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Division: Worldwide Development
Retention Category: GRS019
Information Type: Clinical Study Report

Title:	A Randomized, Parallel Group, Double-Blind, Comparative Trial Assessing Lung Function and Other Measures of Asthma Control in Adults and Adolescents, at least 12 Years of Age, with Asthma, Who Have Either a B16-Arg/Arg, a B16-Gly/Gly or a B16-Arg/Gly Genotype and are Treated With Fluticasone Propionate/Salmeterol DISKUS™ Combination Product 100/50mcg or Salmeterol DISKUS 50mcg BID

Phase: IV

Compound Number: CCI18781+GR33343

Effective Date: 04-Oct-2007

Description: The primary objective of this study was to evaluate lung function as assessed by AM PEF AUC relative to baseline [AUC(bl)] in subjects who have the B16 Arg/Arg genotype compared with that of subjects who have the B16 Gly/Gly genotype over 16 weeks of treatment with FSC DISKUS 100/50mcg BID. This was a multi-center, randomized, double-blind, parallel group, active comparator controlled design.

Secondary measures of efficacy PM PEF and FEV₁ (over time) AUC relative to baseline [AUC(bl)]. Other secondary measures were change from baseline in percent of symptom free days, and supplemental ipratropium bromide use. Evaluation of lung function was assessed by AM PEF AUC(bl) during the last four weeks of open-label treatment with *prn* albuterol versus that during the last four weeks of open-label treatment with *prn* ipratropium bromide by genotype. Other measures of efficacy were the proportion of subjects requiring supplemental albuterol and an evaluation of maximum albuterol dose responses (MADR) by genotype. Evaluation of lung function were also assessed by AM PEF AUC(bl) in other *ADRB2* single nucleotide polymorphisms (SNPs) in the salmeterol (SM) and fluticasone propionate/salmeterol combination (FSC) treatment groups. Safety measurements included the incidence of adverse events and asthma exacerbations.

Changes in overall AM PEF AUC (bl) for the Arg/Arg, Gly/Gly, and Arg/Gly genotypes were not statistically different in the FSC 100/50mcg treatment arm or in the SM 50mcg treatment arm of the double blind treatment period (Weeks 1-16). Changes in PM PEF, FEV₁, percent of symptom free days, supplemental ipratropium use and other efficacy endpoints were similar between the genotypes in each of the treatment arms.

The frequency and type of adverse events reported by subjects were similar across genotypes in each treatment arm. One death occurred during the conduct of the study in the SM 50mcg treatment arm during the double blind treatment period that was not attributed to study drug.

Subject: Asthma, Pharmacogenetics, Peak Expiratory Flow, Salmeterol, Fluticasone propionate

Author(s): [REDACTED]

Indication Studied: Asthma

Initiation Date:	25 October 2004
Completion Date:	21 January 2007
Early Termination Date:	N/A
Date of Report:	04 October 2007
Earlier CSRs	N/A

Sponsor Signatory: [REDACTED] MD
(and Medical Officer) Respiratory MDC
GlaxoSmithKline

This study was performed in compliance with Good Clinical Practices and GlaxoSmithKline Standard Operating Procedures for all processes involved, including the archiving of essential documents.

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Abbreviations

A	Adenine
AE	Adverse Event
<i>ADRB2</i>	Adrenergic Beta ₂ receptor gene
AM	Morning
ANCOVA	Analysis of Covariance
Arg	Arginine
ATC	Anatomical Therapeutic Chemical
ATS	American Thoracic Society
AUC (bl)	Area Under the Curve Relative to Baseline
BARGE	Beta Adrenergic Response by Genotype
BID	Twice Daily
C	Cytosine
CFC	Chlorofluorocarbon
CIB	Clinical Investigator's Brochure
CRF	Case Report Form
DNA	Deoxyribonucleic acid
EDTA	Ethylenediaminetetraacetic acid
5'-FAM	Five Prime-Carboxyfluorescein
FAST	Flow Accelerated SNP Typing
FRET	Fluorescence Resonance Energy Transfer
FEV ₁	Forced Expiratory Volume in one second
FP	Fluticasone Propionate
FRET	Fluorescence Resonance Energy Transfer
FSC	Fluticasone propionate/salmeterol combination product
G	Guanine
GCSP	Global Clinical Safety Pharmacovigilance
Gly	Glycine
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
HARP	Harmonization for Analysis and Reporting Program
HFA	Hydrofluoroalkane 134-A (1,1,1,2-tetrafluoroethane)
HWE	Hardy-Weinberg equilibrium
ICH	International Conference on Harmonization
ICS	Inhaled corticosteroid
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent to Treat
IVP4	Internal Validation Plate 4
IVRS	Interactive Voice Response System
MADR	Maximum Albuterol Dose Response
mcg	Microgram
MCT	Methacholine challenge testing

MDI	Metered Dose Inhaler
MedDRA	Medical Dictionary for Regulatory Authorities
Mg	Milligram
mL	Mililiter
PCR	Polymerase Chain Reaction
PEF	Peak Expiratory Flow
PFT	Pulmonary Function Test
PGx	Pharmacogenetics
PM	Evening
<i>Prn</i>	As needed
QA	Quality Analysis
QC	Quality Control
QD	Once daily
QID	Four times daily
SAE	Serious Adverse Event
SCA	Standard Clarification Agreement
SCAD	Systematic Central Allocation of Drug
SDV	Source Document Verification
SM	Salmeterol
SNP	Single Nucleotide Polymorphism
SOC	System Organ Class
T	Thymine
US	United States

Trademark Information

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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 center 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, and, the guiding principles 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. A case report form was provided for the collection of data for each subject.

2. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This Phase IV multicenter study, sponsored by GlaxoSmithKline (GSK), was conducted at 63 sites in the US, two sites in Peru, and two sites in Kenya. Of these, 54 sites in the US, two sites in Peru, and two sites in Kenya randomized 272 subjects into the fluticasone propionate/salmeterol combination (FSC) treatment group. Fifty seven (57) sites in the United States (US), two sites in Peru, and two sites in Kenya randomized 272 subjects in the salmeterol (SM) treatment group. A total of 544 subjects were randomized into the study. The study was initiated on 25 October 2004 and completed on 21 January 2007. GSK provided all investigational study drug materials to the sites.

Prior to study initiation, site personnel attended a meeting organized by GSK to review the protocol and study procedures.

Sites were monitored by GSK Regional Monitors, in accordance with applicable regulations and GCP. The monitors periodically contacted the sites and conducted on-site visits. The extent, nature and frequency of on-site visits were based on such considerations as the study design complexity and enrollment rate. The monitors also performed all activities associated with site closure after study completion.

Quest Nichols Institute, San Juan Capistrano, CA performed the β_2 -adrenergic receptor gene *ADRB2* genotyping assay for this study. Quest Diagnostics Limited, Heston, TW59QA and Quest Diagnostics Clinical Trials, Van Nuys, CA provided kits, manuals, requisitions, shipping supplies for sample collection and transport, extraction of DNA

from a blood specimen and aliquoting, storage of a deoxyribonucleic acid (DNA) aliquot at Quest and transfer of the remainder to GSK for storage and analysis. Additional analyses were conducted by the Pharmacogenetic Division of GSK, Research Triangle Park, North Carolina.

For drug allocation, the study used an interactive voice response system (IVRS) provided by Covance (Princeton, NJ) which provided a system.

Data management and statistical analyses were carried out by GSK's Biomedical Data Sciences Division (Research Triangle Park, NC). GSK authors of this clinical study report were [REDACTED] B.S. (Respiratory Medicine Development Center, Clinical), [REDACTED] M.S. (Respiratory Medicine Development Center, Statistics and Programming), [REDACTED] M.D. (Respiratory Medicine Development Center, Clinical), [REDACTED] M.S. (Respiratory Medicine Development Center, Clinical), and [REDACTED] PhD (Pharmacogenetics, Pharmacovigilance).

3. INTRODUCTION

The β_2 -adrenergic receptor is a 413 amino acid protein encoded by an intronless gene located on chromosome 5q31.32 [Kobilka, 1987; Liggett, 2002]. Variation in the activity of this cell surface receptor is important because it mediates the effects of β_2 -agonists. Previous research on the β_2 -adrenergic receptor gene *ABDR2* identified polymorphisms which may influence response to β_2 -agonists [Reihnsaus, 1993; Israel, 2000]. The receptor variant characterized by substitution of glycine for arginine at position 16 (Arg16Gly) may be an important determinant of receptor function *in vitro* and occurs commonly in the population (minor allele frequency approximately 0.4-0.5) [Taylor, 2000]. It appears that the Gly-16 receptor exhibits enhanced down-regulation *in vitro* after β -agonist exposure, but data from clinical studies are inconsistent.

To date, studies of *ADRB2* have identified at least 49 single nucleotide polymorphisms (SNPs) within the coding, promoter and 3' regions. These sets of polymorphic, linked alleles that are inherited together are referred to as a haplotype. Theoretically, the SNPs can be combined to form 2^{49} possible SNP combinations; however, because these alleles are tightly linked, seven SNP combinations account for approximately 74% of observed haplotype distributions in Caucasians. Approximately 43% of these haplotypes code for an Arg at position 16. Previous studies that have evaluated *ADRB2* pharmacogenetics in asthma patients suggest that haplotypes may be more informative in characterizing genetic/phenotypic associations as compared to analysis of individual genotypes.

Data from clinical studies suggest that genetic variation at loci 16 of *ADRB2* may influence the response to a variety of β_2 -agonists, but the clinical significance of this is not yet clear [Joos, 2002]. Some studies have reported no pharmacogenetic variation in bronchoprotection among asthma patients using either short-acting or long-acting β -agonists [Lipworth, 1999; Hancox, 1998]. Some studies have shown greater bronchodilator response in B16-Arg/Arg homozygotes following acute and chronic β_2 -agonist administration [Lipworth, 1999; Martinez, 1997]. In contrast, increased bronchial hyperresponsiveness to methacholine was reported for B16-Arg/Arg homozygotes [Hancox, 1998].

Israel, *et al*, investigated the genotypes of 190 patients with asthma who had participated in a double-blind, placebo-controlled study comparing scheduled albuterol four times daily versus as-needed albuterol for 16 weeks [Israel, 2000; Israel, 2001].

No clinically significant differences in overall asthma control were found between the groups when genotype was not considered. By contrast, the results of the genotyping showed that there was a small decline in AM PEF (i.e., approximately 7 L/min over a 16-week period) in patients homozygous for Arg16 who used albuterol regularly, which further declined during the run-out period on *prn* albuterol. Gly16/Gly patients did not experience a decline in AM PEF with scheduled albuterol. PM PEF also declined in the Arg16/Arg patients on scheduled albuterol, but not in those who used as-needed albuterol. Of note, a similar response to albuterol QID in patients with the homozygous Arg16 genotype was observed in the Beta-Adrenergic Response by Genotype (BARGE) study, a 16 week, crossover trial [[Israel, 2004](#)].

