medication (other than 'as required' use of salbutamol), receive corticosteroids (oral or inhaled) for respiratory disease, or was hospitalised for COPD/lower respiratory tract infections during the Run-in period.?	☐	☐
2.	Was the subject receiving any other medication during the run-in period which in the opinion of the investigator, is judged as likely to affect baseline assessments?	☐	☐
3.	Was the subject unable to tolerate withdrawal of medications during the Run-in?	☐	☐
4.	Is the subject unable to tolerate or comply with the protocol procedures?	☐	☐

*If any EXCLUSION CRITERIA question is answered **YES**, this subject must **NOT** enter this study.*

Protocol code

207499/181

Exclusion Criteria
Visit 3 (Start of Double-blind Treatment Period)

Instructions to Investigator

Did the subject meet all the entry criteria?

- If the subject met all the entry criteria (all NO answers to the Exclusion questions), ✔ YES. Otherwise ✔ NO.

Exclusion Criteria

- Only ✔ boxes that represent a violation of the Exclusion criteria.

Monitor Data Validation Checks

- If the question "*Did the subject meet all entry criteria*" is answered YES, check that no ✔ are present in the exclusion criteria boxes.
- If the question "*Did the subject meet all entry criteria*" is answered NO, check that a ✔ is present in at least one exclusion criteria box.

Protocol code	Session number	Subject number
207499/181	**3**	

Exclusion Criteria
Visit 3 (Start of Double-blind Treatment Period)

Did the subject meet all entry criteria (i.e., All "NO" answers for exclusion criteria)? *See EXCLUSION* CRITERIA WORKSHEET. Yes ☐ Y No ☐ N

✔ *all boxes that represent a violation of the exclusion criteria:*

Exclusion Criteria

1. ☐ 2. ☐ 3. ☐ 4. ☐

NOTE: If the subject did not meet the randomisation criteria i.e., any of the boxes above have been ✔ as *a violation of the Exclusion criteria, the subject must be* ***withdrawn****. Ensure that the END OF STUDY RECORD section is completed and 'did not fulfil entry criteria' is* ✔ *as the* ***primary*** *reason for discontinuation.*

Protocol code

207499/181

Treatment Allocation
Visit 3 (Start of Double-blind Treatment Period)

Instructions to Investigator

NOTE: All subjects eligible for entry into the Treatment period will be stratified before treatment, according to their smoking history.

- Telephone RAMOS and using the Interactive Voice Response (IVR) system, specify the subject number and subjects smoking status (as defined at Visit 1). RAMOS will randomise the subject, assign the treatment number and assign the study medication, by reading the appropriate Container Number of the Treatment Pack to be dispensed to the subject.
- Record the treatment number (RAMOS randomisation number) on the *FRONT COVER* of the Case Report Form.
- Record the container number of the treatment pack on the facing page.
- Record study medication start date in the *INVESTIGATIONAL PRODUCT* section.

Monitor Data Validation Checks

- Check that the Date Treatment Allocated corresponds with the Visit 3 date.
- Check that the treatment number has been recorded on the *FRONT COVER* of the Case Report Form.
- Check that the treatment start date has been recorded in the *INVESTIGATIONAL PRODUCT* section.

Protocol code	Session number	Subject number
207499/181	3	

Treatment Allocation
Visit 3 (Start of Double-blind Treatment Period)

NOTE: ***Subjects will only be randomised at Visit 3 if the randomisation criteria are met and the sputum sample taken at Visit 3 is satisfactory.***

Using the RAMOS IVR system, obtain the treatment number for this subject and container number (dispensing unit number) for this visit.

Issue the subject with study medication (presented in double-blind bottles) for the 13-week double-blind treatment period. Bottles will contain either 70 tablets of Cilomilast (SB 207499) 15 mg **or** matching placebo. Each bottle will provide a 35-day supply of study medication (28 days worth and an additional 7 days overage).

One tablet of study medication should be taken twice daily, in the morning immediately after breakfast and in the evening immediately after a meal.

. . . . . .
Investigator's or Designee's signature

. . . . . .
Investigator's or Designee's name - print

Date Treatment Allocated | | | | | | | | |
day month year

Container Number (dispensing unit number) | | | | | | | Bottle 1

Container Number (dispensing unit number) | | | | | | | Bottle 2

Container Number (dispensing unit number) | | | | | | | Bottle 3

Container Number (dispensing unit number) | | | | | | | Bottle 4

NOTE: ***The first dose of double-blind study treatment will be taken by the subject in the clinic and this will be recorded in the CRF and in the subject's DRC. The treatment start date must be entered in the INVESTIGATIONAL PRODUCT section in this Case Report Form.***

Pharmacy *(if applicable)*

Dispense 207499/181 Treatment Pack with the appropriate container number (dispensing unit number) for this subject.

Protocol code

207499/181

Investigator's Checklist
Visit 3 (Start of Double-blind Treatment Period)

- Collect **all** Run-in single-blind medication and complete the *COMPLIANCE* section of this CRF.
- Issue ipratropium bromide medication (if a*ppropriate)* for use as a relief medication on an 'as required' basis.
- Issue study medication for 13 weeks of treatment and record study medication start date in the *INVESTIGATIONAL PRODUCT* section.
- Issue the Treatment DRC for Visit 3 - Visit 4 and inform the subject of the importance of completing the DRC correctly and explain how to record the use of study medication and record any exacerbations.
- Review exclusion criteria.
- Ensure any adverse events which have occurred, have been recorded in the *ADVERSE EVENTS* section(s) of the CRF.
- Ensure any changes or additions to the subjects concomitant medications has been recorded in the appropriate *CONCOMITANT MEDICATIONS* section(s) of the CRF.
- Ensure subject's use of salbutamol and/or ipratropium bromide is recorded in the *COPD CONCOMITANT MEDICATION* section of this CRF).
- Ensure all Visit 3 sections have been completed.
- Telephone RAMOS to randomise the subject.
- Make an appointment for the subject to return for Visit 4 (Week +4), 28 (± 3) days from randomisation, at the same time of day.

Remind the subject of the following:

- To take study medication as demonstrated.
- To take their salbutamol and/or ipratropium bromide medication as prescribed and to contact the investigator if they experience symptoms that do not react adequately to salbutamol and/or ipratropium bromide.
- To refrain from using their salbutamol and/or ipratropium bromide medication for at least **6 hours** immediately before Visit 4.
- To refrain from smoking for **2 hours** immediately before Visit 4.
- To attend the clinic for Visit 4 at the same time of day (± 2 hours).
- To bring the Visit 3 - Visit 4 Daily Record Card, study medication and any remaining salbutamol and/or ipratropium bromide medication to the clinic for Visit 4.

NOTE: If the subject discontinues the study during the run-in period, complete the END OF STUDY RECORD section in the Case Report Form.

Protocol code	Session number	Subject number
207499/181	4	

Visit Date
Visit 4 (Treatment Period)

NOTE: If the subject is withdrawing at this visit, complete the EARLY WITHDRAWAL VISIT assessments in this CRF. DO NOT complete the Visit 4 assessments.

Visit Date [ ][ ] [ ][ ][ ] [ ][ ]
day month year

Record the date and time of the subject's last dose of salbutamol and/or ipratropium bromide medication immediately before Visit 4.

Date [ ][ ] [ ][ ][ ] [ ][ ]
day month year

Time [ ][ ] : [ ][ ]
00:00-23:59

If the subject is a **current smoker**, has the subject smoked during the 2 hours before Visit 4? Yes [ ]Y No [ ]N

Protocol code

207499/181

Adverse Event / Concomitant Medication / Exacerbation of COPD
Visit 4 (Treatment Period)

Instructions to Investigator

Adverse Event

- Any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

  An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

Exacerbation of COPD

Definition of a COPD Exacerbation

For the purpose of this study COPD exacerbations are categorised as follows:

Mild

- Acute worsening of COPD that is self-managed by the subject at home by increasing usual COPD bronchodilators medications, and should not be taking any antibiotics (i.e. the subject does not see a doctor for this episode)

Moderate

- Acute worsening of COPD that requires additional treatment (e.g. a short course of oral steroids, antibiotics, etc.) prescribed by primary care physician or as a result of a hospital out-patient visit (including a visit to the Emergency Room)

Severe

- Acute worsening of COPD that requires the subject to be admitted to hospital for treatment

Monitor Data Validation Checks

Adverse Event / Concomitant Medication

- Check that any adverse events are recorded in the *ADVERSE EVENT* section and any changes/new medications are recorded in the *CONCOMITANT MEDICATION* section(s) of the Case Report Form.

  NOTE: ✔ if done box should always be completed to confirm these questions have been asked, regardless of whether an adverse event has occurred or new medicine has been taken.

Exacerbation of COPD

- If the subject has experienced an exacerbation since their last visit, check that the *COPD EXACERBATION and if appropriate, the COPD CONCOMITANT MEDICATION and the ADVERSE EVENT* section(s) have been completed.

  NOTE: ✔ if done box should always be completed to confirm DRC has been checked, regardless of whether the subject has experienced an exacerbation.

Protocol code

207499/181

Subject number

Adverse Event / Concomitant Medication / Exacerbation of COPD
Visit 4 (Treatment Period)

Adverse Event / Concomitant Medication

Check the subject's Daily Record Card to determine whether they have experienced an adverse event.

Ask the following questions:

(a) "Have you had any (other) medical problems since your last visit/assessment?"

(b) "Have you taken any new medicines, other than those provided in this study, since your last visit/ assessment?"

Adverse events should be recorded in the appropriate ADVERSE EVENTS section(s).

Concomitant medications should be recorded in the CONCOMITANT MEDICATIONS section(s).

Confirm these adverse event and concomitant medication questions have been asked. ☐ ✔ *if done*

Exacerbation of COPD

Check the subject's Daily Record Card to determine whether they have experienced an exacerbation of COPD (according to the definition on the facing page).

Ask the following question:

Have you experienced an exacerbation of your COPD since the last visit?

If necessary, complete the COPD EXACERBATION section and if appropriate, the COPD CONCOMITANT MEDICATION section and ADVERSE EVENTS section in this Case Report Form.

Confirm this exacerbation question has been asked. ☐ ✔ *if done*

*NOTE: Subjects who experience a **severe exacerbation** during the Treatment period will be **withdrawn** from the study. Subjects who experience a **moderate exacerbation requiring the use of oral corticosteroids** will also be **withdrawn** from the study.*
*However, if subjects experience **one moderate exacerbation** requiring the use of antibiotics, they would be allowed to continue. Subjects experiencing **more than one moderate exacerbation** requiring the use of antibiotics will be **withdrawn** from the study.*

Protocol code

207499/181

Daily Record Card / COPD Pulmonary Function Tests
Visit 4 (Treatment Period)

Instructions to Investigator

Daily Record Card

- Check DRC for exacerbations.
- Transcribe any medications from the medication section into the appropriate *CONCOMITANT MEDICATION* section in this Case Report Form.
- Transcribe any Adverse Events that have been reported into the appropriate *ADVERSE EVENT* section(s) of this CRF.
- Any changes, corrections or explanations that you have made regarding dates must be initialled and dated in the presence of the subject.

COPD Pulmonary Function Tests

It is preferable that for any individual subject at each study visit, the same pulmonologist, technician or nurse administers pulmonary function tests, in order to ensure consistency of technique.

Where possible, pulmonary function measurements should be performed at the same time of day under Body Temperature and Pressure Standard (BTPS) conditions, using the same spirometer at each visit. The subject should be in the same position (i.e. sitting or standing) at each visit.

- The highest of three technically acceptable SVC measurements should be recorded **before and after** inhalation of salbutamol.
- Record SVC to 2 decimal places.
- Lung function printouts must be labelled with the Subject Number, Visit Number, date and time of measurement and signed and dated by the person responsible for the data. All printouts should be kept in the subject's notes.

Monitor Data Validation Checks

Daily Record Card

- Check the Treatment Daily Record Card for the period between Visit 3 and Visit 4. Ensure that any adverse events and changes in medication reported in the Treatment Daily Record Card have been transcribed to the appropriate *ADVERSE EVENT*, *and CONCOMITANT MEDICATION* section(s) of the Case Report Form.
- If any corrections are made, the investigator must initial and date them.

COPD Pulmonary Function Tests

- Check that SVC has been rounded to 2 decimal places.
- Check that all spirometry printouts are signed and dated by the responsible person and clearly indicate the clinic visit, the date of the visit, the time of assessment and the GlaxoSmithKline Subject Number. The spirometry printouts must be stored in the subject's notes.

Protocol code	Session number	Subject number
207499/181	**4**	

Daily Record Card / COPD Pulmonary Function Tests
Visit 4 (Treatment Period)

Daily Record Card

Has the Daily Record Card been collected and reviewed? Yes ☐ Y No ☐ N

COPD Pulmonary Function Tests

Date of assessment ☐☐ ☐☐☐ ☐☐
day month year

*NOTE: Subjects must refrain from smoking for **2 hours** immediately before pulmonary function tests.*

Has the subject taken any salbutamol and/or ipratropium bromide in the last 6 hours? Yes ☐ Y No ☐ N

If YES, a 6 hour period should elapse before the pulmonary function tests are performed. Remind the subject to refrain from taking any for 6 hours before the next visit.

Test	Time of assessment pre-salbutamol 00:00-23:59	Actual measurement pre-salbutamol *(highest of 3 measurements)*	Time of assessment 30 minutes post-salbutamol 00:00-23:59	Actual measurement 30 minutes post-salbutamol *(highest of 3 measurements)*
e.g. SVC (L)	***08:00***	***1.75***	***08:30***	***1.80***
SVC (L)	**:**	**.**	**:**	**.**

Protocol code

207499/181

Investigator's Checklist
Visit 4 (Treatment Period)

- Check the Treatment study medication bottles and complete the *COMPLIANCE* section of this CRF. Collect any used study medication bottles.
- Issue salbutamol and/or ipratropium bromide medication (if a*ppropriate)* for use as a relief medication on an 'as required' basis.
- Issue a Treatment DRC for Visit 4 - Visit 5 and remind the subject of the importance of completing the DRC correctly by recording the use of study medication and recording any exacerbations.
- Ensure any adverse events which have occurred, have been recorded in the *ADVERSE EVENTS* section(s) of the CRF.
- Ensure any changes or additions to the subjects concomitant medications has been recorded in the appropriate *CONCOMITANT MEDICATIONS* section(s) of the CRF.
- Ensure subject's use of salbutamol and/or ipratropium bromide is recorded in the *COPD CONCOMITANT MEDICATION* section of this CRF).
- Ensure any exacerbations have been recorded in the *COPD EXACERBATIONS* section of this CRF.
- Ensure all Visit 4 sections have been completed.
- Make an appointment for the subject to return for Visit 5 (Week +8), 56 (± 3) days from randomisation, at the same time of day.

Remind the subject of the following:

- To take study medication as demonstrated.
- To take their salbutamol and/or ipratropium bromide medication as prescribed and to contact the investigator if they experience symptoms that do not react adequately to salbutamol and/or ipratropium bromide.
- To refrain from using their salbutamol and/or ipratropium bromide medication for at least **6 hours** immediately before Visit 5.
- To refrain from smoking for **2 hours** immediately before Visit 5.
- To attend the clinic for Visit 5 at the same time of day (± 2 hours).
- To bring the Visit 4 - Visit 5 Daily Record Card, study medication and any remaining salbutamol and/or ipratropium bromide medication to the clinic for Visit 5.

Protocol code	Session number	Subject number
207499/181	5	

Visit Date
Visit 5 (Treatment Period)

NOTE: ***If the subject is withdrawing at this visit, complete the EARLY WITHDRAWAL VISIT assessments in this CRF. DO NOT complete the Visit 5 assessments.***

Visit Date [ ][ ] [ ][ ][ ] [ ][ ]
day month year

Record the date and time of the subject's last dose of salbutamol and/or ipratropium bromide medication immediately before Visit 5.

Date [ ][ ] [ ][ ][ ] [ ][ ] Time [ ][ ] : [ ][ ]
day month year 00:00-23:59

If the subject is a **current smoker**, has the subject smoked during the 2 hours before Visit 5? Yes [ ]Y No [ ]N

Protocol code

207499/181

Adverse Event / Concomitant Medication / Exacerbation of COPD
Visit 5 (Treatment Period)

Instructions to Investigator

Adverse Event

- Any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

  An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

Exacerbation of COPD

Definition of a COPD Exacerbation

For the purpose of this study COPD exacerbations are categorised as follows:

Mild

- Acute worsening of COPD that is self-managed by the subject at home by increasing usual COPD bronchodilators medications, and should not be taking any antibiotics (i.e. the subject does not see a doctor for this episode)

Moderate

- Acute worsening of COPD that requires additional treatment (e.g. a short course of oral steroids, antibiotics, etc.) prescribed by primary care physician or as a result of a hospital out-patient visit (including a visit to the Emergency Room)

Severe

- Acute worsening of COPD that requires the subject to be admitted to hospital for treatment

Monitor Data Validation Checks

Adverse Event / Concomitant Medication

- Check that any adverse events are recorded in the *ADVERSE EVENT* section and any changes/new medications are recorded in the *CONCOMITANT MEDICATION* section(s) of the Case Report Form.

  NOTE: ✔ if done box should always be completed to confirm these questions have been asked, regardless of whether an adverse event has occurred or new medicine has been taken.

Exacerbation of COPD

- If the subject has experienced an exacerbation since their last visit, check that the *COPD EXACERBATION and if appropriate, the COPD CONCOMITANT MEDICATION and the ADVERSE EVENT* section(s) have been completed.

  NOTE: ✔ if done box should always be completed to confirm DRC has been checked, regardless of whether the subject has experienced an exacerbation.

Protocol code

207499/181

Subject number

Adverse Event / Concomitant Medication / Exacerbation of COPD
Visit 5 (Treatment Period)

Adverse Event / Concomitant Medication

Check the subject's Daily Record Card to determine whether they have experienced an adverse event.

Ask the following questions:

(a) "Have you had any (other) medical problems since your last visit/assessment?"

(b) "Have you taken any new medicines, other than those provided in this study, since your last visit/ assessment?"

Adverse events should be recorded in the appropriate ADVERSE EVENTS section(s).

Concomitant medications should be recorded in the CONCOMITANT MEDICATIONS section(s).