Other retrospective studies investigating the role of long-acting β_2 -agonists at codon 16 of *ADRB2* include the retrospective analysis by Wechsler, *et al.* They concluded that compared to Gly/Gly patients, Arg/Arg patients may have an impaired therapeutic response to salmeterol in either the absence or presence of concurrent ICS use [[Wechsler, 2006](#)]. In another study, major exacerbations were more frequent in Arg/Arg homozygous asthma patients receiving QID albuterol, but not regular salmeterol [[Taylor, 2000](#)]. However, it was still unclear whether genetic variations at loci 16 of the β_2 -AR gene have unequivocal clinical significance for asthma patients receiving maintenance treatment with long-acting β_2 -agonists when combined with an ICS. Therefore, an investigation of whether the phenotypic response to salmeterol was altered by genotypic variation at the B16 position was warranted.

Given the fact that most previous studies were underpowered to detect an overall effect and/or retrospective in nature, we aimed to prospectively evaluate the influence of genotype in lung function and other asthma-related outcomes. In the context of this study, Arg/Arg, Gly/Gly and Arg/Gly genotypes describe the genetic constitution resulting from a SNP within codon 16 of *ADRB2* corresponding to arginine homozygous, glycine homozygous and arginine/glycine heterozygous subjects, respectively, in terms of the amino acid sequence of *ADRB2*.

4. STUDY OBJECTIVES

PRIMARY

The primary objective of this study was to evaluate lung function as assessed by AM PEF AUC relative to baseline [AUC(bl)] in subjects who have the B16 Arg/Arg genotype compared with that of subjects who have the B16 Gly/Gly genotype over 16 weeks of treatment with FSC DISKUS 100/50mcg BID.

SECONDARY

The secondary objective of this study was to evaluate lung function as assessed by AM PEF AUC(bl) and other measures in other *ADRB2* genotypes in the SM and FSC treatment groups over 16 weeks of treatment.

OTHER

Other objectives included:

- Evaluation by genotype of lung function as assessed by AM PEF AUC(bl) and other measures during the last four weeks of open-label treatment with *prn* albuterol versus that during the last four weeks of open-label treatment with *prn* ipratropium bromide;
- Evaluation of maximum albuterol dose response (MADR) by genotype;
- Evaluation of lung function as assessed by AM PEF AUC(bl) in other *ADRB2* haplotypes in the SM and FSC treatment groups over 16 weeks of treatment;
- Evaluation of assay sensitivity;
- Evaluation of screen failures to address concerns regarding possible selection bias in the two prevalent genotypes.

5. INVESTIGATIONAL PLAN

5.1. Overall Study Design

Screening (2-4 weeks)	Open-Label Treatment Period (8 weeks)		Open-Label Treatment Period (8 weeks)		Double-Blind Treatment Period (16 weeks)			Washout Period (2 weeks)
					FSC 100/50mcg BID (n=270)			n= 90 Arg/Arg n= 90 Glg/Gly n= 90 Arg/Gly
genetic screening	Alb <i>prn</i>		IB <i>prn</i>		SM 50mcg BID (n=270)			n= 90 Arg/Arg n= 90Glg/Gly n= 90 Arg/Gly
NGT 4 weeks	4 weeks	4 weeks	4 weeks	4 weeks	4 weeks	4 weeks	4 weeks	4 weeks
V ₁	V ₂	V ₃	V ₄	V ₅	V ₆ **	V ₇	V ₈	V ₉

** Randomization visit

Alb – albuterol

BID – twice daily

FSC – fluticasone propionate/salmeterol combination
product

IB ipratropium bromide

NGT – not greater than

prn – as needed

SM - salmeterol

The study included a screening period not greater than 4 weeks during which genotyping for each subject was determined, followed by two 8-week open-label treatment periods that were followed by randomization and a double-blind treatment period of 16 weeks. After subjects completed the double-blind treatment period, they entered a 2-week washout period and were continued on open-label Atrovent (ipratropium bromide) *prn*. Ipratropium bromide has been used in a number of asthma clinical trials as the primary rescue therapy [Vathenen, 1988; Tan, 1997; Israel, 2004]. No adverse outcomes have been reported as a result of this use of ipratropium. The experiences in clinical trials with this drug indicate that it can be used safely in this trial, as proposed.

5.1.1. Discussion of Study Design

This was a multi-center, randomized, double-blind, parallel group, active comparator controlled design study. Five hundred forty four (544) randomized subjects provided data on 272 evaluable subjects per treatment group for FSC DISKUS 100/50 and SM DISKUS 50mcg BID. Ninety (90) subjects per genotype (3) per blinded treatment group (2) were targeted for randomization in order to complete at least 82 evaluable subjects per genotype per treatment group. An evaluable subject was defined as a subject who completed at least 2 weeks of double-blind treatment, as documented in the patient diary card.

Subjects with the Arg/Arg genotype (which occurs at a frequency of about 15% in the general population) were compared to subjects with the Gly/Gly genotype (which occurs with approximately a 35% frequency) and to subjects with the Gly/Arg genotype (which occurs with approximately a 50% frequency).

To recruit 90 subjects in each of the genotypic categories per treatment group, it was estimated that a minimum of 1,200 subjects needed to be screened. Allowing for exclusions, refusals to participate and withdrawals, 1,429 subjects were screened. (See Section 6.1 Disposition of Subjects for specific details/numbers for subjects who failed and withdrew during each of the treatment periods.) In order to ensure that ethnic groups were equally represented across treatment groups, randomization to treatment groups was stratified by genotype and race.

5.2. Protocol Amendments

The original protocol, dated 15 June 2004, was submitted 25 August 2004 to the FP/salmeterol combination product DISKUS IND 50,703. The protocol was also submitted to the salmeterol DISKUS IND 43,097 on 25 August 2005 and was submitted to the Ventolin HFA IND 46-269 on 01 November 2004. The protocol was amended three times. The amendments applied to all investigative sites participating in SFA100062.

Amendment 1, dated 17 November 2004, was submitted 23 November 2004 to the FP/salmeterol combination product DISKUS IND 50,703, the salmeterol DISKUS IND 43, 097, and to the Ventolin IND 46,269. This amendment was implemented following the first site initiation and Investigator Meeting held on 11 and 12 October 2004. The following revisions were made:

- Updated sponsor contact information
- Removed the limitation for methacholine challenge testing only on subject ≥ 18 years of age
- Added historical $PC_{20} < 8\text{mg/ml}$ as acceptable
- Added exclusion criterion of exercise induced bronchospasm
- Modified time intervals for anti-asthma medications
- Clarified use of corticosteroids in the Exclusion Criteria
- Added an exclusion criterion for peanut and soybean food allergy
- Added AM PEF stability limits
- Added a requirement to obtain vital signs data during MADR testing
- Removed Appendices 5 and 7
- Corrected administrative and typographical errors

Amendment 2, dated 14 June 2005, was submitted 05 July 2005 to all INDs noted for the protocol. This amendment was implemented 29 June 2005, after approximately 49% of subjects were randomized. The following revisions were made in the identified sections:

- Clarifications in the Protocol Summary, Open-Label Treatment periods (continuation criteria added at Visit 2)
- Study population (number of screened subjects)
- Section 5, Inclusion criteria numbers 3, 6, and 7 regarding pregnancy testing, historical reversibility, and pre-study anti-asthma medication use required for participation
- Section 5, Exclusion Criteria numbers 4, 5, 6, 9, and 10 regarding exercise induced bronchospasm, prohibited anti-asthma medications, prohibited concurrent medications, respiratory tract infection and antibiotic use
- Section 6 Study Assessments, Rescreening (use of historical reversibility), Visit 2 continuation criteria added, premature discontinuation visit (open-label and washout periods), methacholine challenge testing (manual), albuterol and ipratropium bromide use (during open-label, randomization, and washout periods)
- Section 7. Dosage and Administration to include the washout period
- Section 8. Concomitant Medications, permitted and prohibited medications to agree with Section 5, inclusion and exclusion criteria

- Section 9. Subject Completion to include a discontinuation visit and Withdrawal to include screen and open-label, washout failures (data collection)
- Section 11. Data Analysis and Statistical Considerations, Other Comparisons of Interest and Sample Size Considerations modified;
- Corrections of administrative and reference errors.

Amendment 3, dated 16 February 2006 was submitted 28 February 2006 to all INDs noted for the protocol. This amendment was implemented 23 February 2006, after approximately 88% of subjects were randomized. The following revision was made:

- Replacement of the investigational product open label ipratropium bromide CFC inhalation aerosol 18mcg with ipratropium bromide HFA inhalation aerosol 21mcg.

5.3. Selection of Study Population

The study population was selected based on the inclusion and exclusion criteria that follow, as well as a determination of the genotype (and race) of a potential subject.

5.3.1. Inclusion Criteria

A subject was eligible for inclusion in this study only if all of the following criteria applied:

1. **Type of Subject:** A subject was treatable as an outpatient.
2. **Age:** A subject was 12 years of age or older at Visit 1.
3. **Gender:** Male or Female.

Females were eligible to participate only if they were currently non-pregnant and non-lactating. There were no birth control restrictions for this study. Female subjects of childbearing potential had a urine pregnancy test at the beginning of the study (Visit 2) and at Visit 4, 6, 8, 10, and at the end of the study (Visit 11 or a Premature Discontinuation Visit which may have occurred during the open-label periods, the double-blind treatment period, or the washout period.) Any female who became pregnant during the study was withdrawn. Female subjects could not be enrolled if they planned to become pregnant during the time of study participation.

4. **Disease:** Each subject had a diagnosis of persistent asthma for at least 3 months prior to Visit 1. Asthma is defined by the American Thoracic Society as follows:

“Asthma is a clinical syndrome characterized by increased responsiveness of the tracheobronchial tree to a variety of stimuli. The major symptoms of asthma are paroxysms of dyspnea, wheezing, and cough, which may vary from mild and almost undetectable to severe and unremitting (status asthmaticus). The primary physiological manifestation of this hyperresponsiveness is variable airways obstruction. This can take the form of spontaneous fluctuations in the severity of

obstruction, substantial improvements in the severity of obstruction following bronchodilators or corticosteroids, or increased obstruction caused by drugs or other stimuli” [[American Thoracic Society](#), 1987].

5. **FEV₁ Component:** The subject had a best FEV₁ that was $\geq 70\%$ and $\leq 100\%$ of predicted normal at Visit 1 after withholding asthma medications as detailed in the protocol and Section 5.3.2. Exclusion Criteria. Predicted FEV₁ was based on the National Health and Nutrition Examination Survey (NHANES III) predicted normal values for ages 8 years and older [[Hankinson](#), 1999].
6. **Reversibility Component:** The subject had reversible airways disease as demonstrated by an increase in FEV₁ of $\geq 12\%$ and 200ml over baseline within 30 minutes after the inhalation of 2-4 puffs (180mcg -360mcg) of albuterol (with or without a spacer) or 1-2 nebulized albuterol (2 puffs = 1 nebule) treatments at Visit 1 or at a visit that was within the 7-day period immediately following Visit 1. If the subject failed to reverse at least 12% during Visit 1, a second attempt to reverse was allowed to be scheduled within 7 days.