Confirm these adverse event and concomitant medication questions have been asked. ☐ ✔ *if done*

Exacerbation of COPD

Check the subject's Daily Record Card to determine whether they have experienced an exacerbation of COPD (according to the definition on the facing page).

Ask the following question:

Have you experienced an exacerbation of your COPD since the last visit?

If necessary, complete the COPD EXACERBATION section and if appropriate, the COPD CONCOMITANT MEDICATION section and ADVERSE EVENTS section in this Case Report Form.

Confirm this exacerbation question has been asked. ☐ ✔ *if done*

*NOTE: Subjects who experience a **severe exacerbation** during the Treatment period will be **withdrawn** from the study. Subjects who experience a **moderate exacerbation requiring the use of oral corticosteroids** will also be **withdrawn** from the study.*
*However, if subjects experience **one moderate exacerbation** requiring the use of antibiotics, they would be allowed to continue. Subjects experiencing **more than one moderate exacerbation** requiring the use of antibiotics will be **withdrawn** from the study.*

Protocol code

207499/181

Daily Record Card / COPD Pulmonary Function Tests / Blood Tests
Visit 5 (Treatment Period)

Instructions to Investigator

Daily Record Card

- Check DRC for exacerbations.
- Transcribe any medications from the medication section into the appropriate *CONCOMITANT MEDICATION* section in this Case Report Form.
- Transcribe any Adverse Events that have been reported into the appropriate *ADVERSE EVENT* section(s) of this CRF.
- Any changes, corrections or explanations that you have made regarding dates must be initialled and dated in the presence of the subject.

COPD Pulmonary Function Tests

It is preferable that for any individual subject at each study visit, the same pulmonologist, technician or nurse administers pulmonary function tests, in order to ensure consistency of technique.

Where possible, pulmonary function measurements should be performed at the same time of day under Body Temperature and Pressure Standard (BTPS) conditions, using the same spirometer at each visit. The subject should be in the same position (i.e. sitting or standing) at each visit.

- The highest of three technically acceptable SVC measurements should be recorded **before and after** inhalation of salbutamol.
- Record SVC to 2 decimal places.
- Lung function printouts must be labelled with the Subject Number, Visit Number, date and time of measurement and signed and dated by the person responsible for the data. All printouts should be kept in the subject's notes.

Blood Tests

- Subjects must provide a blood sample for pre-biopsy analysis of blood clotting test within **4 weeks prior to Visit 6**. Samples are to be processed at the site where possible and results **must** be available before the biopsy procedure is conducted.

Monitor Data Validation Checks

Daily Record Card

- Check the Treatment Daily Record Card for the period between Visit 4 and Visit 5. Ensure that any adverse events and changes in medication reported in the Treatment Daily Record Card have been transcribed to the appropriate *ADVERSE EVENT*, *and CONCOMITANT MEDICATION* section(s) of the Case Report Form.
- If any corrections are made, the investigator must initial and date them.

COPD Pulmonary Function Tests

- Check that SVC has been rounded to 2 decimal places.
- Check that all spirometry printouts are signed and dated by the responsible person and clearly indicate the clinic visit, the date of the visit, the time of assessment and the GlaxoSmithKline Subject Number. The spirometry printouts must be stored in the subject's notes.

Protocol code	Session number	Subject number
207499/181	5	

Daily Record Card / COPD Pulmonary Function Tests / Blood Tests
Visit 5 (Treatment Period)

Daily Record Card

Has the Daily Record Card been collected and reviewed? Yes ☐ Y No ☐ N

COPD Pulmonary Function Tests

Date of assessment ☐☐ ☐☐☐ ☐☐
day month year

*NOTE: Subjects must refrain from smoking for **2 hours** immediately before pulmonary function tests.*

Has the subject taken any salbutamol and/or ipratropium bromide in the last 6 hours? Yes ☐ Y No ☐ N

If YES, a 6 hour period should elapse before the pulmonary function tests are performed. Remind the subject to refrain from taking any for 6 hours before the next visit.

Test	Time of assessment pre-salbutamol 00:00-23:59	Actual measurement pre-salbutamol *(highest of 3 measurements)*	Time of assessment 30 minutes post-salbutamol 00:00-23:59	Actual measurement 30 minutes post-salbutamol *(highest of 3 measurements)*
e.g. SVC	***08:00***	***1.75***	***08:30***	***1.80***
SVC (L)	:	.	:	.

Blood Tests

Has a blood sample been taken from the subject for blood clotting analysis? Yes ☐ Y No ☐ N

Date sample taken ☐☐ ☐☐☐ ☐☐
day month year

Were there any **clinically significant abnormal** laboratory values? Yes ☐ Y No ☐ N

NOTE: All clinically significant abnormal laboratory findings are to be repeated until the values return to normal. Record all clinically significant abnormalities in the appropriate ADVERSE EVENT section.

NOTE: If results are not available at Visit 5, they must be available prior to the bronchial biopsy at Visit 6.

Protocol code

207499/181

Investigator's Checklist
Visit 5 (Treatment Period)

- Check the Treatment study medication bottles and complete the *COMPLIANCE* section of this CRF. Collect any used study medication bottles.
- Issue salbutamol and/or ipratropium bromide medication (if a*ppropriate)* for use as a relief medication on an 'as required' basis.
- Issue a Treatment DRC for Visit 5 - Visit 6/6A and remind the subject of the importance of completing the DRC correctly by recording the use of study medication and recording any exacerbations.
- Ensure any adverse events which have occurred, have been recorded in the *ADVERSE EVENTS* section(s) of the CRF.
- Ensure any changes or additions to the subjects concomitant medications has been recorded in the appropriate *CONCOMITANT MEDICATIONS* section(s) of the CRF.
- Ensure subject's use of salbutamol and/or ipratropium bromide is recorded in the *COPD CONCOMITANT MEDICATION* section of this CRF).
- Ensure any exacerbations have been recorded in the *COPD EXACERBATIONS* section of this CRF.
- Ensure all Visit 5 sections have been completed.
- Ensure a blood sample has been taken for pre-biopsy analysis of blood clotting.
- Make an appointment for the subject to return for Visit 6 (Week +12), 84 (± 3) days from randomisation, at the same time of day.

Remind the subject of the following:

- To take study medication as demonstrated.
- To take their salbutamol and/or ipratropium bromide medication as prescribed and to contact the investigator if they experience symptoms that do not react adequately to salbutamol and/or ipratropium bromide.
- To refrain from using their salbutamol and/or ipratropium bromide medication for at least **6 hours** immediately before Visit 5.
- **Not** to eat or drink anything for **8 hours** before the bronchial biopsy at Visit 6.
- **Not** to use asprin/NSAIDs in the **5-day** period before Visit 6.
- To refrain from smoking for **2 hours** immediately before Visit 6.
- To attend the clinic for Visit 6 at the same time of day (± 2 hours).
- To bring the Visit 5 - Visit 6 Daily Record Card, study medication and any remaining salbutamol and/or ipratropium bromide medication to the clinic for Visit 6.

Protocol code	Session number	Subject number
207499/181	6	

Visit Date
Visit 6 (Treatment Period)

NOTE: ***If the subject is withdrawing at this visit, complete the EARLY WITHDRAWAL VISIT assessments in this CRF. DO NOT complete the Visit 6 assessments.***

Visit Date ☐☐ ☐☐☐ ☐☐
day month year

Record the date and time of the subject's last dose of salbutamol and/or ipratropium bromide medication immediately before Visit 6.

Date ☐☐ ☐☐☐ ☐☐ Time ☐☐ : ☐☐
day month year 00:00-23:59

If the subject is a **current smoker**, has the subject smoked during the 2 hours before Visit 6? Yes ☐ Y No ☐ N

Blood Test Check

Was a blood sample taken at Visit 5 for pre-biopsy analysis of blood clotting? Yes ☐ Y No ☐ N

Were there any clinically significant abnormal laboratory values? Yes ☐ Y No ☐ N

NOTE: All clinically significant abnormal laboratory findings are to be repeated until the values return to normal. Record all clinically significant abnormalities in the appropriate ADVERSE EVENT section(s).

Protocol code

207499/181

Adverse Event / Concomitant Medication / Exacerbation of COPD
Visit 6 (Treatment Period)

Instructions to Investigator

Adverse Event

- Any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

  An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

Exacerbation of COPD

Definition of a COPD Exacerbation

For the purpose of this study COPD exacerbations are categorised as follows:

Mild

- Acute worsening of COPD that is self-managed by the subject at home by increasing usual COPD bronchodilators medications, and should not be taking any antibiotics (i.e. the subject does not see a doctor for this episode)

Moderate

- Acute worsening of COPD that requires additional treatment (e.g. a short course of oral steroids, antibiotics, etc) prescribed by primary care physician or as a result of a hospital out-patient visit (including a visit to the Emergency Room)

Severe

- Acute worsening of COPD that requires the subject to be admitted to hospital for treatment

Monitor Data Validation Checks

Adverse Event / Concomitant Medication

- Check that any adverse events are recorded in the *ADVERSE EVENT* section and any changes/new medications are recorded in the *CONCOMITANT MEDICATION* section(s) of the Case Report Form.

  NOTE: "✔ if done" box should always be completed to confirm these questions have been asked, regardless of whether an adverse event has occurred or new medicine has been taken.

Exacerbation of COPD

- If the subject has experienced an exacerbation since their last visit, check that the *COPD EXACERBATION and if appropriate, the COPD CONCOMITANT MEDICATION and the ADVERSE EVENT* section(s) have been completed.

  NOTE: ✔ if done box should always be completed to confirm DRC has been checked, regardless of whether the subject has experienced an exacerbation.

Protocol code

207499/181

Subject number

Adverse Event / Concomitant Medication / Exacerbation of COPD
Visit 6 (Treatment Period)

Adverse Event / Concomitant Medication

Check the subject's Daily Record Card to determine whether they have experienced an adverse event.

Ask the following questions:

(a) "Have you had any (other) medical problems since your last visit/assessment?"

(b) "Have you taken any new medicines, other than those provided in this study, since your last visit/ assessment?"

Adverse events should be recorded in the appropriate ADVERSE EVENTS section(s).

Concomitant medications should be recorded in the CONCOMITANT MEDICATIONS section(s).

Confirm these adverse event and concomitant medication questions have been asked. ☐ ✔ *if done*

Exacerbation of COPD

Check the subject's Daily Record Card to determine whether they have experienced an exacerbation of COPD (according to the definition on the facing page).

Ask the following question:

Have you experienced an exacerbation of your COPD since the last visit?

If necessary, complete the COPD EXACERBATION section and if appropriate, the COPD CONCOMITANT MEDICATION section and ADVERSE EVENTS section in this Case Report Form.

Confirm this exacerbation question has been asked. ☐ ✔ *if done*

*NOTE: Subjects who experience a **severe exacerbation** during the Treatment period will be **withdrawn** from the study. Subjects who experience a **moderate exacerbation requiring the use of oral corticosteroids** will also be **withdrawn** from the study.*
*However, if subjects experience **one moderate exacerbation** requiring the use of antibiotics, they would be allowed to continue. Subjects experiencing **more than one moderate exacerbation** requiring the use of antibiotics will be **withdrawn** from the study.*

Protocol code

207499/181

Daily Record Card / Vital Signs / COPD Pulmonary Function Tests
Visit 6 (Treatment Period)

Instructions to Investigator

Daily Record Card

- Check DRC for exacerbations.
- Transcribe any medications from the medication section into the appropriate *CONCOMITANT MEDICATION* section in this Case Report Form.
- Transcribe any Adverse Events that have been reported into the appropriate *ADVERSE EVENT* section(s) of this CRF.
- Any changes, corrections or explanations that you have made regarding dates must be initialled and dated in the presence of the subject.

COPD Pulmonary Function Tests

It is preferable that for any individual subject at each study visit, the same pulmonologist, technician or nurse administers pulmonary function tests, in order to ensure consistency of technique.

Where possible, pulmonary function measurements should be performed at the same time of day under Body Temperature and Pressure Standard (BTPS) conditions, using the same spirometer at each visit. The subject should be in the same position (i.e. sitting or standing) at each visit.

- The highest of three technically acceptable SVC measurements should be recorded **before and after** inhalation of salbutamol.
- Record SVC to 2 decimal places.
- Lung function printouts must be labelled with the Subject Number, Visit Number, date and time of measurement and signed and dated by the person responsible for the data. All printouts should be kept in the subject's notes.

Vital Signs

- Salbutamol and/or ipratropium bromide must not be taken for 6 hours prior to vital signs being measured.

Monitor Data Validation Checks

Daily Record Card

- Check the Treatment Daily Record Card for the period between Visit 5 and Visit 6. Ensure that any adverse events and changes in medication reported in the Treatment Daily Record Card have been transcribed to the appropriate *ADVERSE EVENT*, *and CONCOMITANT MEDICATION* section(s) of the Case Report Form.
- If any corrections are made, the investigator must initial and date them.

Vital Signs

- Check that blood pressure values are within reasonable limits and systolic blood pressure is greater than diastolic blood pressure.
- Check that heart rate value is within reasonable limits for beats per minute.

COPD Pulmonary Function Tests

- Check that SVC has been rounded to 2 decimal places.
- Check that all spirometry printouts are signed and dated by the responsible person and clearly indicate the clinic visit, the date of the visit, the time of assessment and the GlaxoSmithKline Subject Number. The spirometry printouts must be stored in the subject's notes.

Protocol code	Session number	Subject number
207499/181	**6**	

Daily Record Card / Vital Signs / COPD Pulmonary Function Tests
Visit 6 (Treatment Period)

Daily Record Card

Has the Daily Record Card been collected and reviewed? Yes ☐ Y No ☐ N

Vital Signs

*Vital signs must be measured at least **6 hours after** the subject's last salbutamol and/or ipratropium bromide administration after the subject has been sitting for 5 minutes.*

Date	Blood pressure mmHg		Heart rate	Temperature
day month year	systolic	diastolic	beats/min	°C
e.g., 06 JAN 02	***110***	***80***	***75***	***36.5***
				.

Record all clinically significant abnormalities in the appropriate ADVERSE EVENT section(s).

COPD Pulmonary Function Tests

Date of assessment ☐☐ ☐☐☐ ☐☐
day month year

*NOTE: Subjects must refrain from smoking for **2 hours** immediately before pulmonary function tests.*

Has the subject taken any salbutamol and/or ipratropium bromide in the last 6 hours? Yes ☐ Y No ☐ N

If YES, a 6 hour period should elapse before the pulmonary function tests are performed. Remind the subject to refrain from taking any for 6 hours before the next visit.

Test	Time of assessment pre-salbutamol 00:00-23:59	Actual measurement pre-salbutamol *(highest of 3 measurements)*	Time of assessment 30 minutes post-salbutamol 00:00-23:59	Actual measurement 30 minutes post-salbutamol *(highest of 3 measurements)*
e.g. SVC (L)	***08:00***	***1.75***	***08:30***	***1.80***
SVC (L)	:	.	:	.

Protocol code

207499/181

Subject number

Pre Bronchial Biopsy Checklist
Visit 6 (Treatment Period)

Has the subject consumed any food or drink since midnight? Yes ☐ No ☐

Has the subject used asprin or NSAIDS in the 5 days preceding the biopsy? Yes ☐ No ☐

NOTE: If either of the above is answered YES, the procedure must be rescheduled for within 1-7 days.

The subject must meet the following safety criteria on the scheduled day of the biopsy procedure:

	Criteria met? Yes	No
Pre-salbutamol FEV_1 40-80% predicted normal value.	☐	☐
No history of bleeding diathesis. Normal blood clotting parameters.	☐	☐
Ability to be collected by a friend/relative at the end of the biopsy procedure	☐	☐

*NOTE: If any of the safety criteria questions are answered **NO**, the subject is unsuitable for the bronchoscopy on the scheduled day and the procedure must be rescheduled for within 1-7 days. If the procedure is rescheduled, **do not** complete the remaining Visit 6 assessments.*

All safety criteria must be re-checked on the day of the rescheduled procedure.

Protocol code

207499/181

Bronchial Biopsy
Visit 6 (Treatment Period)

Instructions to Investigator

NOTE: Refer to the Bronchial Biopsy Procedure (BBP) document prior to starting the biopsy.

- The subject must meet specific safety criteria on the day of the bronchoscopy, before the procedure can proceed.
- A **Biopsy Safety Form must** be completed and stored in the subject's notes prior to performing the bronchoscopy.
- The procedure should be performed using the methodology described in the Bronchial Biopsy Procedure (BBP).
- Bronchoscopies should be performed using an Olympus BF fibreoptic bronchoscope (type IT40, 2.8 mm channel or similar) or equivalent. Use of any other type of bronchoscope must be pre-agreed with GSK.
- Cup forceps [FB-35C-1, 2.8 mm (fenestrated forceps)] or equivalent should be used for all subjects and each set should be replaced after every 5-biopsy occasions. Use of any other type of forceps must be pre-agreed with GSK.
- Six biopsies of adequate size (2mm) should be performed on the right side beginning at the subcarinae in the right lower lobe (2 biopsies), then the right middle lobe (2 biopsies) and finally the right upper lobe (2 biopsies).
- Report any serious complications relating to the bronchoscopy, e.g. severe bleeding or pneumothorax, to the study monitor as soon as possible (within 24 hours).
- The **Biopsy Sample Worksheet** and the **Processing of Biopsy Sample Worksheet** must be sent with the samples via QUEST to Dr Q. Hamid's laboratory.

Protocol code	Session number	Subject number
207499/181	**6**	

Bronchial Biopsy
Visit 6 (Treatment Period)

Confirm all safety criteria have been met. ☐ ✔ *if met*

Complete a Biopsy Safety Form prior to the biopsy.

Date of biopsy ☐☐ (day) ☐☐☐ (month) ☐☐ (year) Time of biopsy ☐☐ : ☐☐ (00:00-23:59)

Record below, all medication administered at the time of the bronchoscopy:

Drug name	Medication administered		Time administered 00:00-23:59
	Yes (Y)	No (N)	
e.g., Atropine	✔		***10:30***
Atropine			:
Midazolam			:
Salbutamol			:
Intravenous flumazenil			:
Topical lignocaine			:
Lignocaine gel			:

Record number of mucosal biopsies taken.