If the second attempt to document reversibility was unsuccessful, a methacholine challenge test (MCT) was permitted. A PC₂₀ result of $< 8\text{mg/ml}$ obtained at an unscheduled visit prior to Visit 2 was required. A historical PC₂₀ value of $< 8\text{mg/ml}$ that was documented at the investigative site within the past 12 months and was obtained using American Thoracic Society (ATS) or Asthma Clinical Research Network (ACRN) guidelines for MCT was also acceptable [[American Thoracic Society](#), 2000; [ACRN](#), 2002]. Methacholine challenge testing was performed only at sites that had past experience performing this test.

Note: Documentation of historical reversibility within one year of the Screening Visit demonstrating an increase in FEV₁ of $\geq 12\%$ and 200ml over baseline was acceptable and precluded the requirement for reversibility testing at the Screening Visit.

7. **Concurrent Anti-Asthma Therapy:** Eligible subjects reported short-acting β_2 -agonist for use on a *prn* (or scheduled) basis for at least 4 weeks prior to Visit 1. Each subject was judged by the investigator to be able to withhold short-acting β_2 -agonist therapy for at least 6 hours prior to clinic visits when FEV₁ was performed.
8. The subject agreed to allow a venipuncture for blood draw.
9. The subject demonstrated correct use of the DISKUS device and a metered dose inhaled (MDI), as well as correct use of a peak flow meter.
10. **Literacy:** A subject was able to read, comprehend and record information.

5.3.2. Exclusion Criteria

A subject was not eligible for inclusion in this study if any of the following criteria applied:

1. **Life-Threatening Asthma:** A subject had life-threatening asthma. Life-threatening asthma was defined for this study as a history of significant asthma episode(s) requiring intubation, associated with hypercapnia, respiratory arrest, hypoxic seizures, or asthma-related syncopal episode(s).
2. **Asthma instability:** A subject was hospitalized due to asthma within 6 months prior to Visit 1.
3. **Respiratory Disease:** Current evidence of cystic fibrosis, pneumonia, pneumothorax, atelectasis, pulmonary fibrotic disease, chronic bronchitis or any other respiratory abnormalities other than asthma excluded a subject from participation.
4. **Exercise-Induced Bronchospasm Alone:** A subject was diagnosed with exercise-induced bronchospasm alone, in the absence of a diagnosis of persistent asthma within the last 3 months prior to Visit 1.
5. **Anti-Asthma Medications:** Asthma medications listed below must not have been used prior to Screening (Visit 1) for the required interval indicated below and not taken during study.

Oral short-acting beta ₂ -agonists	6 hours
Inhaled short-acting anticholinergics	6 hours
Inhaled long-acting anticholinergics	24 hours
Leukotriene modifiers	4 weeks
Inhaled long-acting beta ₂ -agonists	4 weeks
Theophylline products	48 hours
Oral long-acting beta ₂ -agonists	4 weeks
Inhaled corticosteroids	4 weeks
Inhaled corticosteroid/ Inhaled long-acting beta ₂ -agonist combination products	4 weeks
Oral corticosteroids	4 weeks ^{1,2}
Parenteral corticosteroids	4 weeks ²
Inhaled cromolyn sodium or nedocromil	4 weeks

1. Any subject who has received oral corticosteroid treatment for any reason for 2 months or longer must have discontinued use for at least 6 months prior to Visit 1.
 2. A subject must not have had two courses of oral or parenteral corticosteroids for any reason in the 6 months prior to Visit 1
6. **Concurrent medications:** Concurrent use of any of the following medications that may have affected the course of asthma or interact with sympathomimetic amines was not allowed. Specifically:
 - beta blockers
 - polycyclic antidepressants

- monoamine oxidase inhibitors
- phenobarbital
- rifampin.

Note: Regular use of short-acting nasal decongestants was allowed. Other intranasal medications including antihistamines and intranasal corticosteroids for the treatment of rhinitis were also allowed. Topical hydrocortisone cream or ointment (1% or less) was also allowed.

7. **Immunosuppressive Medications:** Use of immunosuppressive medications was not allowed at any time during the study.

Note: Immunotherapy for the treatment of allergies was allowed during the study, provided that the subject has received a constant dose for 30 days prior to Visit 1 and the same dose was continued throughout the study.

8. **Other Medications:** The medications listed below must not have been used prior to Screening (Visit 1) for the required interval indicated below, and not taken during the study.

- Methotrexate, gold, cyclosporine and azathioprine 12 months
- Ritonovir 12 months

9. **Respiratory Tract Infection:** The subject had a respiratory infection that was suspected or diagnosed within 4 weeks immediately preceding Visit 1 or during the period from Visit 1 to Visit 2. The subject was allowed to be re-screened one time. Re-screening must have been no sooner than 4 weeks following resolution of any suspected or diagnosed respiratory infection (whether treated or not).

10. **Antibiotic Usage:** The subject used an antibiotic (or other medication) for treatment of a suspected or diagnosed upper or lower respiratory tract infection within 4 weeks of Visit 1 or during the periods from Visit 1 to Visit 2. The subject could be re-screened one time. Antibiotics for other infections or acne were permitted.

11. **Other Concurrent Conditions/Diseases:** Any clinically significant, uncontrolled condition or disease state that, in the opinion of the investigator, would put the safety of the subject at risk through study participation or would confound the interpretation of the results if the condition/disease exacerbated during the study excluded a subject from participation. The list of conditions/diseases that resulted in exclusion if such a condition/disease was determined to be clinically significant included, but was not limited to: cardiac arrhythmias, congestive heart failure, coronary artery disease, Cushing's or Addison's disease, diabetes mellitus, dyspnea by any cause other than asthma, hematological, hepatic, neurological, thyroid, peptic ulcer, or renal disease, uncontrolled hypertension, immunologic compromise, current malignancy, current or quiescent tuberculosis.

12. **Drug Allergy:** The subject had any adverse reaction, including immediate or delayed hypersensitivity, to study medications, severe milk protein allergy, or allergies to soya lecithin or related food products such as soybeans or peanuts.
13. **Tobacco Use:** The subject had a greater than a 10 pack-year history of cigarette smoking and/or use of any tobacco products within 1 year of Visit 1.
14. **Positive Pregnancy Test (for females of childbearing potential):** A current positive pregnancy test.
15. **Questionable Validity of Consent:** The subject or parent (caregiver) had a history of psychiatric disease, intellectual deficiency, poor motivation, substance abuse (including drug and alcohol), or other conditions which would limit the validity of informed consent to participate in the study.
16. **Investigational Drug:** A subject was exposed to an investigational drug within 30 days prior to Visit 1.
17. **Affiliation with Investigational Site:** A subject could not participate if he or she was a participating investigator, a sub-investigator, a study coordinator, an employee of a participating investigator, or was an immediate family member of the aforementioned.
18. **Questionable Compliance with Medications or Visits:** A subject could not participate if he or she had an infirmity, disability or geographical location which seemed likely, in the opinion of the investigator, to impair compliance with any aspect of the study protocol or scheduled visits.

5.3.3. Subject Completion

A subject, who completed the 16 week double-blind treatment period and all Visit 11 evaluations, completed the study. At the conclusion of Visit 11, each subject was provided with instructions on continued self-monitoring of pulmonary function, medications, and timely communication with a healthcare provider to help assure informed management of his/her asthma.

Note: Medications (asthma and non-asthma) that were prescribed at the last clinic visit recorded in the source documents for the subject and not recorded on the CRF for the subject unless the medication was administered prior to the completion of all study procedures at the last clinic visit.

Any clinically significant adverse events or clinically significant unfavorable changes observed during a physical examination at Visit 11 (Completion Visit) necessitated that the subject be followed or treated until satisfactory resolution occurs.

5.3.4. Predetermined Criteria for Subject Discontinuation/Withdrawal

A subject could voluntarily discontinue/withdraw participation in this study at any time. The investigator could also, at his or her discretion, discontinue the subject from participating in this study at any time.

Criteria for subject withdrawal were identified in the protocol as follows:

Screening period

Subject discontinuation and withdrawal from the screening period (Visit 1 to Visit 2) of the study was required, when:

- A subject was significantly non-compliant with the requirements of the protocol
- A subject became pregnant
- A subject had an adverse event that would, in the investigator's judgement, make continued participation in the study an unacceptable risk
- The subject experienced an asthma exacerbation as defined by the protocol, i.e. a clinical exacerbation was defined as worsening asthma requiring emergency intervention, hospitalization, or treatment with asthma medication in addition to those allowed by the protocol
- The number of subjects per genotype required for each treatment group was met
- GlaxoSmithKline discontinued the study.

Open-label period

A subject who took open-label study drug, but either did not complete the 16 week open-label treatment period or did not complete Visit 6 evaluations was considered discontinued and withdrawn from the study.

Subject withdrawal from the open-label period of the study was required, and discontinuation procedures were performed, when:

- A subject was significantly non-compliant with the requirements of the protocol
- A subject became pregnant
- A subject had an adverse event that would, in the investigator's judgement, make continued participation in the study an unacceptable risk
- The subject experienced more than one asthma exacerbation as defined by the protocol, i.e. a clinical exacerbation was defined as worsening asthma requiring emergency intervention, hospitalization, or treatment with asthma medication in addition to those allowed by the protocol

- The number of subjects per genotype required for each treatment group was met
- GlaxoSmithKline discontinued the study.

Double-blind Period and Washout Period

A subject who took double-blinded study drug, but either did not complete the 16 week treatment period or did not complete Visit 10 evaluations was considered discontinued and withdrawn from the study. Discontinued subjects were not replaced.

Subject withdrawal from the study was required, and Discontinuation Visit procedures were performed during the double-blind period or during the washout period when:

- A subject was significantly non-compliant with the requirements of the protocol
- A subject became pregnant
- A subject had an adverse event that would, in the investigator's judgement, make continued participation in the study an unacceptable risk
- The treatment blind was broken for a subject
- The subject experienced an asthma exacerbation as defined by the protocol, i.e. a clinical exacerbation was defined as worsening asthma requiring emergency intervention, hospitalization, or treatment with asthma medication in addition to those allowed by the protocol
- GlaxoSmithKline discontinued the study.

If a subject was prematurely discontinued from participation in the study for any reason including voluntary withdrawal, the investigator was required to make every effort to perform all evaluations specified for the Discontinuation Visit. See Section 5.6.1. Demographic and Baseline Assessments, Premature Discontinuation Visit, for discontinuation procedures. At the conclusion of the Discontinuation Visit, each subject was provided with instructions on continued self-monitoring of pulmonary function, medications, and timely communication with a healthcare provider to help assure informed management of his/her asthma.

Note: Medications (asthma and non-asthma) that were prescribed at the last clinic visit were only recorded in the subject's source documents and not recorded on the subject's CRF unless the medication was administered prior to the completion of all study procedures at the last clinic visit.

Any clinically significant adverse events or clinically significant unfavorable changes on physical examination observed during the discontinuation visit necessitated that the subject be followed or treated until satisfactory resolution occurred.

In the event that a subject was prematurely discontinued from the study at any time due to an adverse event (AE) or a serious adverse event (SAE), a Discontinuation Visit was required.