Biopsy site	Number of biopsies taken	Biopsy lung ✔ *one*	
		Left	Right
Lower lobe (Level A)			
Middle lobe (Level B)			
Upper lobe (Level C)			

continued...

Protocol code

207499/181

Investigator's Checklist
Visit 6 (Treatment Period)

- Check the Treatment study medication bottles and complete the *COMPLIANCE* section of this CRF. Collect any used study medication bottles.
- Issue salbutamol and/or ipratropium bromide medication (if a*ppropriate)* for use as a relief medication on an 'as required' basis.
- Issue a Treatment DRC for Visit 6/6A - Visit 7 and remind the subject of the importance of completing the DRC correctly by recording the use of study medication and recording any exacerbations.
- Ensure any adverse events which have occurred, have been recorded in the *ADVERSE EVENTS* section(s) of the CRF.
- Ensure any changes or additions to the subjects concomitant medications has been recorded in the appropriate *CONCOMITANT MEDICATIONS* section(s) of the CRF.
- Ensure subject's use of salbutamol and/or ipratropium bromide is recorded in the *COPD CONCOMITANT MEDICATION* section of this CRF).
- Ensure any exacerbations have been recorded in the *COPD EXACERBATIONS* section of this CRF.
- Ensure the subject has taken their next dose of study medication in the clinic after recovery from the biopsy procedure and prior to discharge.
- Issue the FOB kit to the subject, to be collected at Visit 7.
- Ensure all Visit 6 sections have been completed.
- Make an appointment for the subject to return for Visit 7 (Week 13), 91 (± 3) days from randomisation, at the same time of day.

Remind the subject of the following:

- To take study medication as demonstrated.
- To take their salbutamol and/or ipratropium bromide medication as prescribed and to contact the investigator if they experience symptoms that do not react adequately to salbutamol and/or ipratropium bromide.
- To refrain from using their salbutamol and/or ipratropium bromide medication for at least **6 hours** immediately before Visit 7.
- To refrain from smoking for **2 hours** immediately before Visit 7.
- To attend the clinic for Visit 7 at the same time of day (± 2 hours).
- To bring the Visit 6/6A - Visit 7 Daily Record Card, and any remaining salbutamol and/or ipratropium bromide medication to the clinic for Visit 7.

If the Biopsy is rescheduled for Visit 6A:

- Ask subject to return to the clinic for Visit 6A in 7 days (±3) days at the same time of day.
- To take study medication as demonstrated.
- To take their salbutamol and/or ipratropium bromide medication as prescribed.
- To refrain from using their salbutamol and/or ipratropium bromide medication for **6 hours** immediately before Visit 6A.
- To refrain from smoking for **2 hours** immediately before Visit 6A.
- **Not** to eat or drink anything for **8 hours** before the bronchial biopsy at Visit 6A.
- **Not** to use asprin/NSAIDs in the **5-day** period before Visit 6A.
- To bring the Visit 6/6A - Visit 7 Daily Record Card, study medication and any remaining ipratropium bromide medication to the clinic for Visit 6A.

Protocol code	Session number	Subject number
207499/181	6.5	

Visit Date
Visit 6A (Treatment Period)

NOTE: ***If the subject is withdrawing at this visit, complete the EARLY WITHDRAWAL VISIT assessments in this CRF. DO NOT complete the Visit 6A assessments.***

Visit Date ☐☐ ☐☐☐ ☐☐
day month year

Record the date and time of the subject's last dose of salbutamol and/or ipratropium bromide medication immediately before Visit 6A.

Date ☐☐ ☐☐☐ ☐☐ Time ☐☐ : ☐☐
day month year 00:00-23:59

If the subject is a **current smoker**, has the subject smoked during the 2 hours before Visit 6A? Yes ☐ Y No ☐ N

Blood Test Check

Was a blood sample taken at Visit 5 for pre-biopsy analysis of blood clotting? Yes ☐ Y No ☐ N

Were there any clinically significant abnormal laboratory values? Yes ☐ Y No ☐ N

NOTE: All clinically significant abnormal laboratory findings are to be repeated until the values return to normal. Record all clinically significant abnormalities in the appropriate ADVERSE EVENT section(s).

Protocol code

207499/181

Adverse Event / Concomitant Medication / Exacerbation of COPD
Visit 6A (Treatment Period)

Instructions to Investigator

Adverse Event

- Any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

  An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

Exacerbation of COPD

Definition of a COPD Exacerbation

For the purpose of this study COPD exacerbations are categorised as follows:

Mild

- Acute worsening of COPD that is self-managed by the subject at home by increasing usual COPD bronchodilators medications, and should not be taking any antibiotics (i.e. the subject does not see a doctor for this episode)

Moderate

- Acute worsening of COPD that requires additional treatment (e.g. a short course of oral steroids, antibiotics, etc.) prescribed by primary care physician or as a result of a hospital out-patient visit (including a visit to the Emergency Room)

Severe

- Acute worsening of COPD that requires the subject to be admitted to hospital for treatment

Monitor Data Validation Checks

Adverse Event / Concomitant Medication

- Check that any adverse events are recorded in the *ADVERSE EVENT* section and any changes/new medications are recorded in the *CONCOMITANT MEDICATION* section(s) of the Case Report Form.

  NOTE: "✔ if done " box should always be completed to confirm these questions have been asked, regardless of whether an adverse event has occurred or new medicine has been taken.

Exacerbation of COPD

- If the subject has experienced an exacerbation since their last visit, check that the *COPD EXACERBATION and if appropriate, the COPD CONCOMITANT MEDICATION and the ADVERSE EVENT* section(s) have been completed.

  NOTE: ✔ if done box should always be completed to confirm DRC has been checked, regardless of whether the subject has experienced an exacerbation.

Protocol code

207499/181

Subject number

Adverse Event / Concomitant Medication / Exacerbation of COPD
Visit 6A (Treatment Period)

Adverse Event / Concomitant Medication

Check the subject's Daily Record Card to determine whether they have experienced an adverse event.

Ask the following questions:

(a) "Have you had any (other) medical problems since your last visit/assessment?"

(b) "Have you taken any new medicines, other than those provided in this study, since your last visit/ assessment?"

Adverse events should be recorded in the appropriate ADVERSE EVENTS section(s).

Concomitant medications should be recorded in the CONCOMITANT MEDICATIONS section(s).

Confirm these adverse event and concomitant medication questions have been asked. ☐ ✔ *if done*

Exacerbation of COPD

Check the subject's Daily Record Card to determine whether they have experienced an exacerbation of COPD (according to the definition on the facing page).

Ask the following question:

Have you experienced an exacerbation of your COPD since the last visit?

If necessary, complete the COPD EXACERBATION section and if appropriate, the COPD CONCOMITANT MEDICATION section and ADVERSE EVENTS section in this Case Report Form.

Confirm this exacerbation question has been asked. ☐ ✔ *if done*

*NOTE: Subjects who experience a **severe exacerbation** during the Treatment period will be **withdrawn** from the study. Subjects who experience a **moderate exacerbation requiring the use of oral corticosteroids** will also be **withdrawn** from the study.*
*However, if subjects experience **one moderate exacerbation** requiring the use of antibiotics, they would be allowed to continue. Subjects experiencing **more than one moderate exacerbation** requiring the use of antibiotics will be **withdrawn** from the study.*

Protocol code

207499/181

Daily Record Card / Vital Signs / COPD Pulmonary Function Tests
Visit 6A (Treatment Period)

Instructions to Investigator

Daily Record Card

- Check DRC for exacerbations.
- Transcribe any medications from the medication section into the appropriate *CONCOMITANT MEDICATION* section in this Case Report Form.
- Transcribe any Adverse Events that have been reported into the appropriate *ADVERSE EVENT* section of this CRF.
- Any changes, corrections or explanations that you have made regarding dates must be initialled and dated in the presence of the subject.

COPD Pulmonary Function Tests

It is preferable that for any individual subject at each study visit, the same pulmonologist, technician or nurse administers pulmonary function tests, in order to ensure consistency of technique.

Where possible, pulmonary function measurements should be performed at the same time of day under Body Temperature and Pressure Standard (BTPS) conditions, using the same spirometer at each visit. The subject should be in the same position (i.e. sitting or standing) at each visit.

- The highest of three technically acceptable SVC measurements should be recorded **before and after** inhalation of salbutamol.
- Record SVC to 2 decimal places.
- Lung function printouts must be labelled with the Subject Number, Visit Number, date and time of measurement and signed and dated by the person responsible for the data. All printouts should be kept in the subject's notes.

Vital Signs

- Salbutamol and/or ipratropium bromide must not be taken for 6 hours prior to vital signs being measured.

Monitor Data Validation Checks

Daily Record Card

- Check the Treatment Daily Record Card for the period between Visit 5 and Visit 6. Ensure that any adverse events and changes in medication reported in the Treatment Daily Record Card have been transcribed to the appropriate *ADVERSE EVENT*, *and CONCOMITANT MEDICATION* section(s) of the Case Report Form.
- If any corrections are made, the investigator must initial and date them.

Vital Signs

- Check that blood pressure values are within reasonable limits and systolic blood pressure is greater than diastolic blood pressure.
- Check that heart rate value is within reasonable limits for beats per minute.

COPD Pulmonary Function Tests

- Check that SVC has been rounded to 2 decimal places.
- Check that all spirometry printouts are signed and dated by the responsible person and clearly indicate the clinic visit, the date of the visit, the time of assessment and the GlaxoSmithKline Subject Number. The spirometry printouts must be stored in the subject's notes.

Protocol code	Session number	Subject number
207499/181	**6.5**	

Daily Record Card / Vital Signs / COPD Pulmonary Function Tests
Visit 6A (Treatment Period)

Daily Record Card

Has the Daily Record Card been collected and reviewed? Yes ☐ Y No ☐ N

Vital Signs

*Vital signs must be measured at least **6 hours after** the subject's last salbutamol and/or ipratropium bromide administration after the subject has been sitting for 5 minutes.*

Date	Blood pressure mmHg		Heart rate	Temperature
day month year	systolic	diastolic	beats/min	°C
e.g., 06 JAN 02	***110***	***80***	***75***	***36.5***
				.

Record all clinically significant abnormalities in the appropriate ADVERSE EVENT section(s).

COPD Pulmonary Function Tests

Date of assessment ☐☐ ☐☐☐ ☐☐
day month year

*NOTE: Subjects must refrain from smoking for **2 hours** immediately before pulmonary function tests.*

Has the subject taken any salbutamol and/or ipratropium bromide in the last 6 hours? Yes ☐ Y No ☐ N

If YES, a 6 hour period should elapse before the pulmonary function tests are performed. Remind the subject to refrain from taking any for 6 hours before the next visit.

Test	Time of assessment pre-salbutamol 00:00-23:59	Actual measurement pre-salbutamol *(highest of 3 measurements)*	Time of assessment 30 minutes post-salbutamol 00:00-23:59	Actual measurement 30 minutes post-salbutamol *(highest of 3 measurements)*
e.g. SVC	***08:00***	***1.75***	***08:30***	***1.80***
SVC (L)	:	.	:	.

Protocol code

207499/181

Subject number

Pre Bronchial Biopsy Checklist
Visit 6A (Treatment Period)

Has the subject consumed any food or drink since midnight? Yes ☐ No ☐

Has the subject used asprin or NSAIDS in the 5 days preceding the biopsy? Yes ☐ No ☐

If either of the above is answered YES, the subject must be withdrawn.

The subject must meet the following safety criteria on the scheduled day of the biopsy procedure:

	Criteria met? Yes	No
Pre-salbutamol FEV_1 40-80% predicted normal value.	☐	☐
No history of bleeding diathesis. Normal blood clotting parameters.	☐	☐
Ability to be collected by a friend/relative at the end of the biopsy procedure	☐	☐

NOTE: ***If any of the safety criteria questions are answered NO, the subject is unsuitable for the bronchoscopy. Do not complete biopsy procedure. Subject are NOT to be withdrawn, but are to continue in the study and return for Visit 7 assessments.***

Protocol code

207499/181

Bronchial Biopsy
Visit 6A (Treatment Period)

Instructions to Investigator

NOTE: Refer to the Bronchial Biopsy Procedure (BBP) document prior to starting the biopsy.

- The subject must meet specific safety criteria on the day of the bronchoscopy, before the procedure can proceed.
- A **Biopsy Safety Form must** be completed and stored in the subject's notes prior to performing the bronchoscopy.
- The procedure should be performed using the methodology described in the Bronchial Biopsy Procedure (BBP).
- Bronchoscopies should be performed using an Olympus BF fibreoptic bronchoscope (type IT40, 2.8 mm channel or similar) or equivalent. Use of any other type of bronchoscope must be pre-agreed with GSK.
- Cup forceps [FB-35C-1, 2.8 mm (fenestrated forceps)] or equivalent should be used for all subjects and each set should be replaced after every 5-biopsy occasions. Use of any other type of forceps must be pre-agreed with GSK.
- Six biopsies of adequate size (2mm) should be performed on the right side beginning at the subcarinae in the right lower lobe (2 biopsies), then the right middle lobe (2 biopsies) and finally the right upper lobe (2 biopsies).
- Report any serious complications relating to the bronchoscopy, e.g. severe bleeding or pneumothorax, to the study monitor as soon as possible (within 24 hours).
- The **Biopsy Sample Worksheet** and the **Processing of Biopsy Sample Worksheet** must be sent with the samples via QUEST to Dr Q. Hamid's laboratory.

Protocol code	Session number	Subject number
207499/181	**6.5**	

Bronchial Biopsy
Visit 6A (Treatment Period)

Confirm all safety criteria have been met. ☐ ✔ *if met*

Complete a Biopsy Safety Form prior to the biopsy.

Date of biopsy ☐☐ (day) ☐☐☐ (month) ☐☐ (year) Time of biopsy ☐☐ : ☐☐ (00:00-23:59)

Record below, all medication administered at the time of the bronchoscopy:

Drug name	Medication administered		Time administered 00:00-23:59
	Yes (Y)	No (N)	
e.g., Atropine	✔		***10:30***
Atropine			:
Midazolam			:
Salbutamol			:
Intravenous flumazenil			:
Topical lignocaine			:
Lignocaine gel			:

Record number of mucosal biopsies taken.

Biopsy site	Number of biopsies taken	Biopsy lung ✔ *one*	
		Left	Right
Lower lobe (Level A)			
Middle lobe (Level B)			
Upper lobe (Level C)			

continued...

Protocol code

207499/181

Investigator's Checklist
Visit 6A (Treatment Period)

- Check the Treatment study medication bottles and complete the *COMPLIANCE* section of this CRF. Collect any used study medication bottles.
- Issue salbutamol and/or ipratropium bromide medication (if a*ppropriate)* for use as a relief medication on an 'as required' basis.
- Issue a Treatment DRC for Visit 6/6A - Visit 7 and remind the subject of the importance of completing the DRC correctly by recording the use of study medication and recording any exacerbations.
- Ensure any adverse events which have occurred, have been recorded in the *ADVERSE EVENTS* section(s) of the CRF.
- Ensure any changes or additions to the subjects concomitant medications has been recorded in the appropriate *CONCOMITANT MEDICATIONS* section(s) of the CRF.
- Ensure subject's use of salbutamol and/or ipratropium bromide is recorded in the *COPD CONCOMITANT MEDICATION* section of this CRF).
- Ensure any exacerbations have been recorded in the *COPD EXACERBATIONS* section of this CRF.
- Ensure the subject has taken their next dose of study medication in the clinic after recovery from the biopsy procedure and prior to discharge.
- Issue the FOB kit to the subject, to be collected at Visit 7.
- Ensure all Visit 6 sections have been completed.
- Make an appointment for the subject to return for Visit 7 (Week 13), 91 (± 3) days from randomisation, at the same time of day.

Remind the subject of the following:

- To take study medication as demonstrated.
- To take their salbutamol and/or ipratropium bromide medication as prescribed and to contact the investigator if they experience symptoms that do not react adequately to salbutamol and/or ipratropium bromide.
- To refrain from using their salbutamol and/or ipratropium bromide medication for at least **6 hours** immediately before Visit 5.
- To refrain from smoking for **2 hours** immediately before Visit 7.
- To attend the clinic for Visit 7 at the same time of day (± 2 hours).
- To bring the Visit 6/6A - Visit 7 Daily Record Card, study medication and any remaining salbutamol and/or ipratropium bromide medication to the clinic for Visit 7.

Protocol code	Session number	Subject number
207499/181	7	

Visit Date / Smoking Status
Visit 7 (End of Double-blind Treatment Period)

Visit Date ☐☐ ☐☐☐ ☐☐
day month year

Record the date and time of the subject's last dose of salbutamol and/or ipratropium bromide medication immediately before Visit 7.

Date ☐☐ ☐☐☐ ☐☐ Time ☐☐ : ☐☐
day month year 00:00-23:59

Smoking Status

Does the subject currently smoke? Yes ☐ Y No ☐ N

If current smoker, record the average number of cigarettes smoked per day ☐☐☐

If the subject no longer smokes . . .

Date subject stopped smoking ☐☐ ☐☐☐ ☐☐
day month year

If the subject is a **current smoker**, has the subject smoked during the 2 hours before Visit 7? Yes ☐ Y No ☐ N

Protocol code

207499/181

Adverse Event / Concomitant Medication / Exacerbation of COPD
Visit 7 (End of Double-blind Treatment Period)

Instructions to Investigator

Adverse Event

- Any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

  An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

Exacerbation of COPD

Definition of a COPD Exacerbation

For the purpose of this study COPD exacerbations are categorised as follows:

Mild

- Acute worsening of COPD that is self-managed by the subject at home by increasing usual COPD bronchodilators medications, and should not be taking any antibiotics (i.e. the subject does not see a doctor for this episode)

Moderate

- Acute worsening of COPD that requires additional treatment (e.g. a short course of oral steroids, antibiotics, etc.) prescribed by primary care physician or as a result of a hospital out-patient visit (including a visit to the Emergency Room)

Severe

- Acute worsening of COPD that requires the subject to be admitted to hospital for treatment

Monitor Data Validation Checks

Adverse Event / Concomitant Medication

- Check that any adverse events are recorded in the *ADVERSE EVENT* section and any changes/new medications are recorded in the *CONCOMITANT MEDICATION* section(s) of the Case Report Form.

  NOTE: "✔ if done" box should always be completed to confirm these questions have been asked, regardless of whether an adverse event has occurred or new medicine has been taken.

Exacerbation of COPD

- If the subject has experienced an exacerbation since their last visit, check that the *COPD EXACERBATION and if appropriate, the COPD CONCOMITANT MEDICATION and the ADVERSE EVENT* section(s) have been completed.

  NOTE: ✔ if done box should always be completed to confirm DRC has been checked, regardless of whether the subject has experienced an exacerbation.

Protocol code

207499/181

Subject number

Adverse Event / Concomitant Medication / Exacerbation of COPD
Visit 7 (End of Double-blind Treatment Period)

Adverse Event / Concomitant Medication

Check the subject's Daily Record Card to determine whether they have experienced an adverse event.

Ask the following questions:

(a) "Have you had any (other) medical problems since your last visit/assessment?"

(b) "Have you taken any new medicines, other than those provided in this study, since your last visit/ assessment?"

Adverse events should be recorded in the appropriate ADVERSE EVENTS section(s).

Concomitant medications should be recorded in the CONCOMITANT MEDICATIONS section(s).

Confirm these adverse event and concomitant medication questions have been asked. ☐ ✔ *if done*

Exacerbation of COPD

Check the subject's Daily Record Card to determine whether they have experienced an exacerbation of COPD (according to the definition on the facing page).

Ask the following question:

Have you experienced an exacerbation of your COPD since the last visit?

If necessary, complete the COPD EXACERBATION section and if appropriate, the COPD CONCOMITANT MEDICATION section and ADVERSE EVENTS section in this Case Report Form.

Confirm this exacerbation question has been asked. ☐ ✔ *if done*

Protocol code

207499/181

Daily Record Card / Vital Signs / COPD Pulmonary Function Tests
Visit 7 (End of Double-blind Treatment Period)

Instructions to Investigator

Daily Record Card

- Check DRC for exacerbations.
- Transcribe any medications from the medication section into the appropriate *CONCOMITANT MEDICATION* section in this Case Report Form.
- Transcribe any Adverse Events that have been reported into the appropriate *ADVERSE EVENT* section of this CRF.
- Any changes, corrections or explanations that you have made regarding dates must be initialled and dated in the presence of the subject.

COPD Pulmonary Function Tests

It is preferable that for any individual subject at each study visit, the same pulmonologist, technician or nurse administers pulmonary function tests, in order to ensure consistency of technique.

Where possible, pulmonary function measurements should be performed at the same time of day under Body Temperature and Pressure Standard (BTPS) conditions, using the same spirometer at each visit. The subject should be in the same position (i.e. sitting or standing) at each visit.

- The highest of three technically acceptable SVC measurements should be recorded **before and after** inhalation of salbutamol.
- Record SVC to 2 decimal places.
- Lung function printouts must be labelled with the Subject Number, Visit Number, date and time of measurement and signed and dated by the person responsible for the data. All printouts should be kept in the subject's notes.

Vital Signs

- Salbutamol and/or ipratropium bromide must not be taken for 6 hours prior to vital signs being measured.

Monitor Data Validation Checks

Daily Record Card

- Check the Treatment Daily Record Card for the period between Visit 5 and Visit 6. Ensure that any adverse events and changes in medication reported in the Treatment Daily Record Card have been transcribed to the appropriate *ADVERSE EVENT*, *and CONCOMITANT MEDICATION* section(s) of the Case Report Form.
- If any corrections are made, the investigator must initial and date them.

Vital Signs

- Check that blood pressure values are within reasonable limits and systolic blood pressure is greater than diastolic blood pressure.
- Check that heart rate value is within reasonable limits for beats per minute.

COPD Pulmonary Function Tests

- Check that SVC has been rounded to 2 decimal places.
- Check that all spirometry printouts are signed and dated by the responsible person and clearly indicate the clinic visit, the date of the visit, the time of assessment and the GlaxoSmithKline Subject Number. The spirometry printouts must be stored in the subject's notes.

Protocol code	Session number	Subject number
207499/181	**7**	

Daily Record Card / Vital Signs / COPD Pulmonary Function Tests
Visit 7 (End of Double-blind Treatment Period)

Daily Record Card

Has the Daily Record Card been collected and reviewed? Yes ☐ Y No ☐ N

Vital Signs

*Vital signs must be measured at least **6 hours after** the subject's last salbutamol and/or ipratropium bromide administration after the subject has been sitting for 5 minutes.*

Date	Blood pressure mmHg		Heart rate	Temperature
day month year	systolic	diastolic	beats/min	°C
e.g., 06 JAN 02	***110***	***80***	***75***	***36.5***
				.

Record all clinically significant abnormalities in the appropriate ADVERSE EVENT section(s).

COPD Pulmonary Function Tests

Date of assessment ☐☐ ☐☐☐ ☐☐
day month year

*NOTE: Subjects must refrain from smoking for **2 hours** immediately before pulmonary function tests.*

Has the subject taken any salbutamol and/or ipratropium bromide in the last 6 hours? Yes ☐ Y No ☐ N

If YES, a 6 hour period should elapse before the pulmonary function tests are performed. Remind the subject to refrain from taking any for 6 hours before the next visit.

Test	Time of assessment pre-salbutamol 00:00-23:59	Actual measurement pre-salbutamol *(highest of 3 measurements)*	Time of assessment 30 minutes post-salbutamol 00:00-23:59	Actual measurement 30 minutes post-salbutamol *(highest of 3 measurements)*
e.g. SVC	***08:00***	***1.75***	***08:30***	***1.80***
SVC (L)	:	.	:	.

Protocol code	Session number	Subject number
207499/181	7	

Laboratory Tests / Faecal Occult Blood
Visit 7 (End of Double-blind Treatment Period)

Laboratory Tests

Take blood samples for hematology and blood chemistry and a urine sample for urinalysis.

Date sample taken ☐☐ ☐☐☐ ☐☐ (day / month / year)

Are there any **clinically significant abnormal** laboratory values? Yes ☐ Y No ☐ N

NOTE: All clinically significant abnormal laboratory findings are to be repeated until the values return to normal. Record all clinically significant abnormalities in the appropriate ADVERSE EVENT section.

Faecal Occult Blood

Three tests will be collected on consecutive bowel movements, (if possible). The tests are to be performed according to the instructions provided with the faecal occult blood kits. Faecal occult blood will also be tested in subjects who report gastrointestinal symptoms which are of concern to them or interfere with daily activities.

Sample	Date of collection day month year	Result	
		Positive (Pos)	Negative (Neg)
e.g., 1	***06 JAN 02***		✔
1			
2			
3			

NOTE: If the faecal occult blood test is positive, 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.

Record all clinically significant abnormalities in the appropriate ADVERSE EVENT section.

Has a faecal occult blood kit been issued for the sample analysis at Follow-up? Yes ☐ Y No ☐ N

Protocol code

207499/181

Sputum Induction
Visit 7 (End of Double-blind Treatment Period)

Instructions to Investigator

NOTE: ***Refer to the Sputum Procedures (SP) document prior to starting the sputum induction.***

NOTE: ***All subjects must have post bronchodilator spirometry prior to the sputum induction (within 60 minutes). If the FEV_1 after β_2 agonist is ≤0.8 L, or less than 40% predicted, DO NOT proceed with the test.***

- A doctor must be nearby during each procedure.
- Sputum induction must only be undertaken with trained medical personnel within easy access.
- The usual laboratory resuscitation apparatus plus nebulised salbutamol must be readily available.
- Collect and process sputum according to the methodology described in the Sputum Procedures (SP) document.
- Prior to commencing the induction it is essential that the procedure be explained in full to the subject.
- If at any time that the subject complains of chest discomfort or tightness, the test must be interrupted and the FEV_1 checked.
- All data generated during sputum processing must be recorded on the Sputum Processing Worksheet.
- All subjects that present with a fall in FEV_1 of > 5%, will receive VENTOLIN and must return to within 5% of best post VENTOLIN baseline before discharge.

Monitor Data Validation Checks

- If sputum sample was satisfactory, check that the Sputum Processing Worksheet has been completed.

Protocol code	Session number	Subject number
207499/181	**7**	

Sputum Induction
Visit 7 (End of Double-blind Treatment Period)

NOTE: ***If the subject's sputum sample at Visit 3 was unsatisfactory, no sputum sample is to be induced at Visit 7.***

Has a sample of induced sputum been collected at Visit 7? Yes ☐ Y No ☐ N

If Yes,

Date sample collected: ☐☐ ☐☐☐ ☐☐
day month year

Is the induced sputum sample satisfactory? Yes ☐ Y No ☐ N

If YES, complete the ***Sputum Processing Worksheet*** *and the* ***Slide Identification Tracking Form****.*

Protocol code

207499/181

Pregnancy Test
Visit 7 (End of Double-blind Treatment Period)

Monitor Data Validation Checks

Pregnancy Test

- If the Pregnancy Test question is ✔ as Not Applicable (Not of Childbearing Potential), check that this is consistent with the answer to the Childbearing Potential question.

Protocol code	Session number	Subject number
207499/181	**7**	

Pregnancy Test
Visit 7 (End of Double-blind Treatment Period)

Pregnancy Test

Pregnancy test result, ✔*one:*

Positive ☐ P

Negative ☐ N

Not applicable ☐ X (Not of childbearing potential or male subject)

Protocol code

207499/181

Investigator's Checklist
Visit 7 (End of Double-blind Treatment Period)

- Collect **all** used and unused study medication and bottles. Complete the *COMPLIANCE* section of this CRF.
- Record study medication stop date in the *INVESTIGATIONAL PRODUCT* section.
- Issue salbutamol and/or ipratropium bromide medication (if a*ppropriate)* for use as a relief medication on an 'as required' basis.
- Ensure any adverse events which have occurred, have been recorded in the *ADVERSE EVENTS* section(s) of the CRF.
- Ensure any changes or additions to the subjects concomitant medications has been recorded in the appropriate *CONCOMITANT MEDICATIONS* section(s) of the CRF.
- Ensure subject's use of salbutamol and/or ipratropium bromide is recorded in the *COPD CONCOMITANT MEDICATION* section of this CRF).
- Ensure any exacerbations have been recorded in the *COPD EXACERBATIONS* section of this CRF.
- Issue the FOB kit to the subject, to be collected at Follow-up.
- Ensure all Visit 7 sections have been completed.
- Make an appointment for the subject to return for Follow-up Visit 8 (Week +14), 98 (± 3) days from randomisation, at the same time of day.

Remind the subject of the following:

- To resume their normal COPD medication.
- To take their salbutamol and/or ipratropium bromide medication as prescribed and to contact the investigator if they experience symptoms that do not react adequately to salbutamol and/or ipratropium bromide.
- To refrain from using their salbutamol and/or ipratropium bromide medication for at least **6 hours** immediately before Visit 8.
- To refrain from smoking for **2 hours** immediately before Visit 8.
- To refrain from taking any COPD medication for at least **6 hours** immediately before Visit 8.
- To attend the clinic for Visit 8 at the same time of day (± 2 hours).

NOTE: Schedule a safety Follow-up visit for 1 week (±3 days) after study medication discontinuation.

Protocol code	Session number	Subject number
207499/181	8	

Visit Date / Smoking Status
Early Withdrawal Visit

*NOTE: These EARLY WITHDRAWAL VISIT assessments **must** be completed for **all** subjects who withdraw from the study at a scheduled visit or between scheduled clinic visits.*

Visit Date ☐☐ ☐☐☐ ☐☐
day month year

Record the date and time of the subject's last dose of salbutamol and/or ipratropium bromide medication immediately before Early Withdrawal Visit.

Date ☐☐ ☐☐☐ ☐☐
day month year

Time ☐☐ : ☐☐
00:00-23:59

Smoking Status

Does the subject currently smoke? Yes ☐ Y No ☐ N

If current smoker, record the average number of cigarettes smoked per day ☐☐☐

If the subject no longer smokes . . .

Date subject stopped smoking ☐☐ ☐☐☐ ☐☐
day month year

If the subject is a **current smoker**, has the subject smoked during the 2 hours before this Early Withdrawal Visit? Yes ☐ Y No ☐ N

Protocol code

207499/181

Adverse Event / Concomitant Medication / Exacerbation of COPD
Early Withdrawal Visit

Instructions to Investigator

Adverse Event

- Any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

  An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

Exacerbation of COPD

Definition of a COPD Exacerbation

For the purpose of this study COPD exacerbations are categorised as follows:

Mild

- Acute worsening of COPD that is self-managed by the subject at home by increasing usual COPD bronchodilators medications, and should not be taking any antibiotics (i.e. the subject does not see a doctor for this episode)

Moderate

- Acute worsening of COPD that requires additional treatment (e.g. a short course of oral steroids, antibiotics, etc.) prescribed by primary care physician or as a result of a hospital out-patient visit (including a visit to the Emergency Room)

Severe

- Acute worsening of COPD that requires the subject to be admitted to hospital for treatment

Monitor Data Validation Checks

Adverse Event / Concomitant Medication

- Check that any adverse events are recorded in the *ADVERSE EVENT* section and any changes/new medications are recorded in the *CONCOMITANT MEDICATION* section(s) of the Case Report Form.

  NOTE: "✔ if done" box should always be completed to confirm these questions have been asked, regardless of whether an adverse event has occurred or new medicine has been taken.

Exacerbation of COPD

- If the subject has experienced an exacerbation since their last visit, check that the *COPD EXACERBATION and if appropriate, the COPD CONCOMITANT MEDICATION and the ADVERSE EVENT* section(s) have been completed.

  NOTE: ✔ if done box should always be completed to confirm DRC has been checked, regardless of whether the subject has experienced an exacerbation.

Protocol code

207499/181

Subject number

Adverse Event / Concomitant Medication / Exacerbation of COPD
Early Withdrawal Visit

Adverse Event / Concomitant Medication

Check the subject's Daily Record Card to determine whether they have experienced an adverse event.

Ask the following questions:

(a) "Have you had any (other) medical problems since your last visit/assessment?"

(b) "Have you taken any new medicines, other than those provided in this study, since your last visit/ assessment?"

Adverse events should be recorded in the appropriate ADVERSE EVENTS section(s).

Concomitant medications should be recorded on the CONCOMITANT MEDICATIONS section(s).

Confirm these adverse event and concomitant medication questions have been asked. ☐ ✔ *if done*

Exacerbation of COPD

Check the subject's Daily Record Card to determine whether they have experienced an exacerbation of COPD (according to the definition on the facing page).

Ask the following question:

Have you experienced an exacerbation of your COPD since the last visit?

If necessary, complete the COPD EXACERBATION section and if appropriate, the COPD CONCOMITANT MEDICATION section and ADVERSE EVENTS section(s) in this Case Report Form.

Confirm this exacerbation question has been asked. ☐ ✔ *if done*

Protocol code

207499/181

Daily Record Card / Vital Signs / COPD Pulmonary Function Tests
Early Withdrawal Visit

Instructions to Investigator

Daily Record Card

- Check DRC for exacerbations.
- Transcribe any medications from the medication section into the appropriate *CONCOMITANT MEDICATION* section in this Case Report Form.
- Transcribe any Adverse Events that have been reported into the appropriate *ADVERSE EVENT* section(s) of this CRF.
- Any changes, corrections or explanations that you have made regarding dates must be initialled and dated in the presence of the subject.

COPD Pulmonary Function Tests

It is preferable that for any individual subject at each study visit, the same pulmonologist, technician or nurse administers pulmonary function tests, in order to ensure consistency of technique.

Where possible, pulmonary function measurements should be performed at the same time of day under Body Temperature and Pressure Standard (BTPS) conditions, using the same spirometer at each visit. The subject should be in the same position (i.e. sitting or standing) at each visit.

- The highest of three technically acceptable SVC measurements should be recorded **before and after** inhalation of salbutamol.
- Record SVC to 2 decimal places.
- Lung function printouts must be labelled with the Subject Number, Visit Number, date and time of measurement and signed and dated by the person responsible for the data. All printouts should be kept in the subject's notes.

Vital Signs

- Salbutamol and/or ipratropium bromide must not be taken for 6 hours prior to vital signs being measured.

Monitor Data Validation Checks

Daily Record Card

- Check the Treatment Daily Record Card for the period between Visit 5 and Visit 6. Ensure that any adverse events and changes in medication reported in the Treatment Daily Record Card have been transcribed to the appropriate *ADVERSE EVENT*, *and CONCOMITANT MEDICATION* section(s) of the Case Report Form.
- If any corrections are made, the investigator must initial and date them.

Vital Signs

- Check that blood pressure values are within reasonable limits and systolic blood pressure is greater than diastolic blood pressure.
- Check that heart rate value is within reasonable limits for beats per minute.

COPD Pulmonary Function Tests

- Check that SVC has been rounded to 2 decimal places.
- Check that all spirometry printouts are signed and dated by the responsible person and clearly indicate the clinic visit, the date of the visit, the time of assessment and the GlaxoSmithKline Subject Number. The spirometry printouts must be stored in the subject's notes.

Protocol code	Session number	Subject number
207499/181	8	

Daily Record Card / Vital Signs / COPD Pulmonary Function Tests
Early Withdrawal Visit

Daily Record Card

Has the Daily Record Card been collected and reviewed? Yes ☐ Y No ☐ N

Vital Signs

*Vital signs must be measured at least **6 hours after** the subject's last salbutamol and/or ipratropium bromide administration after the subject has been sitting for 5 minutes.*

Date	Blood pressure mmHg		Heart rate	Temperature
day month year	systolic	diastolic	beats/min	°C
e.g., 06 JAN 02	***110***	***80***	***75***	***36.5***
				.

Record all clinically significant abnormalities in the appropriate ADVERSE EVENT section(s).

COPD Pulmonary Function Tests

Date of assessment ☐☐ ☐☐☐ ☐☐
day month year

*NOTE: Subjects must refrain from smoking for **2 hours** immediately before pulmonary function tests.*

Has the subject taken any salbutamol and/or ipratropium bromide in the last 6 hours? Yes ☐ Y No ☐ N

If YES, a 6 hour period should elapse before the pulmonary function tests are performed. Remind the subject to refrain from taking any for 6 hours before the next visit.