5.3.4.1. Subject discontinuation/withdrawal from the investigational product

If study drug was permanently discontinued during the course of the study, the subject was withdrawn from the study. The investigator was required to make every effort to perform the evaluations specified for the Discontinuation Visit.

Subjects who were discontinued from the study due to premature discontinuation of study drug were not replaced.

5.3.4.2. Subject discontinuation/withdrawal from the study during the screening period or open-label periods

A subject who had at least one study procedure performed (in addition to signing a consent form), and was assigned a subject number, but did not participate in the open-label period(s), was classified as having failed screening (Visit 1), discontinued and withdrawn from the study. The following information was collected in the CRF on subjects who failed at the Screening Visit (Visit 1) or any time prior to Visit 2. The following information was also collected in the CRF on subjects who failed at Visit 2, or any time during the open-label periods prior to or at Visit 6, and was withdrawn from the study:

- Demographic information (including race, age and gender)
- Inclusion/exclusion criteria
- Duration of asthma
- Asthma concomitant medications
- Non-asthma concomitant medications
- Reversibility assessment
- Pulmonary function tests (including MADR, if applicable)
- Continuation criteria, if applicable
- Reason subject was a screening or open-label failure
- Pharmacogenetic (PGx) information
- Investigational product information
- Asthma exacerbation data

- Any adverse events/SAEs that occurred during the screening and open-label periods
- Investigator comments
- Investigator signature
- Diary cards, if applicable.

5.4. Investigational Product(s)

5.4.1. Description of Investigational Product(s)

Double-blind study drugs were manufactured by GSK. Each site was supplied with sufficient supplies to conduct the trial. Open-label albuterol sulfate MDI CFC and HFA were also manufactured by GSK. Open label ipratropium bromide MDI CFC and HFA were manufactured by 3M Pharmaceuticals. The following clinical trial materials were shipped to the sites.

Product	Strength	Batch ID Number	Review Date
Fluticasone propionate/salmeterol DISKUS	100/50mcg/blister		7/31/2005 1/31/2006 7/31/2006 2/28/2007
Salmeterol DISKUS	50mcg/blister		11/30/2005 2/28/2006 2/28/2006 10/31/2006 4/30/2007
Albuterol sulfate MDI	90mcg MDI CFC		5/31/2007 2/28/2007 6/30/2007 9/30/2007
Albuterol sulfate MDI	90mcg MDI HFA		8/31/2005 12/31/2005 3/31/2006 8/31/2006
Ipratropium bromide MDI/ACT	18mcg MDI CFC		3/31/2006 3/31/2006 8/31/2006 3/31/2007 4/30/2007
Ipratropium bromide MDI/ACT	18mcg MDI HFA		5/31/2007
Placebo ZG, MDPI, BW	N/A		5/31/2007
Leaflet DISKUS, Multi Language	N/A N/A		6/30/2007 8/29/2008

Each double-blind DISKUS was provided in a numbered treatment pack and was labeled with a 1-part, 1-panel double-blind label. The carton was labeled with a 3-panel blinded

label. The second and third panels were removed from the carton label and placed in the source documents.

Albuterol inhalation aerosol MDI and ipratropium bromide MDI were provided to each subject as appropriate within the study design for use as needed.

All investigational products were stored in a secure area with access limited to the investigator and authorized site staff, and under physical conditions that were consistent with investigational product-specific requirements.

5.4.2. Dosages and Administration

At Visit 2, (open-label albuterol period) eligible subjects were given open-label albuterol 90mcg for use as needed (*prn*) to relieve asthma symptoms for 8 weeks (56 days $\pm$ 2 days). Visit 3 occurred 4 weeks following Visit 2. After this 8-week treatment period, at Visit 4, (open-label ipratropium period), subjects were given open-label ipratropium 18mcg for use as needed (*prn*) to relieve asthma symptoms for 8 weeks (56 days $\pm$ 2 days). Subjects also received open-label albuterol 90mcg for *prn* use in the event that asthma symptoms responded incompletely to ipratropium, in which case albuterol would be used as a superceding medication. Visit 5 occurred 4 weeks following Visit 4.

At Visit 6 (randomization visit), subjects were assigned a double-blind treatment for 16 weeks (112 days $\pm$ 2 days). Each subject received a supply of study medication via the DISKUS for one of two possible treatment groups. Double-blind medication was dispensed according to the Time and Events Table shown in Section 13. Time and Events Table.

Subjects inhaled the first dose of double-blind study medication in the clinic on the day of randomization (Visit 6). Subjects received a DISKUS inhaler. The subject was instructed to administer one inhalation each morning and one inhalation each evening, approximately 12 hours apart, after obtaining their morning and evening PEF measurements. Each subject was to be advised to adhere to this dosing regimen throughout the study.

All eligible subjects were given open-label ipratropium bromide 18mcg for use only as needed throughout the double-blind period of the trial. Subjects also received open-label albuterol 90mcg for *prn* use in the event that asthma symptoms respond incompletely to ipratropium bromide, in which case albuterol would be used as a superceding medication for acute relief.

All subjects who completed Visit 10 of the double-blind treatment period were given open-label ipratropium bromide 18mcg for use during the washout period. Subjects also received open-label albuterol 90mcg for *prn* use in the event that asthma symptoms responded incompletely to ipratropium bromide, in which case albuterol was to be used as a superceding medication for acute relief.

5.4.3. Dose Rationale

Doses of blinded study medication were selected for the following reasons.

- The 100/50mcg strength of FSC DISKUS is approved in the US for the maintenance treatment of asthma in adults and adolescents at least 12 years of age and provided subjects with the lowest approved daily dose of fluticasone propionate (FP) and salmeterol (SM) as a combination product.
- SM 50mcg BID via the DISKUS inhaler is approved in the US for the maintenance treatment of asthma in adults and children 4 years of age and older.

5.4.4. Blinding

A label was attached, with the protocol number and instructions for use and storage, to each double-blind DISKUS device.

All double-blind study drugs were supplied in identical DISKUS devices to blind the treatments. A pre-determined supply of double-blind study drug packs was dispatched to each site for allocation via a centralized distribution. The medication packs were not subject specific and were not necessarily sequentially numbered. Additional treatment packs were supplied to the sites as needed.

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 by accessing the IVRS. If the blind was broken for any reason, the investigator had to notify GSK immediately of the unblinding incident without revealing the subject's study treatment assignment. In addition, the date and reason for revealing the blinded treatment assignment was recorded in the case report form. GSK clinical personnel and their designees remained blinded.

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

This study used an interactive voice response system (IVRS) for an emergency unblinding.

5.4.5. Treatment Assignment

At Visit 1, a unique Subject Number was assigned to any subject who had at least one Visit 1 procedure performed, other than informed consent. This Subject Number was used to identify individual subjects during the course of the study. If the subject repeated Visit 1 for any reason, the original subject number assigned was retained.

Subjects who were eligible to participate in the double-blind phase of the trial were randomized to a treatment group through a telephone call to the designated IVRS system. During this call, the IVRS confirmed the CRF number (Subject Number) and provided two additional numbers:

- A medication pack number that identified the DISKUS of double-blind medication dispensed to the subject from the Investigator's inventory.
- A randomization number (Treatment Number) that was an identification number assigned from a randomization schedule created by GlaxoSmithKline.

For subsequent visits when study medication was to be dispensed, a telephone call was made to the IVRS for the next medication pack number to be assigned from the investigator's inventory.

Although study medication was stored at each site, the investigator, or designee, was required to telephone into the IVRS to obtain study medication assignments. All calls to the IVRS were confirmed with faxes that were sent to the investigator upon completion of each call. Detailed IVRS use instructions and worksheets were provided at study start.

Subjects were assigned to study treatment in accordance with the randomization schedule. This study utilized an IVRS, which provided a means for systematic central allocation of drug (SCAD). Each investigator was supplied with sufficient supplies to conduct the trial. Additional double-blind medication packs were supplied as needed to the sites.

5.4.6. Assessment of Treatment Compliance

At each visit during open-label treatment, study site personnel assessed subject compliance with study drug by assessing diary cards completed by subjects. At each visit during double-blind treatment, study site personnel assessed subject compliance with study drug by reviewing the diary card completed by each subject and by the number of doses remaining in the DISKUS device per the counter contained within the device. The number of doses remaining was recorded in the source documents for the subject and in the CRF when a new DISKUS device was dispensed.

5.4.7. Treatment of Investigational Product Overdose

An overdose was defined as a dose greater than the total doses described above which results in clinical signs and symptoms. In the event of an overdose of study medication, the investigator was required to use clinical judgement in treating the overdose and contact the study medical monitor.

GlaxoSmithKline (GSK) did not recommend specific treatment guidelines for overdose and toxicity management. The investigator was advised to refer to the relevant document(s) for detailed information regarding warnings, precautions, contraindications, adverse events, and other significant data pertaining to the study drug(s) being used in this study. Such documents included, but were not be limited to, the Clinical Investigator's Brochure (CIB) or equivalent document provided by GSK, the approved

product label (if applicable), or both. Clinical judgement was required to be used in treating the overdose.

5.5. Prior and Concomitant Medications and Non-Drug Therapies

5.5.1. Permitted Medications

Short acting beta₂-agonist medication(s) and any other anti-asthma medications taken four weeks prior to Visit 1 were to be recorded in the CRF.

All concomitant medications and any anti-asthma medications other than study medications taken during the study were recorded in the CRF.

5.5.2. Prohibited Medications

Concurrent use of any of the following medications that may have affected the course of asthma or interact with sympathomimetic amines were not allowed. Specifically:

- beta blockers
- polycyclic antidepressants
- monoamine oxidase inhibitors
- phenobarbital
- rifampin
- methotrexate, gold, cyclosporine and azathioprine
- ritonavir

Also see Section 5.3.2 Exclusion Criteria for anti-asthma medications that were prohibited during the conduct of this study. Exception: a short course of an oral corticosteroid was allowed for the treatment of an exacerbation during the open-label period.

5.5.3. Medical Device(s)

Daily PEF was measured by the subject using a peak flow meter in accordance with specific instructions explained by the study staff. The subject was required to demonstrate correct use of the peak flow meter at Visit 2.

5.6. Study Assessments and Procedures

A time and events schedule detailed the timeframe in which visits occurred and the procedures performed at each study visit (See Section 13. Time and Events Table). The following were general criteria to be followed during the conduct of the study:

- All visits (when clinic FEV₁ was performed) started between 6 AM and 11 AM

- During the open-label periods and washout period, subjects withheld all short-acting β_2 -agonist and ipratropium bromide medication(s) for at least 6 hours prior to spirometry
- During the double-blind period, subjects withheld double-blind study medication on the mornings of clinic visits, as well as ipratropium (and albuterol) within 6 hours of spirometry
- Visits were allowed to be rescheduled once. (See Section 5.6.3. Assessment of pulmonary function, Clinic FEV₁).

5.6.1. Demographic and Baseline Assessments

Informed Consent

The informed consent was signed by the subject and witnessed prior to performance of any study procedures, evaluations or changes in medications required for study participation.