Test	Time of assessment pre-salbutamol 00:00-23:59	Actual measurement pre-salbutamol *(highest of 3 measurements)*	Time of assessment 30 minutes post-salbutamol 00:00-23:59	Actual measurement 30 minutes post-salbutamol *(highest of 3 measurements)*
e.g. SVC	***08:00***	***1.75***	***08:30***	***1.80***
SVC (L)	:	.	:	.

Protocol code	Session number	Subject number
207499/181	8	

Laboratory Tests / Faecal Occult Blood
Early Withdrawal Visit

Laboratory Tests

Take blood samples for hematology and blood chemistry and a urine sample for urinalysis.

Date sample taken ☐☐ ☐☐☐ ☐☐ (day / month / year)

Are there any **clinically significant abnormal** laboratory values? Yes ☐ Y No ☐ N

NOTE: All clinically significant abnormal laboratory findings are to be repeated until the values return to normal. Record all clinically significant abnormalities in the appropriate ADVERSE EVENT section.

Faecal Occult Blood

Three tests will be collected on consecutive bowel movements, (if possible). The tests are to be performed according to the instructions provided with the faecal occult blood kits. Faecal occult blood will also be tested in subjects who report gastrointestinal symptoms which are of concern to them or interfere with daily activities.

Sample	Date of collection day month year	Result	
		Positive (Pos)	Negative (Neg)
e.g., 1	***06 JAN 02***		✔
1			
2			
3			

NOTE: If the faecal occult blood test is positive, 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.

Record all clinically significant abnormalities in the appropriate ADVERSE EVENT section.

Has a faecal occult blood kit been issued for the sample analysis at Follow-up? Yes ☐ Y No ☐ N

Protocol code

207499/181

Subject number

Pre Bronchial Biopsy Checklist
Early Withdrawal Visit

NOTE: ***The biopsy at this visit should be performed ONLY if the subject is withdrawing at Visit 4 or Visit 5. The biopsy should be performed 1 week AFTER the Withdrawal visit, providing all the safety criteria below and in the Bronchial Biopsy Procedures document are met.***

Has the subject consumed any food or drink since midnight? Yes ☐ No ☐

Has the subject used asprin or NSAIDS in the 5 days preceding the biopsy? Yes ☐ No ☐

If either of the above is answered YES, the subject is unsuitable for the bronchoscopy.

The subject must meet the following safety criteria on the scheduled day of the biopsy procedure:

	Criteria met? Yes	No
Pre-salbutamol FEV_1 40-80% predicted normal value.	☐	☐
No history of bleeding diathesis. Normal blood clotting parameters.	☐	☐
Ability to be collected by a friend/relative at the end of the biopsy procedure	☐	☐

NOTE: ***If any of the safety criteria questions are answered NO, the subject is unsuitable for the bronchoscopy.***

Protocol code

207499/181

Bronchial Biopsy
Early Withdrawal Visit

Instructions to Investigator

NOTE: Refer to the Bronchial Biopsy Procedure (BBP) document prior to starting the biopsy.

- The subject must meet specific safety criteria on the day of the bronchoscopy, before the procedure can proceed.
- A **Biopsy Safety Form must** be completed and stored in the subject's notes prior to performing the bronchoscopy.
- The procedure should be performed using the methodology described in the Bronchial Biopsy Procedure (BBP).
- Bronchoscopies should be performed using an Olympus BF fibreoptic bronchoscope (type IT40, 2.8 mm channel or similar) or equivalent. Use of any other type of bronchoscope must be pre-agreed with GSK.
- Cup forceps [FB-35C-1, 2.8 mm (fenestrated forceps)] or equivalent should be used for all subjects and each set should be replaced after every 5-biopsy occasions. Use of any other type of forceps must be pre-agreed with GSK.
- Six biopsies of adequate size (2mm) should be performed on the right side beginning at the subcarinae in the right lower lobe (2 biopsies), then the right middle lobe (2 biopsies) and finally the right upper lobe (2 biopsies).
- Report any serious complications relating to the bronchoscopy, e.g. severe bleeding or pneumothorax, to the study monitor as soon as possible (within 24 hours).
- The **Biopsy Sample Worksheet** and the **Processing of Biopsy Sample Worksheet** must be sent with the samples via QUEST to Dr Q. Hamid's laboratory.

Protocol code	Session number	Subject number
207499/181	**8**	

Bronchial Biopsy
Early Withdrawal Visit

NOTE: ***The biopsy at this visit should be performed ONLY if the subject is withdrawing at Visit 4 or Visit 5. The biopsy should be performed 1 week AFTER the Withdrawal visit, providing all the safety criteria below and in the Bronchial Biopsy Procedures document are met.***

Confirm all safety criteria have been met. ☐ ✔ *if met*

Complete a Biopsy Safety Form prior to the biopsy.

Date of biopsy ☐☐ ☐☐☐ ☐☐ (day / month / year) Time of biopsy ☐☐ : ☐☐ (00:00-23:59)

Record below, all medication administered at the time of the bronchoscopy:

Drug name	Medication administered		Time administered 00:00-23:59
	Yes (Y)	No (N)	
e.g., Atropine	✔		***10:30***
Atropine			:
Midazolam			:
Salbutamol			:
Intravenous flumazenil			:
Topical lignocaine			:
Lignocaine gel			:

Record number of mucosal biopsies taken.

Biopsy site	Number of biopsies taken	Biopsy lung ✔ *one*	
		Left	Right
Lower lobe (Level A)			
Middle lobe (Level B)			
Upper lobe (Level C)			

Protocol code

207499/181

Sputum Induction
Early Withdrawal Visit

Instructions to Investigator

NOTE: If possible, the sputum induction should be performed 7 days AFTER the Withdrawal biopsy procedure.

NOTE: Refer to the Sputum Procedures (SP) document prior to starting the sputum induction.

- A doctor must be nearby during each procedure.
- Sputum induction must only be undertaken with trained medical personnel within easy access.
- The usual laboratory resuscitation apparatus plus nebulised salbutamol must be readily available.
- Collect and process sputum according to the methodology described in the Sputum Procedures (SP) document.
- Prior to commencing the induction it is essential that the procedure be explained in full to the subject.
- If at any time that the subject complains of chest discomfort or tightness, the test must be interrupted and the FEV_1 checked.
- All data generated during sputum processing must be recorded on the Sputum Processing Worksheet.
- All subjects that present with a fall in FEV_1 of > 5%, will receive VENTOLIN and must return to within 5% of best post VENTOLIN baseline before discharge.

Monitor Data Validation Checks

- If sputum sample was satisfactory, check that the Sputum Processing Worksheet has been completed.

Protocol code	Session number	Subject number
207499/181	**8**	

Sputum Induction
Early Withdrawal Visit

NOTE: ***If possible, the sputum induction should be performed 7 days AFTER the Withdrawal biopsy procedure. If the subject's sputum sample at Visit 3 was unsatisfactory, no sputum sample is to be induced at this visit.***

Has a sample of induced sputum been collected? Yes ☐ Y No ☐ N

If Yes,

Date sample collected: ☐☐ ☐☐☐ ☐☐
day month year

Is the induced sputum sample satisfactory? Yes ☐ Y No ☐ N

If YES, ***complete the Sputum Processing Worksheet*** *and the* ***Slide Identification Tracking Form****.*

Protocol code

207499/181

Pregnancy Test
Early Withdrawal Visit

Monitor Data Validation Checks

Pregnancy Test

- If the Pregnancy Test question is ✔ as Not Applicable (Not of Childbearing Potential), check that this is consistent with the answer to the Childbearing Potential question.

Protocol code	Session number	Subject number
207499/181	**8**	

Pregnancy Test
Early Withdrawal Visit

Pregnancy Test

Pregnancy test result, ✔*one:*

Positive ☐ P

Negative ☐ N

Not applicable ☐ X (Not of childbearing potential or male subject)

Protocol code

207499/181

Investigator's Checklist
Early Withdrawal Visit

- Collect **all** used and unused study medication and bottles. Complete the *COMPLIANCE* section of this CRF.
- Collect all study medication and rescue medication.
- Complete drug accountability records.
- Record study medication stop date in the *INVESTIGATIONAL PRODUCT* section.
- Ensure any adverse events which have occurred, have been recorded in the *ADVERSE EVENTS* section(s) of the CRF.
- Ensure any changes or additions to the subjects concomitant medications has been recorded in the appropriate *CONCOMITANT MEDICATIONS* section(s) of the CRF.
- Ensure subject's use of ipratropium bromide is recorded in the *COPD CONCOMITANT MEDICATION* section of this CRF).
- Ensure any exacerbations have been recorded in the *COPD EXACERBATIONS* section of this CRF.
- Ensure the *UNSCHEDULED/EMERGENCY VISITS* section has been completed (*if applicable*).
- Perform a physical examination if abnormalities were present at previous visit.
- Schedule an appointment for the subject to return1 week after withdrawal visit, for a bronchial biopsy.
- Schedule an appointment for the subject to return for a sputum induction, **7 days** after the biopsy procedure.
- Issue the FOB kit to the subject, to be collected at Follow-up.
- Ensure all *EARLY WITHDRAWAL VISIT* sections have been completed.
- Call RAMOS, specify the subject number and log the subject as withdrawn.
- Schedule an appointment for the subject to return 7 (± 3) days after discontinuation of study medication, for Visit 8 Follow-up.

Remind the subject of the following:

- To resume their normal COPD medication.
- To take their salbutamol and/or ipratropium bromide medication as prescribed and to contact the investigator if they experience symptoms that do not react adequately to salbutamol and/or ipratropium bromide.
- To refrain from using their salbutamol and/or ipratropium bromide medication for at least **6 hours** immediately before Visit 8.
- To refrain from smoking for **2 hours** immediately before Visit 8.
- To refrain from taking any other COPD medication for at least **6 hours** immediately before Visit 8.
- To attend the clinic for Visit 8 at the same time of day (± 2 hours).

NOTE: Schedule a safety Follow-up visit for 1 week (±3 days) after study medication discontinuation.

Protocol code	Session number	Subject number
207499/181	9	

Visit Date
Visit 8 (Follow-up)

Visit Date [ ][ ] [ ][ ][ ] [ ][ ]
day month year

Record the date and time of the subject's last dose of salbutamol and/or ipratropium bromide medication immediately before Visit 8.

Date [ ][ ] [ ][ ][ ] [ ][ ] Time [ ][] : [ ][ ]
day month year 00:00-23:59

Record the date and time of the subject's last dose of normal COPD medication immediately before Visit 8.

Date [ ][ ] [ ][ ][ ] [ ][ ] Time [ ][ ] : [ ][ ]
day month year 00:00-23:59

Protocol code

207499/181

Adverse Event / Concomitant Medication / Exacerbation of COPD
Visit 8 (Follow-up)

Instructions to Investigator

Adverse Event

- Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
  An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.

Exacerbation of COPD

Definition of a COPD Exacerbation

For the purpose of this study COPD exacerbations are categorised as follows:

Mild

- Acute worsening of COPD that is self-managed by the subject at home by increasing usual COPD bronchodilators medications, and should not be taking any antibiotics (i.e. the subject does not see a doctor for this episode)

Moderate

- Acute worsening of COPD that requires additional treatment (e.g. a short course of oral steroids, antibiotics, etc.) prescribed by primary care physician or as a result of a hospital out-patient visit (including a visit to the Emergency Room)

Severe

- Acute worsening of COPD that requires the subject to be admitted to hospital for treatment

Monitor Data Validation Checks

Adverse Event / Concomitant Medication

- Check that any adverse events are recorded in the *ADVERSE EVENT* section and any changes/new medications are recorded in the *CONCOMITANT MEDICATION* section(s) of the Case Report Form.

NOTE: ✔ if done box should always be completed to confirm these questions have been asked, regardless of whether an adverse event has occurred or new medicine has been taken.

Exacerbation of COPD

- If the subject has experienced an exacerbation since their last visit, check that the *COPD EXACERBATION and if appropriate, the COPD CONCOMITANT MEDICATION and the ADVERSE EVENT* section(s) have been completed.

NOTE: ✔ if done box should always be completed to confirm DRC has been checked, regardless of whether the subject has experienced an exacerbation.

Protocol code

207499/181

Subject number

Adverse Event / Concomitant Medication / Exacerbation of COPD
Visit 8 (Follow-up)

Adverse Event / Concomitant Medication

Ask the following questions:

(a) "Have you had any (other) medical problems since your last visit?"

(b) "Have you taken any new medicines, other than those provided in this study, since your last visit?"

Adverse events should be recorded in the appropriate ADVERSE EVENTS section(s).

Concomitant medications should be recorded in the CONCOMITANT MEDICATIONS section(s).

Confirm these adverse event and concomitant medication questions have been asked. ☐ ✔ *if done*

Exacerbation of COPD

Ask the following question:

Have you experienced an exacerbation of your COPD since the last visit?

If necessary, complete the COPD EXACERBATION section and if appropriate, the COPD CONCOMITANT MEDICATION section and ADVERSE EVENTS section in this Case Report Form.

Confirm this exacerbation question has been asked. ☐ ✔ *if done*

Protocol code

207499/181

Subject number

Physical Examination Worksheet
Visit 8 (Follow-up)

Indicate current physical findings by ✔ the appropriate box(es) below and if ABNORMAL, describe concisely: [different findings should be separated by either a (;) or a (/)].

	Not Done	Normal	Abnormal	*If Abnormal, specify:*
1. Hair and Skin		☐	☐	. . . . .
2. Lymph nodes		☐	☐	. . . . .
3. Eyes		☐	☐	. . . . .
4. Ears, Nose and Throat		☐	☐	. . . . .
5. Breasts	☐	☐	☐	. . . . .
6. Respiratory		☐	☐	. . . . .
7. Cardiovascular		☐	☐	. . . . .
8. Abdomen		☐	☐	. . . . .
9. Urogenital	☐	☐	☐	. . . . .
10. Pelvic	☐	☐	☐	. . . . .
11. Rectal	☐	☐	☐	. . . . .
12. Musculoskeletal		☐	☐	. . . . .
13. Neurological		☐	☐	. . . . .
14. Mental Status		☐	☐	. . . . .

Were any abnormalities present at the previous physical examination? Yes ☐ No ☐

Has there been a clinically significant worsening since the last assessment in the subject's physical condition? Yes ☐ No ☐

If YES, record in the appropriate ADVERSE EVENT section.

Protocol code

207499/181

Vital Signs / COPD Pulmonary Function Tests
Visit 8 (Follow-up)

Instructions to Investigator

COPD Pulmonary Function Tests

It is preferable that for any individual subject at each study visit, the same pulmonologist, technician or nurse administers pulmonary function tests, in order to ensure consistency of technique.

Where possible, pulmonary function measurements should be performed at the same time of day under Body Temperature and Pressure Standard (BTPS) conditions, using the same spirometer at each visit. The subject should be in the same position (i.e. sitting or standing) at each visit.

- The highest of three technically acceptable SVC measurements should be recorded **before and after** inhalation of salbutamol.
- Record SVC to 2 decimal places.
- Lung function printouts must be labelled with the Subject Number, Visit Number, date and time of measurement and signed and dated by the person responsible for the data. All printouts should be kept in the subject's notes.

Vital Signs

- Salbutamol and/or ipratropium bromide must not be taken for 6 hours prior to vital signs being measured.

Monitor Data Validation Checks

Vital Signs

- Check that blood pressure values are within reasonable limits and systolic blood pressure is greater than diastolic blood pressure.
- Check that heart rate value is within reasonable limits for beats per minute.

COPD Pulmonary Function Tests

- Check that SVC has been rounded to 2 decimal places.
- Check that all spirometry printouts are signed and dated by the responsible person and clearly indicate the clinic visit, the date of the visit, the time of assessment and the GlaxoSmithKline Subject Number. The spirometry printouts must be stored in the subject's notes.

Protocol code	Session number	Subject number
207499/181	9	

Vital Signs / COPD Pulmonary Function Tests
Visit 8 (Follow-up)

Vital Signs

*NOTE: Vital signs must be measured at least **6 hours after** the subject's last salbutamol and/or ipratropium bromide administration after the subject has been sitting for 5 minutes.*

Date	Blood pressure mmHg		Heart rate	Temperature
day month year	systolic	diastolic	beats/min	°C
e.g., 06 JAN 02	***110***	***80***	***75***	***36.5***
				.

Record all clinically significant abnormalities in the appropriate ADVERSE EVENT section(s).

COPD Pulmonary Function Tests

Date of assessment ☐☐ ☐☐☐ ☐☐ (day / month / year)

*NOTE: Subjects must refrain from smoking for **2 hours** immediately before pulmonary function tests.*

Has the subject taken any salbutamol and/or ipratropium bromide in the last 6 hours? Yes ☐ Y No ☐ N

If YES, a 6 hour period should elapse before the pulmonary function tests are performed.

Test	Time of assessment pre-salbutamol 00:00-23:59	Actual measurement pre-salbutamol *(highest of 3 measurements)*	Time of assessment 30 minutes post-salbutamol 00:00-23:59	Actual measurement 30 minutes post-salbutamol *(highest of 3 measurements)*
e.g. SVC	***08:00***	***1.75***	***08:30***	***1.80***
SVC (L)	:	.	:	.

Protocol code	Session number	Subject number
207499/181	**9**	

Laboratory Tests / Faecal Occult Blood
Visit 8 (Follow-up)

Laboratory Tests - ***To be completed only if abnormal at Visit 7 or Early Withdrawal Visit***

Take blood samples for hematology and blood chemistry and a urine sample for urinalysis.

Date sample taken [ ][ ] [ ][ ][ ] [ ][ ]
day month year

Are there any **clinically significant abnormal** laboratory values? Yes [ ] Y No [ ] N

NOTE: All clinically significant abnormal laboratory findings are to be repeated until the values return to normal. Record all clinically significant abnormalities in the appropriate ADVERSE EVENT section.

Faecal Occult Blood - ***To be completed only if abnormal at Visit 7 or Early Withdrawal Visit***

Three tests will be collected on consecutive bowel movements, (if possible). The tests are to be performed according to the instructions provided with the faecal occult blood kits. Faecal occult blood will also be tested in subjects who report gastrointestinal symptoms which are of concern to them or interfere with daily activities.