Study Visit Assessments

Screening Visit (Visit 1)

Each subject was evaluated to determine if the selection criteria were met (Section 5.3.1. Inclusion Criteria, and Section 5.3.2., Exclusion Criteria).

All procedures in this period were completed and results made available prior to Visit 2. All procedures were performed on the day of Visit 1.

The following assessments/procedures were performed at Visit 1:

- Verification of inclusion/exclusion criteria
- Medical history
- Physical examination (results recorded in source documents only)
- Concomitant medication assessment
- Vital signs (blood pressure and pulse), recorded in source documents only
- Clinic FEV₁ (including calculation of FEV₁ percent predicted)
- FEV₁ reversibility assessment (historical assessment allowed)
- Blood draw
- Adverse event assessment (study participation related events only)

The blood samples were taken on a single occasion unless a duplicate sample was required due to inability to use the original sample. Blood samples were taken at Visit 1, unless the patient did not meet the FEV₁ or reversibility requirement and planned to re-screen, in which case, the blood samples were drawn during the re-screening visit.

Re-Screening: If a subject did not meet the Screening (Visit 1) inclusion criteria based upon FEV₁ percent predicted or reversibility, the subject was rescheduled once within 1 week to conduct the Visit 1 pulmonary function tests again. The subject was required to wait at least 48 hours before returning to the site to repeat pulmonary function testing for FEV₁ percent predicted or reversibility and the conduct of other Visit 1 procedures.

If a subject required re-screening for reasons other than failure to achieve criteria for FEV₁ percent predicted or reversibility, historical reversibility obtained at Visit 1 was acceptable to allow the subject to participate, if all other required inclusion and exclusion criteria were met.

If methacholine challenge testing was performed and a PC₂₀ of <8mg/ml was obtained within 2 weeks, adverse events reported and medication use was recorded. If methacholine challenge testing was performed more than 2 weeks following Visit 1, then all other Visit 1 procedures were performed on the date that the MCT was performed.

Note: A subject was required to meet both FEV₁ criteria (FEV₁ percent predicted and reversibility) on the same study visit day.

Visit 2 (Open-Label Treatment Period 1 - Albuterol)

Visit 2 was conducted after the pharmacogenetic testing was performed. This visit was to be 4 weeks +2 days after Visit 1.

The following assessments/procedures were performed at Visit 2:

- Adverse event assessment (study participation related events only)
- Concomitant medication assessment
- Urine pregnancy test for all females of childbearing potential
- Clinic FEV₁
- Assess continuation criterion
- Dispense peak flow meter
- Dispense diary card
- Dispense open-label study medication (albuterol)

Visit 3

Visit 3 was conducted 4 weeks $\pm$ 2 days after Visit 2.

The following assessments/procedures were performed at Visit 3:

- Adverse event assessment
- Concomitant medication assessment
- Clinic FEV₁
- Assess continuation criteria
- Collect and review diary card
- Collect study medication
- Calculate PEF Stability Limit
- Dispense diary card
- Dispense open-label study medication (albuterol)

Visit 4 (Open-Label Treatment Period 2 - Ipratropium bromide)

Visit 4 was conducted 4 weeks $\pm$ 2 days after Visit 3.

The following assessments/procedures were performed at Visit 4:

- Adverse event assessment
- Concomitant medication assessment
- Urine pregnancy test for all females of childbearing potential
- Clinic FEV₁
- Assess continuation criteria
- Maximum albuterol dose assessment (MADR)
- Collect and review diary card
- Collect study medication
- Dispense diary card
- Dispense open-label study medication (ipratropium bromide & albuterol)

Visit 5

Visit 5 was conducted 4 weeks $\pm$ 2 days after Visit 4.

The following assessments/procedures were performed at Visit 5:

- Adverse event assessment
- Concomitant medication assessment
- Clinic FEV₁
- Assess continuation criteria
- Collect and review diary card
- Collect study medication
- Dispense diary card
- Dispense open-label study medication (ipratropium bromide & albuterol)

Note: No subject was permitted to experience more than one exacerbation between Visit 2 and Visit 6 and remain in the study. Any subject who experienced an exacerbation at or following Visit 6 was discontinued from the study.

Visit 6 (Randomization Visit – Double Blind Period)

Visit 6 was conducted 4 weeks $\pm$ 2 days after Visit 5.

The following assessments/procedures were performed at Visit 6:

- Adverse event assessment
- Concomitant medication assessment
- Urine pregnancy test for all females of childbearing potential
- Clinic FEV₁
- Assess continuation criteria
- Maximum albuterol dose response (MADR)
- Collect and review diary card
- Collect study medication
- Dispense diary card

- Dispense rescue medication (ipratropium bromide & albuterol)
- Dispense double-blind study medication

Visit 7

Visit 7 was conducted 4 weeks $\pm$ 2 days after Visit 6.

The following assessments/procedures were performed at Visit 7:

- Adverse event assessment
- Concomitant medication assessment
- Clinic FEV₁
- Collect and review diary card
- Collect study medication
- Dispense diary card
- Dispense rescue medication (ipratropium bromide & albuterol)
- Dispense double-blind study medication

Visit 8 - 10

Visit 8, Visit 9, and Visit 10 were conducted 4 weeks $\pm$ 2 days after each preceding visit.

The following assessments/procedures were performed at Visit 8, Visit 9 and Visit 10:

- Adverse event assessment
- Concomitant medication assessment
- Urine pregnancy test for all females of childbearing potential (only at Visit 8 and 10)
- Physical examination (results recorded in source documents only, unless there was a clinically significant change from baseline) (only at Visit 10)
- Vital signs (blood pressure and pulse, only at Visit 10), recorded in source documents only
- Maximum albuterol dose assessment (MADR) (only at Visit 10)
- Clinic FEV₁
- Collect study medication

- Collect and review diary card
- Dispense rescue medication (ipratropium bromide & albuterol)
- Dispense double blind study medication (Visit 8 and Visit 9)
- Dispense diary card

Visit 11 (Washout Period)

Visit 11 was conducted 2 weeks $\pm$ 2 days after Visit 10.

The following assessments/procedures were performed at Visit 11:

- Adverse event assessment
- Concomitant medication assessment
- Urine pregnancy test for all females of childbearing potential
- Clinic FEV₁
- Collect study medication
- Collect and review diary card

At this visit, each subject was provided with instructions on continued self-monitoring of pulmonary function, medications, and timely communication with a healthcare provider to help assure informed management of his/her asthma.

Premature Discontinuation Visit

The following assessments/procedures were performed at a Premature Discontinuation visit that may have occurred during the open-label period(s), double-blind treatment period, or washout period:

- Physical examination (results recorded in source documents only, unless there was a clinically significant change from baseline)
- Adverse event assessment
- Concomitant medication assessment
- Vital signs (blood pressure and pulse), recorded in source documents only
- Urine pregnancy test for all females of childbearing potential
- Clinic FEV₁
- Collect and review diary card

- Collect study medication

At this visit, each subject was provided with instructions on continued self-monitoring of pulmonary function, medications, and timely communication with a healthcare provider to help assure informed management of his/her asthma.

5.6.2. Efficacy Assessments

5.6.2.1. Primary efficacy endpoint

The primary measure of efficacy was area under the curve describing AM PEF relative to baseline [AUC(bl)] over the sixteen-week double-blind treatment period. The primary comparison of interest was between the Arg/Arg and Gly/Gly genotypes in the FSC treatment group.

5.6.2.2. Secondary efficacy endpoints

Secondary measures of efficacy included area under the curve (describing PM PEF and FEV₁ over time) relative to baseline [AUC(bl)]. Other secondary measures were change from baseline in percent of symptom free days, and supplemental Atrovent (ipratropium bromide) use.

5.6.2.3. Other efficacy endpoints

Other endpoints were as follows:

- Evaluation of lung function as assessed by AM PEF AUC(bl) during the last four weeks of open-label treatment with *prn* albuterol versus that during the last four weeks of open-label treatment with *prn* ipratropium bromide by genotype
- Other measures of efficacy included the proportion of subjects requiring supplemental albuterol and an evaluation of maximum albuterol dose responses (MADR) by genotype
- Evaluation of lung function was assessed by AM PEF AUC(bl) in other *ADRB2* haplotype pairs in the SM and FSC treatment groups over 16 weeks of treatment.

5.6.3. Assessment of pulmonary function

PEF

Peak expiratory flow (PEF) measurements were collected via a study-issued Peak Flow Meter. The subject was instructed on proper use of the peak flow meter and on recording the results on the diary card.

Each subject was instructed to perform triplicate PEF measurements in the morning and evening of each day during the study. The morning determinations were performed prior to the subject taking the morning dose of study medication or rescue medication. The evening measurements were performed after recording the asthma symptom scores and prior to the subject taking the evening dose of study medication or rescue medication.

The highest of the 3 values of morning and evening PEF were recorded on the subject diary card.

AM PEF Stability Limit

For those who qualified for the study, an AM PEF Stability Limit was calculated at Visit 3 as follows:

- The AM PEF Stability Limit was calculated using the mean morning PEF from the 7 consecutive days preceding Visit 3, using the morning PEF from the day prior to Visit 3 as day 7. The AM PEF Stability Limit was defined as 80% of the mean morning PEF and used for the duration of the study.

The subject was counselled on the usefulness of the peak flow meter as a means of monitoring his/her asthma status. Subjects were informed of their AM PEF Stability Limit and educated to be alert to a pattern of consistently decreasing PEF as a warning of possible worsening of asthma/asthma exacerbation. Subjects were instructed to call the investigator if such a profile of declining PEF was observed, or if their PEF fell below the AM PEF Stability Limit for 2 or more consecutive days. If such a pattern was observed, it was not a protocol-defined exacerbation unless it met the definition of an asthma exacerbation.

Clinic FEV₁

FEV₁ was performed on all subjects using the spirometry equipment at each site. The equipment met or exceeded the minimal performance recommendations of the ATS.

Spirometry equipment used to perform FEV₁ was calibrated according to the manufacturer's recommendation on a frequent and regular schedule, but not less than once per week. The calibration results were recorded on a PFT calibration log, which was monitored during site visits.

For each time observation, triplicate measurements were performed with the subject in one position (i.e. sitting or standing) for all his/her pulmonary function test (PFT) determinations. For the FEV₁, the "best effort" was defined as the effort (or each triplicate set) with the highest value. This result was entered into the CRF.

It was the responsibility of the investigator (or designee), to print a hard copy of each measurement and review the results to ensure that the subject met all inclusion criteria, continuation criteria, and randomization criteria. The hard copy of each measurement is maintained in the subject's study file.

The FEV₁ was performed between 6:00 – 11:00 AM on clinic visits (see Section 13, Time and Events Table for visits when FEV₁ was performed). In addition, FEV₁ was performed:

- $\geq$ 6 hours after use of albuterol
- $\geq$ 6 hours after use of ipratropium bromide

- ≥ 6 hours after caffeine consumption
- ≥ 2 hours after exercise (or strenuous activity)
- ≥ 15 minutes after prolonged exposure to cold air
- Prior to the administration of the morning dose of double-blind study medication.

Note: If all these criteria were not met prior to testing, the visit was scheduled for another day within the ± 2 day window. A visit could only be rescheduled once.