Sample	Date of collection day month year	Result	
		Positive (Pos)	Negative (Neg)
e.g., 1	***06 JAN 02***		✔
1			
2			
3			

NOTE: If the faecal occult blood test is positive, 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.

Record all clinically significant abnormalities in the appropriate ADVERSE EVENT section.

Protocol code

207499/181

Investigator's Checklist
Visit 8 (Follow-up)

- Record date of subject completion in the *END OF STUDY RECORD* section.
- Ensure all appropriate Visit 8 sections have been completed.
- Ensure any exacerbations which have occurred, have been recorded in the *COPD EXACERBATION* section of the CRF.
- Ensure any adverse events which have occurred, have been recorded in the *ADVERSE EVENTS* section(s) of the CRF.
- Ensure any changes or additions to the subjects concomitant medications has been recorded in the *CONCOMITANT MEDICATIONS* section(s) of the CRF.
- Call RAMOS, specify the subject number and record Follow-up visit.

Protocol code	Session number	Subject number
207499/181		

Unscheduled/Repeat Laboratory Tests

Laboratory Tests

Visit Number (or last scheduled visit number): ☐☐

Date sample taken ☐☐ ☐☐☐ ☐☐
day month year

Take blood samples for hematology and blood chemistry and a urine sample for urinalysis.

Are there any **clinically significant abnormal** laboratory values? Yes ☐ Y No ☐ N

If YES, all clinically significant abnormal laboratory findings are to be repeated until the values return to normal. If such values do not return to normal within a period judged reasonable by the Investigator, the aetiology should be identified and GSK notified.

Clinically significant worsenings must be recorded in the ADVERSE EVENTS section of the CRF.

Protocol code	Session number	Subject number
207499/181		

Unscheduled/Repeat Laboratory Tests

Laboratory Tests

Visit Number (or last scheduled visit number): ☐☐

Date sample taken ☐☐ ☐☐☐ ☐☐
day month year

Take blood samples for hematology and blood chemistry and a urine sample for urinalysis.

Are there any **clinically significant abnormal** laboratory values? Yes ☐ Y No ☐ N

If YES, all clinically significant abnormal laboratory findings are to be repeated until the values return to normal. If such values do not return to normal within a period judged reasonable by the Investigator, the aetiology should be identified and GSK notified.

Clinically significant worsenings must be recorded in the ADVERSE EVENTS section of the CRF.

Protocol code	Session number	Subject number
207499/181		

Unscheduled/Repeat Faecal Occult Blood

Faecal Occult Blood

Visit Number (or last scheduled visit number): ☐☐

Three tests will be collected on consecutive bowel movements, (if possible). The tests are to be performed according to the instructions provided with the faecal occult blood kits. Faecal occult blood will also be tested in subjects who report gastrointestinal symptoms which are of concern to them or interfere with daily activities.

Sample	Date of collection day month year	Result	
		Positive (Pos)	Negative (Neg)
e.g., 1	***06 JAN 02***		✔
1			
2			
3			

NOTE: If the faecal occult blood test is positive, the subject should be followed-up by the primary care physician or referred to a gastroenterologist as appropriate.

Record all clinically significant abnormalities in the appropriate ADVERSE EVENT section(s).

Protocol code	Session number	Subject number
207499/181		

Unscheduled/Repeat Faecal Occult Blood

Faecal Occult Blood

Visit Number (or last scheduled visit number): ☐☐

Three tests will be collected on consecutive bowel movements, (if possible). The tests are to be performed according to the instructions provided with the faecal occult blood kits. Faecal occult blood will also be tested in subjects who report gastrointestinal symptoms which are of concern to them or interfere with daily activities.

Sample	Date of collection day month year	Result	
		Positive (Pos)	Negative (Neg)
e.g., 1	***06 JAN 02***		✔
1			
2			
3			

NOTE: If the faecal occult blood test is positive, the subject should be followed-up by the primary care physician or referred to a gastroenterologist as appropriate.

Record all clinically significant abnormalities in the appropriate ADVERSE EVENT section(s).

Protocol code

207499/181

Investigational Product

Monitor Data Validation Checks

- Check that start and stop dates are recorded and that start date is before, or the same as, stop date.
- Check that investigational product start occurs on or after the date of Visit 3.
- If "Were there any significant (or study-specific definition) changes to investigational product?" is ✔YES, check that a concise text entry is present on the line provided.

Protocol code	Session number	Subject number
207499/181	**0**	

Investigational Product

	Start date day month year	Stop date day month year
	e.g., 06 JAN 02	***27 JAN 03***
Run-in Single-blind medication		
Treatment period Double-blind medication		

Were there any significant changes to investigational product? Yes ☐ Y No ☐ N

If YES, specify investigational product changes, dates, and reasons, ...

. . . . . .

. . . . . .

Protocol code

207499/181

Status of Treatment Blind

Instructions to Investigator

- Check whether the treatment blind was broken during the study.
- If YES, provide the date the blind was broken and the reason the blind was broken.

Monitor Data Validation Checks

- Check that either the YES or NO box at the top of the page is answered.
- If YES is ✔, check that a date and reason are present and that the appropriate *NON-SERIOUS ADVERSE EVENT, SERIOUS ADVERSE EVENT* and *END OF STUDY RECORD* sections are completed.
- Check that only one reason is given.
- If the reason for breaking the blind is ✔ “Other”, check that a concise text entry is present in the space provided.

Protocol code	Session number	Subject number
207499/181	**0**	

Status of Treatment Blind

Was the treatment blind for this subject broken during the study? Yes ☐ Y No ☐ N

If YES, complete the following:

Date ☐☐ ☐☐☐ ☐☐
day month year

Reason, ✔*one:*

Medical emergency requiring identity of investigational product for further treatment ☐ E

Other ☐ X *specify*, ...

Complete NON-SERIOUS ADVERSE EVENT, SERIOUS ADVERSE EVENT, and/or INVESTIGATIONAL PRODUCT sections as appropriate.

Compliance

Instructions to Investigator

- Between Visit 4 - Visit 5 and at Visit 5 - Visit 6, the subject **must show ≥ 80% and ≤120%compliance in taking their study medication**. Subjects who do not meet this criterion must be **withdrawn** from the study.
- Record the number of tablets returned/dispensed to the subject at each visit.

Compliance calculation

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

Monitor Data Validation Checks

- Check that the compliance section has been completed appropriately.

Protocol code	Session number	Subject number
207499/181	**0**	

Compliance

The number of remaining doses from each single and double-blinded treatment bottle prescribed to the subject, must be counted and entered in the table below.

Run-in	Single-blind medication					
	Number of tablets dispensed	Number of tablets returned	Number of tablets lost	Number of tablets taken	Days since last visit	% Compliance
e.g., Visit 1	***70***	***28***	***2***	***40***	***21***	***95***
Run-in Period (Visit 1 - Visit 2)	**70**					
Run-in Period (Visit 2 - Visit 2A) *if applicable*						
Run-in Period (Visit 2/2A - Visit 3)						

Treatment Period	Double-blind medication					
	Number of tablets dispensed	Number of tablets returned	Number of tablets lost	Number of tablets taken	Days since last visit	% Compliance
e.g., Visit 3-4	***245***	***189***	***0***	***56***	***28***	***100***
Treatment Period (Visit 3 - Visit 4)						
Treatment Period (Visit 4 - Visit 5)						
Treatment Period (Visit 5 - Visit 6)						
Treatment Period (Visit 6 - Visit 6A) *if applicable*						
Treatment Period (Visit 6/6A - V7)						
Early Withdrawal Visit						

Protocol code

207499/181

Unscheduled / Emergency Visits

Instructions to Investigator

If the unscheduled visit / contact is due to an **adverse event**, complete the *ADVERSE EVENT* form.
If study medication is withdrawn at the unscheduled visit, complete the *EARLY WITHDRAWAL* section and make an appointment for the subject to return for a follow-up visit in 7 (±3) days.

Monitor's Data Validation Checks

- Check either the YES or NO box has been ✔.
- If the *YES* box has been ✔, ensure that at least one unscheduled visit has been recorded.
- Check that data is within the time period of subject's participation in the study.
- Check that type of contact has been recorded as either V or P.
- Check that reason for contact is in precise and legible text.
- If subject withdrawn is answered 'Y', check that the *EARLY WITHDRAWAL VISIT* has been completed.

Protocol code	Session number	Subject number
207499/181	**0**	

Unscheduled / Emergency Visits

Did the subject make any unscheduled emergency visits or contacts during the study? Yes ☐ Y No ☐ N

If YES, indicate below.

*This page should be completed each time the subject makes an **UNSCHEDULED / EMERGENCY VISIT** or **TELEPHONE CONTACT.***

*Ensure that any **ADVERSE EVENTS**, **COPD MEDICATIONS** and/or changes in **CONCOMITANT MEDICATIONS** are also documented on the appropriate sections of the CRF.*
*If the subject is withdrawn, complete **EARLY WITHDRAWAL** and **END OF STUDY RECORD** sections, and make an appointment for the subject to return for a follow-up visit in 7 (±3) days time.*

	Date day month year	Type of Contact V = Visit P = Telephone	Reason for Contact	Subject Withdrawn? Y =Yes N =No
1.				
2.				
3.				
4.				
5.				
6.				
7.				
8.				

NOTE: If the subject returns study medication at an unscheduled / emergency visit, complete the COMPLIANCE section in the Case Report Form.

COPD Exacerbations

Instructions to Investigator

NOTE: *Subjects who experience a **severe exacerbation** during the Treatment period will be **withdrawn** from the study. Subjects who experience a **moderate exacerbation requiring the use of oral corticosteroids** will also be **withdrawn** from the study.*
*However, if subjects experience **one moderate exacerbation** requiring the use of antibiotics, they would be allowed to continue. Subjects experiencing **more than one moderate exacerbation** requiring the use of antibiotics will be withdrawn from the study.*

Definition of a COPD Exacerbation

For the purpose of this study a COPD exacerbation will be defined as follows:

Mild

- Acute worsening of COPD that is self-managed by the subject at home by increasing usual COPD bronchodilators medications, and should not be taking any antibiotics (i.e. the subject does not see a doctor for this episode)

Moderate

- Acute worsening of COPD that requires additional treatment (e.g. a short course of oral steroids, antibiotics, etc.) prescribed by primary care physician or as a result of a hospital out-patient visit (including a visit to the Emergency Room)

Severe

- Acute worsening of COPD that requires the subject to be admitted to hospital for treatment

Monitor Data Validation Checks

- Check that Yes/No question is completed.
- Ensure that Date of onset is a complete date.
- Ensure outcome is completed, and is a valid value. If 'F' (fatal), check that a corresponding *SERIOUS ADVERSE EVENT* section is completed.
- Ensure that Date of resolution or death is complete, if Outcome is resolved or fatal.
- Check that severity result is present and within the protocol specifications.
- Check that response to "Was the subject withdrawn due to this exacerbation?" corresponds to End of Study Record reason for withdrawal.
- Check that the question "Was the exacerbation an SAE?" is answered Y or N. If Y, check that a corresponding serious adverse event is recorded in the *SERIOUS ADVERSE EVENT* section.

Protocol code	Session number	Subject number
207499/181	0	

COPD Exacerbations

Were there any COPD exacerbations during the study? Yes ☐ Y No ☐ N *If YES, record below:*

Date of onset day month year	Outcome R = Resolved F = Fatal N = Not resolved	Date of resolution or death day month year	Severity 1 = Mild 2 = Moderate 3 = Severe	Was the subject withdrawn due to this exacerbation? Y = Yes N = No	Was the exacerbation treated with oral corticosteroids? Y = Yes N = No	Was the exacerbation treated with antibiotics? Y = Yes N = No	Was the exacerbation an SAE? Y = Yes N = No
e.g. ***21 MAY 01***	***R***	***29 MAY 01***	***3***	***Y***	***N***	***Y***	
1.							
2.							
3.							
4.							
5.							
6.							
7.							
8.							
9.							

Enter details in the CONCOMITANT MEDICATION, the SERIOUS ADVERSE EVENT section and the END OF STUDY RECORD section if applicable.

continued...

COPD Exacerbations

Instructions to Investigator

NOTE: *Subjects who experience a **severe exacerbation** during the Treatment period will be **withdrawn** from the study. Subjects who experience a **moderate exacerbation requiring the use of oral corticosteroids** will also be **withdrawn** from the study.*
*However, if subjects experience **one moderate exacerbation** requiring the use of antibiotics, they would be allowed to continue. Subjects experiencing **more than one moderate exacerbation** requiring the use of antibiotics will be withdrawn from the study.*

Definition of a COPD Exacerbation

For the purpose of this study a COPD exacerbation will be defined as follows:

Mild

- Acute worsening of COPD that is self-managed by the subject at home by increasing usual COPD bronchodilators medications, and should not be taking any antibiotics (i.e. the subject does not see a doctor for this episode)

Moderate

- Acute worsening of COPD that requires additional treatment (e.g. a short course of oral steroids, antibiotics, etc.) prescribed by primary care physician or as a result of a hospital out-patient visit (including a visit to the Emergency Room)

Severe

- Acute worsening of COPD that requires the subject to be admitted to hospital for treatment

Monitor Data Validation Checks

- Check that Yes/No question is completed.
- Ensure that Date of onset is a complete date.
- Ensure outcome is completed, and is a valid value. If 'F' (fatal), check that a corresponding *SERIOUS ADVERSE EVENT* section is completed.
- Ensure that Date of resolution or death is complete, if Outcome is resolved or fatal.
- Check that severity result is present and within the protocol specifications.
- Check that response to "Was the subject withdrawn due to this exacerbation?" corresponds to End of Study Record reason for withdrawal.
- Check that the question "Was the exacerbation an SAE?" is answered Y or N. If Y, check that a corresponding serious adverse event is recorded in the *SERIOUS ADVERSE EVENT* section.

Protocol code	Session number	Subject number
207499/181	**0**	

COPD Exacerbations *Continued*

Date of onset day month year	Outcome R = Resolved F = Fatal N = Not resolved	Date of resolution or death day month year	Severity 1 = Mild 2 = Moderate 3 = Severe	Was the subject withdrawn due to this exacerbation? Y = Yes N = No	Was the exacerbation treated with oral corticosteroids? Y = Yes N = No	Was the exacerbation treated with antibiotics? Y = Yes N = No	Was the exacerbation an SAE? Y = Yes N = No
e.g. ***21 MAY 01***	***R***	***29 MAY 01***	***3***	***Y***	***N***	***Y***	
1.							
2.							
3.							
4.							
5.							
6.							
7.							
8.							
9.							

Enter details in the CONCOMITANT MEDICATION, the SERIOUS ADVERSE EVENT section and the END OF STUDY RECORD section if applicable.

Protocol code

207499/181

COPD Concomitant Medications

Instructions to Investigator

- Record the subject's use of salbutamol and/or ipratropium bromide.

Permitted Medications

*The following concomitant medications may be **permitted**:*

- Treatment for smoking cessation (any changes in the smoking status; starting or stop smoking will withdraw subject from the PP population)
- Salbutamol (prn) and/or ipratropium bromide (qid) for use as relief medication will be provided throughout the study. Salbutamol and/or ipratropium bromide for use via a nebuliser will be provided for use as part of the bronchial biopsy, and sputum induction procedures. The use of this medication must be recorded in the concomitant medication of the CRF.
- Between Visits 1 and 7, the subject should NOT take any additional bronchodilators that they possess at home, with the exception of salbutamol and/or ipratropium bromide. *If the subject experiences symptoms, which do not respond adequately to salbutamol and/or ipratropium bromide, the subject must contact the investigator.*
- Combivent

Prohibited Medications

*Except in the short-term management of COPD exacerbations, the following medications are **prohibited** between Visit 1 and Visit 8.*

- Inhaled, oral and systemic corticosteroids (should be stopped 4 weeks before Visit 1)
- Long-acting β_2-agonists (e.g. salmeterol and formoterol should be stopped 2 weeks before Visit 1)
- Oral β_2-agonists (e.g. bambuterol) and nebulised β_2-agonists (except as part of the biopsy or sputum induction procedures)
- Long-acting anticholinergics e.g. tiotropium bromide (should be stopped 4 weeks before Visit 1)
- Xanthines (should be stopped 4 weeks before Visit 1)
- Leukotriene modifiers
- Sodium cromoglycate and nedocromil sodium
- NACs (N-Acetyl Cysteine)

Protocol code

207499/181

COPD Concomitant Medications

Monitor Data Validation Checks

- Check that either the YES or NO box is checked for the leading question "Were any COPD concomitant medications taken by the subject during the study?" If YES, check that at least one drug is recorded.
- Check that the drug name (trade name preferred) is spelled correctly.
- Check that combination drugs are recorded as shown in Example 2.
- Check that the dose is recorded as a single unit.
- If text has been entered in the box check that it is **not** one of the pre-printed units and that nothing has been circled.
- Check that the units/frequency/route are abbreviated appropriately.
- Check that for units/route only one abbreviation is circled or one abbreviation is written in the box.
- Check that Date started is accurate and complete, partial dates are not acceptable.
- If Start Pre-study is ✔ check that Date started is blank.
- Check that Date stopped is accurate and complete, partial dates are not acceptable.
- If Continued Post-study is ✔ check that Date stopped is blank.
- Check that the question "Was drug administered for a COPD exacerbation?" is answered Y or N. If Y, check that a corresponding COPD exacerbation is recorded in the *COPD EXACERBATION* section.
- Check that the question "Was drug administered as a rescue medication? " is answered Y or N.

Protocol code	Session number	Subject number
207499/181	0	

COPD Concomitant Medications

Were any COPD concomitant medications taken by the subject during the study? Yes ☐ Y No ☐ N *If YES, record below:*

Drug [1] (Trade name preferred)	Dose	Units	Fre-quency	Route	Date started (day month year)	✔ if started Pre-study	Date stopped (day month year)	✔ if continued Post-study	Was drug admin-istered for a COPD exacer-bation? Y/N	Was drug administered as a rescue medication? Y/N	Conditions treated/ indication
Example 1 ***Serevent***	***50***	(µg)/mg	***BID***	(IH)/PO	***01 AUG 02***			✔	***N***	***N***	COPD
Example 2 ***DUOVENT (100 / 40 µg)***	***1***	µg/mg ***PUFF***	***BD***	(IH)/PO		✔	***07 AUG 02***		***N***	***N***	COPD
1.		µg/mg		IH/PO							COPD
2.		µg/mg		IH/PO							COPD
3.		µg/mg		IH/PO							COPD
4.		µg/mg		IH/PO							COPD
5.		µg/mg		IH/PO							COPD
6.		µg/mg		IH/PO							COPD
7.		µg/mg		IH/PO							COPD

[1] *If medication is given to treat an exacerbation that meets the definition of serious, then complete the SERIOUS ADVERSE EVENT section.*

continued...