Prior to Visit 1, asthma medications could not be used for the required interval indicated in Section 5.3.2. Exclusion Criteria.

Calculation of FEV₁ percent predicted

Each subject was required to demonstrate an FEV₁ value ≥ 70 -100% of normal predicted at Visit 1. The FEV₁ percent predicted was calculated using the best effort clinic FEV₁ as follows:

$$\% \text{ Predicted} = \frac{\text{FEV}_1 \text{ (Highest)}}{\text{FEV}_1 \text{ (Predicted)}} \times 100$$

FEV₁ percent predicted was based on the National Health and Nutrition Examination Survey (NHANES III) predicted normal values for ages 8 years and older [Hankinson, 1999].

Reversibility assessment

Documentation of historical reversibility within one year of Visit 1 demonstrating an increase in FEV₁ of $\geq 12\%$ and 200ml over baseline was acceptable and precluded the requirement for reversibility testing the Visit 1.

If documentation of historical reversibility within one year of Visit 1 was not available, the subject was required to demonstrate a $\geq 12\%$ and 200 ml improvement in FEV₁ in order to qualify for participation in the study.

Upon confirming at Visit 1 that no asthma medications were used for the required intervals specified in Section 5.3.1. Inclusion Criteria, pulmonary reversibility was assessed after the subject self-administered 2-4 inhalations or 1-2 nebulized inhalation of albuterol (2 puffs = 1 nebule). The FEV₁ was repeated, in triplicate, within 30 minutes. Reversibility was calculated as follows.

$$\% \text{ Reversibility} = \frac{\text{FEV}_1 \text{ after albuterol MDI} - \text{FEV}_1 \text{ before albuterol MDI}}{\text{FEV}_1 \text{ before albuterol}} \times 100$$

Reversibility documentation was maintained in the CRF.

Methacholine challenge test

The subject was allowed to undergo methacholine challenge testing (MCT) once if the second attempt to document reversibility was unsuccessful. A PC₂₀ result of <8mg/ml obtained at an unscheduled visit prior to Visit 2 was required. An historical PC₂₀ value of <8mg/ml was also acceptable if documented at the investigative site within the past 12 months and was obtained using the ATS or ACRN protocol for MCT s [[American Thoracic Society](#), 2000; [ACRN](#), 2002]. Methacholine challenge testing was performed only at sites with past experience performing this test. The testing was performed between 6 AM and 11 AM. All females of childbearing potential had a negative urine pregnancy test prior to initiation of the methacholine challenge. Any female with a positive pregnancy test was excluded from study participation.

A Manual of Procedures was provided to each site with complete instructions on methodology and assessments of a methacholine challenge performed during this study. Briefly, before conducting the test, the vials of reconstituted methacholine were removed from the refrigerator for at least 30 minutes to allow them to warm to room temperature. The vials of methacholine solution were arranged in the order of administration starting with diluent and increasing to 16.0 mg/ml.

METHACHOLINE TEST SEQUENCE

<u>Solution (vial) number</u>	<u>Concentration of methacholine</u>
1 (Control)	Diluent
2	0.031 mg/ml
3	0.0625 mg/ml
4	0.125 mg/ml
5	0.25 mg/ml
6	0.5 mg/ml
7	1.0 mg/ml
8	2.0 mg/ml
9	4.0 mg/ml
10	8.0 mg/ml
11	16.0 mg/ml

Maximum Albuterol Dose Response (MADR)

The bronchodilator response to albuterol has been found to vary by genotype at the B16 locus, and the maximum bronchodilator effect of albuterol may become attenuated during prolonged use (tachyphylaxis) [Martinez, 1997; Tan, 1997]. It was therefore appropriate to take measurements of the maximum albuterol dose response (MADR) for each subject in order to determine whether the MADR magnitude varied by genotype. A MADR was defined as the best FEV₁ recorded after four, six, or eight puffs of albuterol. A MADR assessment was performed at Visit 4 (beginning of the open-label ipratropium bromide treatment period, Visit 6 (randomization visit) and Visit 10 (end of blinded treatment period).

To obtain the MADR, each subject performed baseline spirometry and was then administered four puffs of albuterol. Fifteen minutes following the administration of the albuterol, the subject again performed spirometry, followed by two additional puffs of albuterol, for a cumulative dose of six puffs. After fifteen minutes, spirometry was repeated once more, and the FEV₁ value compared with the FEV₁ obtained after the first four puffs. If the relative change in FEV₁ was 5% or less, the procedure was stopped; if the relative change was more than 5%, then two additional puffs of albuterol were administered, for a cumulative dose of eight puffs, followed by a final spirometry assessment 15 minutes later.

During the MADR testing albuterol was administered using a metered-dose inhaler. The use of a spacer and/or nebulas was not permitted.

To ensure the safety of the subject during the MADR procedure, vital signs were measured before the procedure, and at least once after each dose of albuterol was administered. If, in the opinion of the investigator, significant hypertension, tachycardia, arrhythmia or other side effects of albuterol occurred, MADR testing was stopped and appropriate medical measures were taken.

Continuation assessments

Subjects were required to meet the following criterion at Visit 2 to continue in the study:

A best FEV₁ $\geq$ 70% of predicted.

Subjects were required to meet the following criteria at Visits 3, 4, 5 and 6 to continue in the study:

A best FEV₁ $\geq$ 70% of predicted and $<$ 56 puffs per week of medication.

Diary card data**Albuterol open-label diary card**

Subjects were instructed to record on daily diary cards:

- Morning and evening peak flow measurements

- Total daily albuterol use
- Total daily asthma symptom scores
- Any medical problems the subject experienced (all AEs/SAEs were transcribed into the CRF)
- Any medications taken (other than albuterol)

Ipratropium bromide open-label diary card

Subjects were instructed to record on daily diary cards:

- Morning and evening peak flow measurements
- Total daily ipratropium bromide use
- Total daily supplemental albuterol use (in the event that asthma symptoms respond incompletely to ipratropium bromide)
- Total daily asthma symptom scores
- Any medical problems the subject may have experienced (all AEs/SAEs were transcribed into the CRF)
- Any medications taken (other than ipratropium bromide or albuterol)

Double-blind treatment diary card

Subjects were instructed to record on daily diary cards:

- Morning and evening peak flow measurements
- Total daily supplemental ipratropium bromide use
- Total daily supplemental albuterol use (in the event that asthma symptoms respond incompletely to ipratropium bromide)
- Total daily asthma symptom scores
- Any medical problems the subject may have experienced (all AEs/SAEs will be transcribed into the CRF)
- Any medications taken (other than study medication)

Subjects were instructed to return completed diary cards at each clinic visit.

Note: Diary cards were reviewed by site personnel while the subject was in the clinic and any discrepancies and/or missing data were reviewed with the subject and resolved, if possible.

Subject recorded symptom scores

Throughout the entire study, each subject was instructed to record an asthma symptom score prior to performing the evening peak flow measurement and taking a PM dose of blinded study medication or rescue medication. Subjects were instructed to select a rating from the following list that best described any asthma-related symptoms such as wheeze, shortness of breath or chest tightness experienced during the day and previous night (preceding 24 hours):

0 = No symptoms during the day or previous night

1 = Symptoms for one short period during the day or previous night

2 = Symptoms for two or more short periods during the day or previous night

3 = Symptoms for most of the day or previous night that did not affect my normal daily activities

4 = Symptoms for most of the day or previous night that did affect my normal daily activities

5 = Symptoms so severe that I could not go to school or perform normal daily activities.

The study coordinator reviewed the diaries at each clinic visit for completeness, legibility, and consistency with patient-reported adverse events. Signs and symptoms of asthma (chest tightness, shortness of breath, wheeze) noted by the subject on the diary pages were not to be considered adverse events and were not recorded in the case report form.

Albuterol use in the open-label, double-blind treatment and washout period

All use of open-label albuterol was to be recorded by the subject or parent/caregiver on the diary card.

Subjects received open-label albuterol 90mcg for *prn* use to treat acute asthma symptoms during the first open-label treatment period.

During the second open-label period, in the event that asthma symptoms responded incompletely to ipratropium, albuterol was used as a superceding treatment medication. Albuterol was also used as a superceding relief medication during the randomization and washout periods. The subject was reminded that for subsequent acute asthma symptoms he/she should continue to take ipratropium first, as medication for acute relief during the second open-label period and during the randomization and washout periods.

Subjects were reminded that if their requirement for albuterol during the first open-label period or as supplemental medication during the second open-label period and/or during the double-blind and washout periods increased markedly or if their requirement equalled or exceeded a total of 12 puffs per day (daytime and nighttime combined) for 2 out of 7 consecutive days they should contact the study site.

Ipratropium use in the open-label, double-blind treatment and washout periods

All use of open-label ipratropium was recorded by the subject or parent/caregiver on the diary card.

Subjects received open-label Atrovent (ipratropium) 18mcg to be used as needed to treat acute asthma symptoms for 8 weeks during the second open-label period prior to randomization.

Subjects also received open-label Atrovent (ipratropium) 18mcg to be used as needed to relieve acute asthma symptoms for 16 weeks during the double-blind treatment period. In addition, subjects received open-label albuterol 90mcg for *prn* use in the event that asthma symptoms respond incompletely to ipratropium during the second open-label period and during the randomization and washout periods, in which case albuterol was used as a superceding medication.

Subjects were reminded that if their requirement for Atrovent (ipratropium) during the second open-label period or during the double-blind and washout periods increased markedly or if their requirement equalled or exceeded a total of 12 puffs per day (daytime and nighttime combined) for 2 out of 7 consecutive days they should contact the study site.

5.6.4. Safety Assessments

Safety measurements included the incidence of clinical adverse events and the incidence of asthma exacerbations.

5.6.4.1. Adverse events

The investigator was responsible for the detection and documentation of events meeting the criteria and definition of an adverse event (AE) or serious adverse event (SAE) for this study.

Each subject was instructed to record on the diary card, any medical problems experienced, and any medications used to treat the medical problem during the trial. Site personnel were to review and resolve discrepancies at each clinic visit and record adverse events in the adverse events section of the CRF. Subjects were also questioned about the occurrence of adverse events by site personnel.

DEFINITION OF AN AE

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 is therefore 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 included failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

Examples of an AE included:

- 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 concurrent medication (overdose per se was not reported as an AE/SAE).

Examples of an AE did not include a/an:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that led to the procedure was 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 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, AEs included 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).

TIME PERIOD, FREQUENCY, AND METHOD OF DETECTING AES AND SAEs

Study participation SAE's were collected from the time informed consent was obtained to Visit 2. AEs/SAEs were collected from Visit 2 through the last visit (Visit 11/or Discontinuation Visit). After the subject had an opportunity to spontaneously mention any problems, the investigator inquired about AEs by asking the following standard questions:

1. "Have you had any (other) medical problems since your last visit/assessment?"
2. "Have you taken any new medicines, other than those given to you in this study, since your last visit/assessment?"
3. "How do you feel after taking each dose of study medication?"

Diary cards were reviewed at each visit and if the subject did not mention an event that was recorded, he/she was questioned for further information in order to determine if there was some occurrence of an adverse event. If an AE was unresolved at the time of the last visit (Visit 11/or Discontinuation Visit) follow-up by the investigator was required.

RECORDING OF AES AND SAES

When an AE/SAE 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 then recorded all relevant information regarding an AE/SAE 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 AE/SAE CRF pages. However, there were instances when copies of medical records for certain cases were requested by GSK. In these instances, all subject identifiers were blinded on the copies of the medical records prior to submission to GSK.

The investigator attempted to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis was documented as the AE/SAE and not the individual signs/symptoms.

EVALUATING AES AND SAES

ASSESSMENT OF INTENSITY

The investigator made an assessment of intensity for each AE and SAE reported during the study. The assessment was based on the investigator's clinical judgement. The intensity of each AE and SAE recorded in the CRF was 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 was assessed as severe was not to be confused with a SAE. Severity was a category utilized for rating the intensity of an event; and both AEs and SAEs could be assessed as severe. An event was defined as 'serious' when it met one of the pre-defined outcomes as described in the Definition of a SAE.

ASSESSMENT OF CAUSALITY

The investigator was obligated to assess the relationship between investigational product and the occurrence of each AE/SAE. The investigator used 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 were considered and investigated. The investigator

also consulted the CIB/IB and/or Product Information, for marketed products, in the determination of his/her assessment.

There may have been situations when an SAE occurred and the investigator had minimal information to include in the initial report to GSK. However, it was very important that the investigator always made an assessment of causality for every event prior to transmission of the SAE CRF to GSK. The investigator may have changed his/her opinion of causality in light of follow-up information, amending the SAE CRF accordingly. The causality assessment was one of the criteria used when determining regulatory reporting requirements.

The investigator provided the assessment of causality as per instructions on the SAE form in the CRF.

FOLLOW-UP OF AES AND SAES

After the initial AE/SAE report, the investigator was 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 designated as ongoing, were to be reviewed at subsequent visits/contacts.

All AEs and SAEs were to be followed until resolution, until the condition stabilized, until the event was otherwise explained, or until the subject was lost to follow-up. Once resolved, the appropriate AE/SAE CRF page(s) was updated. The investigator ensured that follow-up included any supplemental investigations as may have been indicated to elucidate the nature and/or causality of the AE or SAE. This may have included additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

GSK may have requested 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 was obligated to assist. If a subject died during participation in the study or during a recognized follow-up period, GSK was provided with a copy of any post-mortem findings, including histopathology.

New or updated information was to be recorded on the originally completed "SAE" CRF, with all changes signed and dated by the investigator.

5.6.4.2. Serious adverse events

DEFINITION OF A SAE

A serious adverse event is defined as 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-patient 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.
- g. All SAES were required to be reported to GSK within 24 hours of the investigator learning of the event.

5.6.4.3. Pregnancies

A urine pregnancy test was performed at all visits on all female subjects of childbearing potential. Any female subject who became pregnant while participating in the study was withdrawn from the study and was followed to determine the outcome of the pregnancy.

Generally, follow-up was no longer than six to eight weeks following the delivery date. The investigator was required to collect pregnancy information and report the information to GSK within 2 weeks of learning of the subject's pregnancy.

5.6.4.4. Clinical laboratory evaluations

Whole blood samples were taken at Visit 1, unless the patient did not meet the FEV₁ or reversibility requirement and planned to re-screen, in which case, the blood samples were drawn during the re-screening visit. The blood samples were collected using tubes containing ethylenediaminetetraacetic acid (EDTA). The samples were labeled (or “coded”) with a study specific number that could be traced or linked back to the subject by the investigator or site staff. Coded samples did not carry personal identifiers such as name or social security number. The blood samples were taken on a single occasion unless a duplicate sample was required due to inability to utilize the original sample.

Blood samples were collected for:

- Genotyping of the *ADRB2* genotype needed to determine study eligibility
- Pharmacogenetic analyses.

5.6.4.5. Physical examination

A physical examination was performed at the screening visit (Visit 1) and Visit 10 (last blinded treatment visit) or at a Premature Discontinuation Visit. Results of the physical examination were maintained in the source documents for the subject at the study site. If any clinically significant, unfavorable change, from baseline to Visit 10 or Premature Discontinuation occurred, this was recorded as an adverse event. Every attempt was made to have the same person perform the physical examination of a subject at Visit 1 and the last clinical visit.

5.6.4.6. Vital signs

Blood pressure (systolic and diastolic) and pulse were determined with the subject in the sitting position. The subject was seated at least 5 minutes before the measurements were taken. Blood pressure and pulse was taken at Visit 1 and Visit 10 (or Premature Discontinuation) prior to any pulmonary function testing.

To ensure subject safety during Maximum Albuterol Dose Response (MADR) testing, vital signs were taken before MADR was performed, and at least once after each dose of albuterol was administered. If, in the opinion of the investigator, significant hypertension, tachycardia, arrhythmia or other side effects of albuterol occurred, MADR testing was stopped and appropriate medical measures were taken. MADR testing was performed at Visits 4, 6 and 10.

Vital signs were documented in the source documents only, unless there was a clinically significant change from baseline. Any clinically significant findings (change from baseline) were captured as an AE/SAE.

5.6.4.7. Asthma exacerbation

A clinical exacerbation was defined as worsening asthma requiring emergency intervention, hospitalization, or treatment with asthma medication in addition to those allowed by the protocol.

If a subject was withdrawn for a clinical exacerbation based upon the above definition, the reason for withdrawal noted in the CRF was recorded as “Exacerbation”. If a clinical exacerbation met the definition of a SAE (Section 5.6.4.2. Serious adverse events), worsening asthma data was collected as a SAE for all subjects who signed an informed consent and participated in this study.

Subjects who experienced an exacerbation during the screening period between Visit 1 and Visit 2 were discontinued.

For the purposes of this study, a subject was permitted to experience one exacerbation during the 16 week combined open-label period that was successfully treated within 10 days and remain in the study, predicated on consultation with GSK. If a subject experienced more than one exacerbation during the open-label treatment periods the subject was discontinued.

A subject was withdrawn due to worsening asthma if he/she experienced an exacerbation during the double-blind treatment period or the washout period. In addition, the investigator was permitted to discontinue a subject at any time, if the investigator believed that the subject was at risk by remaining in the study.

For subjects who entered the screening period between Visit 1 and Visit 2 and experienced an exacerbation, worsening asthma data was recorded only in the source documents. For all subjects who were in the open-label, double-blind, and washout treatment periods, asthma exacerbation data was recorded in the source documents and the Asthma Exacerbation section of the CRF.

5.6.5. Pharmacogenetic Objectives and Assessments**Objectives**

The following objectives were identified for this study:

- Relationship between genetic variants and safety and/or tolerability of investigational product
- Relationship between genetic variants and efficacy of investigational product.

Assessments

In this study, blood samples were collected for:

- Genotyping of the *ADRB2* genotype needed to determine study eligibility
- Pharmacogenetic analysis.

See Section 5.8.8.3 Other efficacy measure(s) Single Marker Analyses and Section 7.3.6. Additional *ADRB2* SNPs – Associations/Comparisons.

5.7. Data Quality Assurance

At the clinical study sites, the investigator or their designee recorded all required subject data in paper Case Report Forms (CRFs). The subject recorded diary data in the Diary cards. 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.

The CRF and CRF completion guidelines were presented at the investigator/monitors meeting. The completed original CRFs and Diary Cards were returned to GSK Data Management for processing. The investigator retained copies of the CRFs and Diary Cards.

Data entry applications were designed and validated using a data entry screen software system (i.e., ClinTrial). Data values recorded on the CRF were entered using double dependent data entry. Computerised data validation was performed on CRF data using ClinTrial validation checks and study-specific data validation checks. Validation discrepancies, if not covered by a Standard Clarification Agreement (SCA), 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 on Harmonisation of Good Clinical Practice (ICH GCP). Adverse events and concomitant medications were coded by the autoencoder using company standard dictionaries or industry standard dictionaries; MedDRA and GSK Drug.

SAE 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 15 Mar 07. The database was frozen on 22 Mar 07 at which time access to the data was also restricted (database lock).

The raw data (CRFs, other) 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 performed.

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

Final data analyses were conducted after the Reporting and Analysis Plan (RAP) was finalized, all protocol deviations were identified, all data queries were resolved and the study database was locked by GSK Data Management, and treatment assignments were unblinded. All analyses described in the RAP were performed.

5.8.2. Sample Size Considerations

The sample size calculation for this study was based on the primary efficacy measure of AM PEF, recorded by subjects in daily diaries over the course of the study.

It was estimated that the standard deviation of mean change from baseline in AM PEF over the 16-week double-blind treatment period in subjects randomized to the FSC treatment group would be 50 L/min. Using 28.5 L/min as the non-inferiority criterion bound (lower confidence interval limit of -28.5 L/min), a sample size of 82 subjects per group (per genotype per treatment group) would provide >90% power to demonstrate non-inferiority of the Arg/Arg genotype to the Gly/Gly genotype within the FSC treatment group in terms of AM PEF mean change from baseline over the 16-week treatment period, based on a 2-sided significance level of 0.05.

It was anticipated that approximately 540 subjects would be randomized to achieve an analysis population of approximately 492 evaluable subjects (82 evaluable subjects per genotype per treatment group). An evaluable subject was defined as a subject that completed at least 2 weeks of double-blind treatment, as documented in the subject diary. A 10% drop-out rate was assumed after randomization based on the fact that the population was stable and mild. Assuming that 15% of the general population has the Arg/Arg genotype, it was anticipated that in order to randomize 90 subjects in each of the genotype and treatment groups, a minimum of 1,200 subjects would need to be screened. Allowing for exclusions and withdrawals, approximately 2,000 subjects were to be screened.

5.8.3. Analysis Populations

The following populations were identified for this study: Total Population, Screen Failure Population, Open-Label Failure Population, Intent-to-Treat (ITT) Population and Per Protocol population.

The Total population included all subjects screened in the study. This population included screen and open-label failures and randomized subjects. This population was used for listings of serious adverse events and pregnancies.

The Screen Failure population included all subjects screened for inclusion in the study but who were discontinued from the study at Visit 1 or during the screening period prior to Visit 2. The Open-Label Failure population included subjects who entered the first open-label treatment period at Visit 2 but who were discontinued from the study prior to randomization to blinded study drug at Visit 6 (Randomization). Data collected until study discontinuations were summarized for these populations and by period of withdrawal (screening, open-label albuterol, and open-label ipratropium).

The ITT population included all subjects who were randomized to blinded study drug. The ITT population was the primary analysis population for summaries and analyses of demographic/background, efficacy and safety data. During the conduct of the study, one investigative site [REDACTED] was closed due to significant deviations in Good Clinical Practice (GCP) identified at the site. Subjects randomized at this site (10 subjects) were not included in the ITT efficacy analyses. Safety data collected at this site were included in the ITT safety summaries. All subjects from this site were included in the Total population and all screen and open-label failures were included in the Screen Failure and Open-Label Failure populations, respectively.