Protocol code	Session number	Subject number
207499/181	0	

COPD Concomitant Medications *Continued*

Drug [1] (Trade name preferred)	Dose	Units	Fre-quency	Route	Date started day month year	✔ if started Pre-study	Date stopped day month year	✔ if continued Post-study	Was drug admin-istered for a COPD exacer-bation? Y/N	Was drug administered as a rescue medication? Y/N	Conditions treated/ indication
Example 1 ***Serevent***	***50***	µg/mg	***BID***	(IH)/PO	***01 AUG 02***			✔	***N***	***N***	COPD
Example 2 ***DUOVENT (100 / 40 µg)***	***1***	µg/mg **PUFF**	***BD***	(IH)/PO		✔	***07 AUG 02***		***N***	***N***	COPD
1.		µg/mg		IH/PO							COPD
2.		µg/mg		IH/PO							COPD
3.		µg/mg		IH/PO							COPD
4.		µg/mg		IH/PO							COPD
5.		µg/mg		IH/PO							COPD
6.		µg/mg		IH/PO							COPD
7.		µg/mg		IH/PO							COPD

[1] *If medication is given to treat an exacerbation that meets the definition of serious, then complete the SERIOUS ADVERSE EVENT section.*

Protocol code

207499/181

Non-COPD Concomitant Medications

Instructions to Investigator

- ✔ either the YES or NO box at the top of the page.
- Record all concomitant medications. Trade names are preferred for all medications; this is particularly encouraged for all combination medications, e.g., multivitamins and cold medications. The subject should be encouraged to disclose all medications he/she is taking, including non-prescribed medications, herbal remedies, and nutritional supplements.
- Record dose, unit and frequency. Commonly used abbreviations are acceptable.
- Record the start date, if known e.g., 0 6 (day) J A N (month) 0 2 (year) . Partial dates are acceptable; i.e. JUN 99 or 99.
- If the concomitant medication start date is prior to the study start date, ✔ '✔ if started pre-study'.
- Record the stop date if concomitant medication is stopped prior to the end of the study.
- If the subject is to continue taking the concomitant medication after the study is over, ✔ '✔ if continued Post-Study'.

Route Key for Concomitant Medication

PO	=	By mouth	SL	=	Sublingual	TD	=	Transdermal
IV	=	Intravenous	IT	=	Intrathecal	IH	=	Inhaled
IM	=	Intramuscular	A	=	Vaginal	SC	=	Subcutaneous
IAR	=	Intra-arterial	NA	=	Nasal	PR	=	Rectal
TO	=	Topical	IA	=	Intra-articular injection	ID	=	Intradermal

Protocol code

207499/181

Non-COPD Concomitant Medications

Monitor Data Validation Checks

- Check that either the YES or NO box at the top of the page is ✔.
  - If NO is ✔, check that no concomitant medications are present.
  - If YES is ✔, check that at least one concomitant medication is present.
- Check that either the 'Date started' is completed or '✔ if started pre-study' is ✔. At least one must be completed, but it is acceptable if both are completed.
  - If a pre-investigational product start date is unknown, check that a ✔ is recorded for '✔ if started Pre-study'.
  - If both 'Date started' and '✔ if started Pre-study' are completed, check that the start date is pre-study.
- Check that either the 'Date stopped' box is completed or the '✔ if continued Post-study' is ✔. **Only one** must be completed.
  - Check that the drug start date is before or equal to the drug stop date.
- Check that the drug name (trade name preferred) is spelled correctly.
- If the subject is female, cross-check with the *DEMOGRAPHY FOR FEMALES* page that any contraceptive drugs taken by the subject are recorded.
- If a concomitant medication was started pre-study, check that the indication is recorded on the *CURRENT MEDICAL CONDITIONS* page.
- If the concomitant medication was taken for an adverse event, check that the event is entered in the appropriate *ADVERSE EVENTS* section(s) and that the dates are consistent with the event.

Protocol code	Session number	Subject number
207499/181	0	

Non-COPD Concomitant Medications

Were any concomitant medications taken by the subject during the study? Yes ☐ Y No ☐ N *If YES, record below:*

Drug [1] (Trade name preferred [2])	Dose	Units	Fre-quency	Date started day month year	✔ *if started Pre-study*	Date stopped day month year	✔ *if continued Post-study*	Conditions treated/ indication
e.g., ZANTAC	***150***	***mg***	***BID***		✔	***27 JAN 02***		***Gastric ulcer***
1.								
2.								
3.								
4.								
5.								
6.								
7.								
8.								

[1] *If medication is given to treat an adverse event, then the ADVERSE EVENT must be recorded on the NON-SERIOUS ADVERSE EVENT or SERIOUS ADVERSE EVENT section(s) at the back of the CRF.*

[2] *Use generic names for studies conducted in Greece, Egypt, China, or other countries where a pharmacopoeia in Latin script is not available.*

Does This Event Meet the Definition of Serious?

(AE Instruction page 1)

YES

Complete SAE pages (in next section)

A serious adverse event is any untoward medical occurrence that, at any dose:

a) results in death

b) is life-threatening

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.

c) requires hospitalization or prolongation of existing hospitalization

NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d) results in disability/incapacity

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e) a congenital anomaly/birth defect

f) other

Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.

Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

NO

Complete Non-serious AE pages (in this section)

NON-SERIOUS ADVERSE EVENT

DEFINITION OF AN ADVERSE EVENT

Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.

Examples of an AE **includes:**

- Significant or unexpected worsening or exacerbation of the condition/ indication under study.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concomitant medication (overdose per se should not be reported as an AE/SAE).
- Significant failure of expected pharmacological or biological action.

Examples of an AE **does NOT include** a/an:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

For GSK clinical studies, AEs may include pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e., invasive procedures, modification of subject's previous therapeutic regimen).

(AE Instruction page 2)

If the event meets the definition of serious, do not complete this non-serious AE page. Complete the SAE pages in the next section.

SERIOUS ADVERSE EVENT

A serious adverse event is any untoward medical occurrence that, at any dose:[1]

a) results in death

b) is life-threatening

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.

c) requires hospitalization or prolongation of existing hospitalization

NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d) results in disability/incapacity

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e) a congenital anomaly/birth defect

f) other

Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.

Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

[1] *NOTE: The phrase "occurrence that, at any dose", does not imply that the subject is receiving investigational product(s).*

INSTRUCTIONS FOR COMPLETING THE NON-SERIOUS ADVERSE EVENT CRF

Ensure all hand writing is clear and legible

DETAILS OF ADVERSE EVENT(S)

Diagnosis

Enter only the diagnosis (if known); otherwise each sign and symptom should be entered on a separate line. If a diagnosis subsequently becomes available, then this should be entered and the signs and symptoms crossed out.

Date of Onset

Record the date of onset of the first occurrence of the AE.

Maximum Intensity

Record the maximum intensity that occurred over the duration of the event. Amend the intensity if it increases.

Outcome

All AEs must be followed until the events are resolved, the condition stabilizes, the events are otherwise explained, or the subject is lost to follow-up. Indicate if the event was "Resolved" or "Resolved with sequelae". If the adverse event is ongoing at the time the subject completes the study or becomes lost to follow-up, the outcome must be recorded as "Not resolved".
Also enter "Not resolved" if the AE was ongoing at the time of death, but was not the cause of death.

Date of Resolution

Record the date of resolution. This is the last date of occurrence of the AE. If the event resolved with sequelae, enter the date the subject's medical condition stabilized. Leave blank if the AE is "Not resolved".

Action Taken with Investigational Product(s) as a Result of the AE

Indicate only for the specific event(s) that were directly responsible for the action taken with investigational product(s):

None	Investigational product(s) continue(s) even though an adverse event has occurred.
Dose adjusted	Dose is increased or decreased for one or more investigational product(s).
Temporarily interrupted	Administration of one or more investigational product(s) was stopped temporarily but then restarted.
Permanently discontinued	Administration of one or more investigational product(s) was stopped permanently and not restarted.
Not applicable	Subject was not receiving investigational product(s) when the event occurred (e.g., pre- or postdosing).

Withdrawal

Indicate only the event(s) directly responsible for the subject's withdrawal as indicated on the End of Study Record page.

Relationship to Investigational Product(s)

It is a regulatory requirement for investigators to assess relationship to investigational product(s) based on information available. The assessment should be reviewed on receipt of any new information and amended if necessary. "A reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship. Facts/evidence/arguments that may support "A reasonable possibility" include, for example, a temporal relationship, a pharmacologically-predicted event, or positive dechallenge or rechallenge. Confounding factors, such as concomitant medication, a concomitant illness, or relevant medical history, should also be considered.

Protocol code	Session number	Subject number
207499/181	0	

Non-Serious Adverse Events

Did the subject experience any non-serious adverse events during the study? Yes ☐ Y No ☐ N *If YES, indicate below:*

Non-serious adverse events	Date of onset	Maximum intensity	Outcome	Date of resolution	Action taken with investigational product(s) as a result of the non-serious AE	Withdrawal	Relationship to investigational product(s)	Seriousness
Diagnosis only (if known) or signs / symptoms (list one per line)	day month year	1 = Mild 2 = Moderate 3 = Severe X = Not applicable	R = Resolved S = Resolved with sequelae N = Not resolved	day month year	0 = None 1 = Dose adjusted 2 = Temporarily interrupted 3 = Permanently discontinued X = Not applicable	Did subject withdraw from study as a result of this non-serious AE? Y = Yes N = No	Is there a reasonable possibility that the non-serious AE may have been caused by the investigational product(s)? Y = Yes N = No	Does the AE meet the definition of serious? Y = Yes N = No
e.g., HEADACHE	***25 JAN 02***	***3***	***R***	***27 JAN 02***	***0***	***N***	***Y***	***N***
1.								N
2.								N
3.								N
4.								N
5.								N
6.								N
7.								N
8.								N

continued...

Protocol code	Session number	Subject number
207499/181	0	

Non-Serious Adverse Events *Continued*

Did the subject experience any non-serious adverse events during the study? Yes ☐ Y No ☐ N *If YES, indicate below:*

Non-serious adverse events	Date of onset	Maximum intensity	Outcome	Date of resolution	Action taken with investigational product(s) as a result of the non-serious AE	Withdrawal	Relationship to investigational product(s)	Seriousness
Diagnosis only (if known) or signs / symptoms (list one per line)	day month year	1 = Mild 2 = Moderate 3 = Severe X = Not applicable	R = Resolved S = Resolved with sequelae N = Not resolved	day month year	0 = None 1 = Dose adjusted 2 = Temporarily interrupted 3 = Permanently discontinued X = Not applicable	Did subject withdraw from study as a result of this non-serious AE? Y = Yes N = No	Is there a reasonable possibility that the non-serious AE may have been caused by the investigational product(s)? Y = Yes N = No	Does the AE meet the definition of serious? Y = Yes N = No
e.g., HEADACHE	***25 JAN 02***	***3***	***R***	***27 JAN 02***	***0***	***N***	***Y***	***N***
1.								N
2.								N
3.								N
4.								N
5.								N
6.								N
7.								N
8.								N

SERIOUS ADVERSE EVENT

If the subject has experienced an SAE (see definition on next page) then:

IMMEDIATE ACTION IS REQUIRED

1) Complete the Serious Adverse Event pages

A separate set of SAE pages should be used for each SAE. However, if at the time of initial reporting, multiple SAEs are apparent that are temporally and/or clinically related, then they can be reported on the same page.

2) Inform GlaxoSmithKline

The investigator must inform GSK of serious adverse events by fax or telephone (fax preferred) within **24 hours** of becoming aware of the event.

The original SAE pages remain in the Case Report Form

(SAE Instruction page 1)

FOLLOW-UP INFORMATION

The investigator and others responsible for subject care should institute any supplementary investigations of SAEs based on their clinical judgment of the likely causative factors. This may include seeking a further opinion from a specialist in the field of the adverse event. GlaxoSmithKline may also request extra tests or extra follow-up information. If a subject dies, any postmortem findings, including histopathology, must be provided to GlaxoSmithKline.

On receipt of follow-up information (e.g., diagnosis, dates of resolution, changes in intensity or causality) the appropriate SAE pages must be amended/updated. These changes must be initialed and dated by the investigator. A copy of the full set of SAE pages must always be faxed or mailed to GlaxoSmithKline within 24 hours of the investigator becoming aware of the new information.

If the event meets the definition of serious, complete these SAE pages. If not, complete a Non-serious AE page (previous section).

SERIOUS ADVERSE EVENT

A serious adverse event is any untoward medical occurrence that, at any dose:[1]

a) results in death

b) is life-threatening

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.

c) requires hospitalization or prolongation of existing hospitalization

NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d) results in disability/incapacity

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e) a congenital anomaly/birth defect

f) other

Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.

Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

[1] *NOTE: The phrase "occurrence that, at any dose", does not imply that the subject is receiving investigational product(s).*

INSTRUCTIONS FOR COMPLETING THE SERIOUS ADVERSE EVENT CRF

Ensure all hand writing is clear and legible

SECTION 1 DEMOGRAPHY

Complete this section using the information recorded in the "Demography" or "Vital Signs" page. Record the most recently measured height and weight.

SECTION 2 DETAILS OF SERIOUS ADVERSE EVENT

Diagnosis

Enter only the diagnosis (if known); otherwise each serious sign and symptom should be entered on a separate line. If a diagnosis subsequently becomes available, then this should be entered and the signs and symptoms crossed out.

Date of Onset

Record the date of onset of the first occurrence of the SAE.

Maximum Intensity

Record the maximum intensity that occurred over the duration of the SAE. Amend the intensity if it increases.

Outcome

All SAEs must be followed until the events are resolved, the condition stabilizes, the events are otherwise explained, or the subject is lost to follow-up. Indicate if the event was "Resolved", "Resolved with sequelae", or was "Fatal". If the SAE is ongoing at the time the subject completes the study or becomes lost to follow-up, the outcome must be recorded as "Not resolved". Also enter "Not resolved" if the SAE was ongoing at the time of death, but was not the cause of death.

Date of Resolution or Death

Record the date of resolution or the date of death. If the event resolved with sequelae, enter the date the subject's medical condition stabilized. Leave blank if the event is "Not resolved".

Action Taken with Investigational Product(s)

Indicate only for the specific event(s) that were directly responsible for the action taken with investigational product(s):

None	Investigational product(s) continue(s) even though an adverse event has occurred.
Dose adjusted	Dose is increased or decreased for one or more investigational product(s).
Temporarily interrupted	Administration of one or more investigational product(s) was stopped temporarily but then restarted.
Permanently discontinued	Administration of one or more investigational product(s) was stopped permanently and not restarted.
Not applicable	Subject was not receiving investigational product(s) when the event occurred (e.g., pre- or postdosing).

Withdrawal

Indicate only the event(s) directly responsible for the subject's withdrawal as indicated on the End of Study Record page.

Relationship to Investigational Product(s)

It is a regulatory requirement for investigators to assess relationship to investigational product(s) based on information available. The assessment should be reviewed on receipt of any new information and amended if necessary. "A reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship. Facts/evidence/arguments that may support "A reasonable possibility" include, for example, a temporal relationship, a pharmacologically-predicted event, or positive dechallenge or rechallenge. Confounding factors, such as concomitant medication, a concomitant illness, or relevant medical history, should also be considered.

SECTION 3 POSSIBLE CAUSES OF THE SERIOUS EVENT OTHER THAN INVESTIGATIONAL PRODUCT(S)

Indicate all possible explanations/circumstances that may have contributed to the SAE, regardless of the relationship to investigational product(s).

SECTION 4 SERIOUSNESS

Indicate all reasons why this adverse event meets the definition of seriousness.

Protocol code	Session number	Investigator number	Treatment number	Subject number
207499/181	0			

Serious Adverse Event (SAE)

Did the subject experience any serious adverse events during the study? Yes ☐ Y No ☐ N *If YES, indicate below:*

SECTION 1 Demography

Date of birth (day / month / year)

Sex: Male ☐ Female ☐

Race: White ☐ Black ☐ Asian ☐ Other ☐

Weight ____.____ kg

Height ____ cm

SECTION 2 Serious Adverse Events

Serious adverse events	Date of onset	Maximum intensity	Outcome	Date of resolution or death	Action taken with investigational product(s) as a result of the SAE	Withdrawal	Relationship to investigational product(s)	Seriousness
Diagnosis only (if known) OR Serious signs / symptoms (*list one per line*)	day month year	1 = Mild 2 = Moderate 3 = Severe X = Not applicable	R = Resolved S = Resolved with Sequelae F = Fatal N = Not Resolved	day month year	0 = None 1 = Dose adjusted 2 = Temporarily interrupted 3 = Permanently discontinued X = Not applicable	Did the subject withdraw from study as a result of this SAE? Y = Yes N = No	Is there a reasonable possibility the SAE may have been caused by the investigational product(s)? Y = Yes N = No	Does the AE meet the definition of serious? Y = Yes N = No
e.g., ANAPHYLAXIS	***25 JAN 02***	***3***	***R***	***26 JAN 02***	***3***	***Y***	***Y***	***Y***
1.								Y
2.								Y
3.								Y

SECTION 3 Possible Causes of SAE other than Investigational Product(s), ✔ *all that apply*

Disease under study ☐
Treatment failure ☐
Withdrawal of investigational product(s) ☐
Concomitant disorder ☐ *specify,* .....
Concomitant medication ☐ *specify,* .....
Activity related to study participation *(e.g., procedures)* ☐ *specify,* .....
Other ☐ *specify,* .....

SECTION 4 Seriousness, ✔ *all that apply*

a. Death ☐
b. Life threatening ☐
c. Hospitalization required or prolonged ☐
d. Disabling or incapacitating ☐
e. Congenital anomaly ☐
f. Other *(see definition)* ☐ *specify,* .....

If fatal, was an autopsy done/to be performed? Yes ☐ No ☐ (*Send autopsy report when available).*

continued...

INSTRUCTIONS FOR COMPLETING THE SERIOUS ADVERSE EVENT CRF

Ensure all hand writing is clear and legible

SECTION 5 RELEVANT MEDICAL CONDITIONS

Provide details of relevant current medical conditions. Include any past medical conditions that may be appropriate. Provide details of the date of onset of these conditions and/or whether they were still present at the time of the SAE.

SECTION 6 OTHER RELEVANT RISK FACTORS

Specify any family history or any social history (e.g., smoking, alcohol, diet, drug abuse, occupational hazard) relevant to the SAE.

SECTION 7 DETAILS OF INVESTIGATIONAL PRODUCT(S)

Complete this section using the information in the "Investigational Product" page.

Details of all investigational product(s) taken until the time of the SAE should be included. Provide specific details in the narrative if the subject has taken an overdose of investigational product(s), including whether it was accidental or intentional.

Protocol code	Session number	Subject number
207499/181	0	

Serious Adverse Event *Continued*

SECTION 5 Relevant Medical Conditions

Specify any relevant past or current medical disorders, allergies, surgeries, etc. that can help explain the SAE.	Date of onset day month year	Condition present at time of the SAE Y = Yes, N = No	If NO, date of last occurrence day month year
1.			
2.			
3.			
4.			

SECTION 6 Other Relevant Risk Factors

Specify any family history or any social history (e.g., smoking, alcohol, diet, drug abuse, occupational hazard) relevant to the SAE.

SECTION 7 Details of Investigational Product(s)

	Start date day month year	Stop date day month year
Run-in		
Study drug		

continued...

INSTRUCTIONS FOR COMPLETING THE SERIOUS ADVERSE EVENT CRF

Ensure all hand writing is clear and legible

SECTION 8 RELEVANT CONCOMITANT MEDICATIONS

Provide details of relevant concomitant medications that the investigator thinks may have contributed to the occurrence of the SAE or otherwise explain it. This may include any concomitant medication taken at the time of the SAE (including any oral contraceptives or prophylactic medication) or other medications temporally associated with the SAE (i.e. preceding the SAE or withdrawn prior to the SAE).

Only if there are extensive relevant concomitant medications should the Concomitant Medications page (if used) be faxed or mailed with the SAE pages.

Medications used to treat the SAE should not be included here but recorded in the narrative instead.

SECTION 9 NARRATIVE/COMMENTS

Provide a textual description of the SAE. This should include but not be limited to the following:

- Any previous occurrences of this type of event
- Any relevant non-serious adverse events that occurred prior to the SAE
- The full clinical presentation and sequelae/evolution of the SAE
- Any associated signs and symptoms of the SAE
- Explain any possible causes of the SAE
- Treatment for the SAE (including any specific medications administered or non-drug treatment)
- Any other action taken for the management of the SAE or the subject
- Duration and outcome of the SAE
- If the SAE is associated with an overdose of investigational product(s), details of the amount of overdose and whether it was intentional or accidental.

SECTION 10 DETAILS OF RELEVANT ASSESSMENTS

Provide details of any other assessments or supplementary investigations/examinations that were conducted as part of the subject's care and/or based on clinical judgment of the likely causative factors of the SAE. This may include, but not be limited to:

- Laboratory data. Always provide the reference range and baseline values (fax or mail pages if extensive supporting data)
- Findings of ECGs, X-rays, etc.
- Results of other diagnostic tests or assays
- Key findings from hospital discharge or pathology reports

SECTION 11 REPORTING INVESTIGATOR SIGNATURE

The reporting investigator (not the study nurse or study monitor) must sign and date the SAE page.

Protocol code	Session number	Subject number
207499/181	0	

Serious Adverse Event *Continued*

SECTION 8 Relevant Concomitant Medications

Include any concomitant medications that may contribute to the occurrence of the SAE

Drug (*Trade name preferred*)	Dose	Unit	Freq-uency	Route	Date started day month year	✔ *if started Pre-study*	Date stopped day month year	✔ *if continued Post-SAE*	Conditions treated / indication
e.g., ZANTAC	***150***	***mg***	***BID***	***PO***		✔	***27 JAN 02***		***Gastric ulcer***
1.									
2.									
3.									

SECTION 9 Narrative / Comments

Provide a textual description of the serious adverse event (including treatment of the event).

SECTION 10 Details of Relevant Assessments

Provide details of other assessments (e.g., laboratory data with normal ranges) or supplemental examinations.

SECTION 11 Reporting Investigator

To the best of my knowledge, all information entered on these Serious Adverse Event pages for this subject is correct.

Name *(print)*	Address	Signature	Date day month year

continued...

INSTRUCTIONS FOR COMPLETING THE SERIOUS ADVERSE EVENT CRF

Ensure all hand writing is clear and legible

ADDITIONAL OR FOLLOW-UP INFORMATION

Use this page to provide any additional details or follow-up information on the SAE not already recorded on the previous pages. On receipt of follow-up information, the appropriate section(s) [1 to 11] must be amended/updated with any changes (i.e., diagnosis, date of resolution of death, change in intensity, or causality). These changes must be initialed and dated with confirmation by the investigator with his/her resigning the forms and forwarding to GCSP within **24 hours**.

The investigator and others responsible for subject care should institute any supplementary investigations of SAEs based on their clinical judgment of the likely causative factors. This may include seeking a further opinion from a specialist in the field of the adverse event. GlaxoSmithKline may also request extra tests or extra follow-up information. If a subject dies, any postmortem findings, including histopathology, must be provided to GlaxoSmithKline.

REPORTING INVESTIGATOR SIGNATURE

The reporting investigator (not the study nurse or study monitor) must sign and date any additional or follow-up information relating to the SAE.

Protocol code	Session number	Subject number
207499/181	0	

Serious Adverse Event *Continued*

Additional or follow-up information

Use this page to provide any additional details on the serious adverse event not already captured on the previous pages.
The appropriate section(s) (1-11) of SAE CRF must be amended/updated with any changes and re-faxed/mailed.

Reporting Investigator

To the best of my knowledge, all information entered on these Serious Adverse Event pages for this subject is correct.

Name (*print*)	Address	Signature	Date day month year

Protocol code

207499/181

End of Study Record

Instructions to Investigator

- Completion of the study is defined as having completed the Run-in, Treatment and Follow-up phases of the study as defined in the protocol.
- "Did the subject become pregnant during the study?"
  - This question must be answered for all subjects. For females not of childbearing potential or males, ✔ NOT APPLICABLE.
  - If no pregnancy was known before a subject was lost to follow-up, ✔ NO.
  - If the subject became pregnant before either premature discontinuation from the study or completion of the study, ✔ YES.
- The device(s) used in this study were the MDI inhaler and the VOLUMATIC spacer.
- "Did the subject experience an incident or near incident with GlaxoSmithKline medical devices provided for use during the study?
  - If a subject never used this/these device(s), ✔ NO.
  - If no incident was known before a subject was lost to follow-up, ✔ NO.
  - If an incident occurred before either premature discontinuation from the study or completion of the study, ✔ YES.

Monitor Data Validation Checks

- Check that the "Date of subject completion or discontinuation from the study" is on or after the last treatment stop date on the *INVESTIGATIONAL PRODUCT* page.
- Check that the pregnancy question is completed. If the pregnancy question is answered YES, check that the *PREGNANCY NOTIFICATION FORM* is completed.
- Check that the medical device question is completed. If the medical device question is answered YES, check that the *MEDICAL DEVICE INCIDENT REPORT FORM* is completed.
- If "Did the subject discontinue the study prematurely?" is ✔YES, check that one "primary reason for discontinuation" is ✔.
- If "Adverse Event" is ✔ as reason for discontinuation, check that consistent details are recorded on the *NON-SERIOUS ADVERSE EVENTS* or *SERIOUS ADVERSE EVENT* page(s).
- If the primary reason for discontinuation is ✔ "Other", check that a concise text entry is present in the space provided.

Protocol code	Session number	Subject number
207499/181	0	

End of Study Record

Date of subject completion or discontinuation from the study ☐☐ ☐☐☐ ☐☐
day month year

Did the subject become pregnant during the study? ✔*one:*

Not applicable ☐ X (Not of childbearing potential or male)

Yes ☐ Y *If YES, record details on PREGNANCY NOTIFICATION FORM.*

No ☐ N

Did the subject experience an incident or near incident **with GlaxoSmithKline medical devices provided for use during the study?** Yes ☐ Y No ☐ N

If YES, record details on the MEDICAL DEVICE INCIDENT REPORT FORM.

Did the subject discontinue the study prematurely? Yes ☐ Y No ☐ N

*If YES, ✔the **primary** reason for discontinuation. ✔one:*

Adverse event ☐ 1 *Record details in NON-SERIOUS ADVERSE EVENTS or SERIOUS ADVERSE EVENT section as appropriate.*

Consent Withdrawn ☐ 5

Lost to follow up ☐ 4

Protocol violation ☐ 3

Lack of efficacy of study medication ☐ 2

COPD exacerbations ☐ 19

Did not fulfil entry criteria ☐ 10

Other ☐ 7 *specify,* . . . . . .

***NOTE TO INVESTIGATOR:** Ensure that either the YES or NO response box has been ✔ for the first question on the NON-SERIOUS ADVERSE EVENTS, SERIOUS ADVERSE EVENT and CONCOMITANT MEDICATIONS sections.*

Protocol code

207499/181

Investigator Comment Log

Monitor Data Validation Checks

- If CRF page numbers are listed, check that they correspond to the documented comment.

Protocol code	Session number	Subject number
207499/181	**0**	

Investigator Comment Log

Use this form to document any other relevant information that is not noted elsewhere in the CRF.

Date of comment day month year	CRF page number if applicable	Comment

Protocol code

207499/181

Investigator's Statement

Instructions to Investigator

- Sign and date this page after all relevant CRF pages, including outstanding test results, are completed.

Monitor Data Validation Checks

- Check that the date of signature is on or after the completion of all protocol activities.

Protocol code	Session number	Subject number
207499/181	**0**	

Investigator's Statement

I confirm that I have carefully examined all entries on the Case Report Form for this subject. All information entered by myself or my colleagues is, to the best of my knowledge, correct as of the date below.

. . . . . .
Investigator's signature

day	month	year

. . . . . .
Investigator's name - print

Protocol code

207499/181

Subject number

Page Count
(For GlaxoSmithKline Use Only)

- *Complete this page for all subjects.*
- *Return this page with the CRF pages.*
- *Indicate below, if the subject was a screen failure.*
- *Place an "X" through the page number of pages that have no data recorded on them and will not be returned.*
- *Enter any additional page numbers in the empty boxes below.*

1	2	3	4	5	6	7	8	9	10
11	12	13	14	15	16	17	18	19	20
21	22	23	24	25	26	27	28	29	30
31	32	33	34	35	36	37	38	39	40
41	42	43	44	45	46	47	48	49	50
51	52	53	54	55	56	57	58	59	60
61	62	63	64	65	66	67	68	69	70
71	72								

Notes: . . . . . .

. . . . . .

. . . . . .

. . . . . .

. . . . . .

GlaxoSmithKline clinical monitor's signature

day | month | year

This section contained Principal Investigator's Curriculum Vitae and has been excluded to protect Principal Investigator privacy.

DATA LISTINGS - OTHER

Page

Other A.1 APPENDIX A: LISTING 1 - TREATMENT RANDOMIZATION WITH PATIENT NUMBER 4
Other B.1 APPENDIX B: LISTING 1 - REASON FOR STUDY CONCLUSION, DAYS OF PARTICIPATING IN THE STUDY AND DEMOGRAPHICS BY PATIENT NUMBER 7
Other B.2A APPENDIX B: LISTING 2A - EXCLUSIONARY MEDICATIONS AND VISIT SPECIFIC PROTOCOL VIOLATIONS BY PATIENT NUMBER 13
Other B.2B APPENDIX B: LISTING 2B - VIOLATIONS OF ELIGIBILITY CRITERIA BY PATIENT NUMBER 15
Other B.2C APPENDIX B: LISTING 2C - CONDUCT OF STUDY DEVIATIONS BY PATIENT NUMBER 16
Other B.4 APPENDIX B: LISTING 4 - CIGARETTE SMOKING HISTORY AT SCREENING BY PATIENT NUMBER 17
Other B.6 APPENDIX B: LISTING 6 - CURRENT/ACTIVE MEDICAL CONDITIONS BY PATIENT NUMBER AND MEDDRA SYSTEM ORGAN CLASS 23
Other B.7 APPENDIX B: LISTING 7 - PRIOR MEDICATIONS BY PATIENT NUMBER 32
Other B.8A APPENDIX B: LISTING 8A - CONCOMITANT MEDICATIONS BY PATIENT NUMBER 108
Other B.10 APPENDIX B: LISTING 10 - BASELINE SIGNS AND SYMPTOMS BY PATIENT NUMBER, SYSTEM ORGAN CLASS, PREFERRED TERM AND VERBATIM TERM 176
Other B.11 APPENDIX B: LISTING 11 - STUDY MEDICATION COMPLIANCE BY PATIENT NUMBER 196
Other B.12 APPENDIX B: LISTING 12 - STUDY MEDICATION RECORD BY PATIENT NUMBER 217
Other C.1 APPENDIX C: LISTING 1 - SPUTUM ANALYSIS BY PATIENT NUMBER 223
Other C.2 APPENDIX C: LISTING 2 - PULMONARY FUNCTION PARAMETERS BY PATIENT NUMBER 234
Other C.3 APPENDIX C: LISTING 3 - BRONCHIAL BIOPSY ANALYSIS BY PATIENT NUMBER 283
Other C.4 APPENDIX C: LISTING 4 - COPD EXACERBATIONS BY PATIENT NUMBER 297

Other D.1 APPENDIX D: LISTING 1 - ON-THERAPY ADVERSE EXPERIENCES BY PATIENT NUMBER, SYSTEM ORGAN CLASS, PREFERRED TERM AND VERBATIM TERM 299
Other D.2A APPENDIX D: LISTING 2A - ON-THERAPY ADVERSE EXPERIENCES POSSIBLY OR PROBABLY RELATED TO TREATMENT BY PATIENT NUMBER, SYSTEM ORGAN CLASS, - PREFERRED TERM AND VERBATIM TERM 325
Other D.2B APPENDIX D: LISTING 2B - ON-THERAPY ADVERSE EXPERIENCES UNLIKELY OR NOT RELATED TO TREATMENT BY PATIENT NUMBER, SYSTEM ORGAN CLASS, - PREFERRED TERM AND VERBATIM TERM 331
Other D.3 APPENDIX D: LISTING 3 - ON-THERAPY ADVERSE EXPERIENCES THAT LED TO DOSE INTERRUPTION BY PATIENT NUMBER, - SYSTEM ORGAN CLASS, PREFERRED TERM AND VERBATIM TERM. 352
Other D.5A APPENDIX D: LISTING 5A - RUN-IN SERIOUS ADVERSE EXPERIENCES BY PATIENT NUMBER, SYSTEM ORGAN CLASS, PREFERRED TERM AND VERBATIM TERM 353
Other D.5B APPENDIX D: LISTING 5B - ON-THERAPY SERIOUS ADVERSE EXPERIENCES BY PATIENT NUMBER, SYSTEM ORGAN CLASS, - PREFERRED TERM AND VERBATIM TERM 354
Other D.5C APPENDIX D: LISTING 5C - POST-THERAPY SERIOUS ADVERSE EXPERIENCES BY PATIENT NUMBER, SYSTEM ORGAN CLASS, - PREFERRED TERM AND VERBATIM TERM 355
Other D.5D APPENDIX D: LISTING 5D - PATIENT FATALITIES BY PATIENT NUMBER 356
Other D.6A APPENDIX D: LISTING 6A - ON-THERAPY ADVERSE EXPERIENCES THAT LED TO WITHDRAWAL BY PATIENT NUMBER, SYSTEM ORGAN CLASS, - PREFERRED TERM AND VERBATIM TERM. 357
Other D.6B APPENDIX D: LISTING 6B - RUN-IN ADVERSE EXPERIENCES THAT LED TO WITHDRAWAL BY PATIENT NUMBER, SYSTEM ORGAN CLASS, - PREFERRED TERM AND VERBATIM TERM. 358
Other D.7 APPENDIX D: LISTING 7 - POST-THERAPY ADVERSE EXPERIENCES BY PATIENT NUMBER, SYSTEM ORGAN CLASS, PREFERRED TERM AND VERBATIM TERM 359

Other D.8 APPENDIX D: LISTING 8 - GASTROINTESTINAL ADVERSE EXPERIENCES OF CONCERN BY PATIENT NUMBER, SYSTEM ORGAN CLASS, - PREFERRED TERM AND VERBATIM TERM 363
Other D.10 APPENDIX D: LISTING 10 - ABDOMINAL PAIN ASSESSMENT BY PATIENT NUMBER. 364
Other D.11 APPENDIX D: LISTING 11 - STOOL ASSESSMENT BY PATIENT NUMBER 365
Other D.12 APPENDIX D: LISTING 12 - PHYSICAL EXAMINATION FOR PATIENTS WITH GASTROINTESTINAL SYMPTOMS OF CONCERN BY PATIENT NUMBER. 366
Other D.13 APPENDIX D: LISTING 13 - FOB TEST RESULTS BY PATIENT NUMBER 367
Other E.1A APPENDIX E: LISTING 1A - STANDARD VITAL SIGNS BY PATIENT NUMBER 388
Other E.1C APPENDIX E: LISTING 1C - ORTHOSTATIC VITAL SIGNS CHANGES BY PATIENT NUMBER 409
Other F.2 APPENDIX F: LISTING 2 - CLINICAL LABORATORY VALUES BY TREATMENT GROUP AND PATIENT NUMBER. 410

This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the ***GSK Clinical Study Register****.*

Sponsor Signatory Signature Page

STUDY TITLE: A 13-week randomised, double-blind, parallel group, multicentre study to compare the bronchial anti-inflammatory activity of oral cilomilast (15 mg bd) with placebo twice daily in subjects with Chronic Obstructive Pulmonary Disease (COPD)

Study: SB-207499/181 Development Phase: IIIb

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 Medicine Development Center, Clinical

Signature: [redacted]

Date: 23-APR-2007