The Per Protocol population included all subjects in the ITT population with no protocol deviations that may have impacted treatment response or the primary efficacy endpoint. These deviations are defined below in Section 5.8.7.2 Protocol deviations. Also, subjects randomized at the closed investigative site [REDACTED] were not included in the Per Protocol population. As this trial was designed to show non-inferiority, analysis of the Per Protocol population served as a supporting analysis for the primary analysis of the ITT population. Analysis of the primary efficacy measure was conducted for this population to assess sensitivity of the trial.

5.8.4. Treatment Comparisons

The primary comparison of interest was that of non-inferiority between the Arg/Arg and Gly/Gly genotypes in the FSC treatment group assessed in terms of overall mean AM PEF change from baseline for the 16-week double-blind treatment period.

Other comparisons included:

- Arg/Arg and Gly/Gly genotypes in the salmeterol treatment group
- Arg/Arg and Arg/Gly genotypes in the FSC and salmeterol treatment groups
- Arg/Gly and Gly/Gly genotypes in the FSC and salmeterol treatment groups

These comparisons also assessed non-inferiority with 95% 2-sided confidence intervals and the same non-inferiority criterion bound as the primary comparison in terms of overall mean AM PEF change from baseline for the 16-week double-blind treatment

period. In addition, statistical comparisons between open-label treatment periods (albuterol versus ipratropium) were made within each genotype (Arg/Arg, Arg/Gly and Gly/Gly).

5.8.5. General Considerations for Data Analyses

Statistical programming and reporting was performed in a UNIX environment using SAS® Version 8.2 and the GSK HARP (Harmonization for Analysis and Reporting Program) reporting environment.

5.8.5.1. Multicenter studies

This was a multi-center study; however, a term for investigative site was not included as a covariate in statistical models. The primary efficacy endpoint was a subject-recorded assessment (daily AM PEF) compared between blinded genotypes. Investigative site was not expected to influence the primary efficacy measure.

5.8.5.2. Other strata and covariates

Randomization to blinded study drug was stratified by genotype as well as by ethnicity (Black; Hispanic or Latino; Caucasian or Other) to ensure that racial/ethnic groups were equally represented across treatment groups. All analyses included a term for racial/ethnicity stratum as a covariate. In general, the baseline value of a continuous efficacy measure also served as a covariate in analyses of change from baseline values of that measure.

5.8.5.3. Examination of subgroups

For the primary efficacy measure of AM PEF mean change from baseline for the overall 16-week double-blind treatment period, the extent to which the treatment response varied across the levels of genotype and racial/ethnicity groups was examined through interaction tests for exploratory purposes only. A separate statistical model included the interaction term (genotype by racial/ethnicity group) with all main effects in the model to explore the significance of the interaction. No interaction terms were found to be statistically significant at the 0.10 significance level and therefore, for the purpose of this report, no subgroup analyses were performed.

5.8.5.4. Multiple comparison/multiplicity

A single primary comparison to assess non-inferiority between the Arg/Arg and Gly/Gly genotypes in the FSC treatment group for overall AM PEF mean change from baseline during the double-blind treatment period was defined for this study. Non-inferiority in terms of overall AM PEF mean change from baseline was also assessed between the other genotypes within the FSC and salmeterol treatment groups. These genotype comparisons as well as those from the secondary and other efficacy measures were interpreted as supporting the primary comparison, secondary or other, respectively. No adjustment for multiplicity was performed.

5.8.6. Data Handling Conventions

5.8.6.1. Premature discontinuation and missing data

Data collected up to the time of study discontinuation for subjects who withdrew from the study prematurely were included in analyses. A subject was included in analyses wherever his/her data were available. No interpolation of missing data was done.

5.8.6.2. Derived and transformed data

In the protocol, analyses of lung function measures, AM and PM PEF and FEV₁, was described in terms of area under the curve relative to baseline. This term was used to reference the area under the 16-week double blind treatment period lung function curves relative to baseline (or the change from baseline curves). Since AUC can be calculated as weighted means, or raw means when time intervals are equally spaced as in this study, AUC for the lung function measures was calculated as the mean of the lung function values collected over the 16-week double-blind treatment period and referenced as overall means and overall change from baseline values in the statistical analysis tables.

Primary and secondary efficacy measures derived from the subject-recorded daily diaries were AM PEF, PM PEF, percentage of symptom-free days and supplemental ipratropium use. For the 16-week double-blind treatment period, diary measures were summarized at baseline, each 4-week interval of the double-blind treatment period and for the overall 16-week treatment period. Baseline week was determined from the 7-day period immediately prior to Randomization (Visit 6). Diary measures were also summarized for the overall 2-week washout period and for each 4-week interval, for the overall 8-week interval, as well as weekly, for each of the open-label (albuterol and ipratropium) treatment periods.

5.8.6.3. Assessment windows

Efficacy data collected during a clinic visit (e.g., FEV₁) were reported by visit at which the data were collected in the CRF. Data collected during a clinic visit were not excluded from analysis for being collected outside of an assessment window.

5.8.7. Study Population

5.8.7.1. Disposition of subjects

Subject disposition in the Total Population was summarized in terms of:

- the number of subjects screened (Total population)
- the number (%) of screen failures (Screen Failure population)
- the number (%) of subjects per screen failure reason
- the number (%) of open-label failures (Open-Label Failure population)
- the number (%) of subjects per open-label failure reason
- the number (%) of subjects randomized (ITT population)

- the number (%) of subjects with no major protocol deviation(s) (as described below in Section 5.8.7.2) (Per Protocol population)

Subject disposition in the ITT population was summarized by treatment group and genotype in terms of:

- the number (%) of subjects randomized at each investigative site
- the number (%) of subjects who completed the study
- the number (%) of subjects who withdrew prematurely from the study
- the number (%) of subjects per primary reason for withdrawal

5.8.7.2. Protocol deviations

Protocol deviations were determined prior to unblinding treatment assignments. Protocol deviations included violations of inclusion/exclusion criteria, use of prohibited medications, unblinding of the study drug, dispensing of incorrect blinded study drug, and incorrect randomization stratum of blinded study drug. Protocol deviations were tabulated by treatment group and genotype for subjects in the ITT population. Data collected following a protocol deviation were not excluded from the ITT analysis. Subjects with a protocol deviation were excluded from the Per Protocol population.

5.8.7.3. Demographic and baseline characteristics

Demographic and baseline characteristics were summarized for the ITT and Screen and Open-Label Failure populations. Demographic characteristics of age, sex, ethnicity and race were summarized. Disease characteristics, current medical conditions and screening pulmonary function tests were also summarized. Disease characteristics included asthma duration and subject and family asthma and atopy history. The summary of screening pulmonary function measurements included pre-bronchodilator FEV₁ and FEV₁ percent predicted, and FEV₁ percent reversibility to albuterol.

Prior asthma medications stopped within 30 days of Screening (Visit 1) and concomitant medications taken during the study were assigned codes using the GSK Drug dictionary and were reported using the Anatomical Therapeutic Chemical (ATC) Level 1 classification and drug terms. Treatment and genotype groups were summarized by reporting the number (%) of subjects taking any medication, the number (%) of subjects taking a medication by ATC classification, and the number (%) of subjects taking a medication by drug term. Summaries were generated for prior asthma medication use, asthma concomitant medications and non-asthma concomitant medications.

Other summaries for the Open-Label Failure population included assessments of FEV₁, MADR and diary measures (AM PEF, PM PEF, percent of symptom-free days and supplemental rescue medication use) collected during the open-label treatment periods. These measures were summarized with descriptive statistics.

5.8.7.4. Treatment compliance

Compliance with the blinded study drug regimen was expressed as an overall percentage of compliance calculated as the total number of doses taken during the treatment period divided by the total expected number of doses taken during the treatment period, multiplied by 100. The total number of doses taken was determined from the DISKUS dose counter of each DISKUS dispensed and returned throughout the study. The total expected number of doses taken was based on BID dosing during each subject's double-blind treatment period. Treatment compliance was summarized with descriptive statistics by treatment group and genotype.

5.8.8. Efficacy Analyses

5.8.8.1. Primary efficacy measure(s)

The primary efficacy measure was mean change from baseline in AM PEF over the 16-week double-blind treatment period, as characterized by AM PEF AUC(bl), compared between the Arg/Arg and Gly/Gly genotypes in the FSC treatment group. AM PEF measures and change from baseline values were summarized with descriptive statistics by genotype for the overall 16-week double-blind treatment period, for each 4-week treatment period interval, as well as over the 2-week washout period. Baseline AM PEF and AM PEF for each week, for each of the 4-week intervals and for the overall 8 weeks of each open-label (albuterol and ipratropium) treatment period were also summarized with descriptive statistics. An analysis of covariance (ANCOVA) model, including terms for genotype, racial/ethnicity stratum and baseline, was used to assess non-inferiority in AM PEF mean change from baseline for the overall 16-week double-blind treatment period. Genotype differences from the ANCOVA model were presented as least square means and standard errors with the corresponding 95% confidence intervals.

5.8.8.2. Secondary efficacy measure(s)

Secondary efficacy measures were PM PEF, pre-dose FEV₁, percent of symptom-free days and supplemental ipratropium use.

PM PEF, Percent of Symptom-Free Days, Supplemental Ipratropium Use: PM PEF, percent of symptom-free days and supplemental ipratropium use were summarized and compared in the same manner as AM PEF. Supplemental albuterol use was also summarized and compared between genotypes. Genotype differences from the ANCOVA models were presented as least square means and standard errors with the corresponding 95% confidence intervals.

FEV₁: FEV₁ measures and change from baseline values were summarized with descriptive statistics by genotype for the overall 16-week double-blind treatment period, at Endpoint and for each visit (Visits 7-11, Weeks 4, 8, 12 and 16, and Washout, respectively). Endpoint was defined as the last scheduled measurement of pre-dose FEV₁ during the 16-week double-blind treatment period and baseline was defined as the pre-dose FEV₁ measure from Randomization (Visit 6). FEV₁ measures collected during the open-label treatment periods were summarized by visit with descriptive statistics. An

ANCOVA model including terms for genotype, racial/ethnicity stratum and baseline was used to compare genotypes for the overall 16-week double-blind treatment period. Genotype differences from the ANCOVA model were presented as least square means and standard errors with the corresponding 95% confidence intervals.

5.8.8.3. Other efficacy measure(s)

Other efficacy measures included assessments of the proportion of subjects taking supplemental albuterol during the 16-week double-blind treatment period and MADR evaluated at the end of each treatment period (open-label albuterol, open-label ipratropium and double-blind).

Supplemental albuterol use: The proportion of subjects requiring supplemental albuterol during the 16-week double-blind treatment period was summarized by genotype. Odds ratios and the corresponding 95% confidence intervals from Cochran-Mantel-Haenszel tests controlling for race/ethnicity were presented for the comparisons of the genotypes.

MADR: MADR FEV₁ values were summarized along with the percent change in maximum post albuterol FEV₁ from baseline FEV₁ recorded prior to albuterol administration. MADR was assessed at Visits 4, 6 and 10 (at the end of the open-label albuterol, open-label ipratropium and 16-week double blind treatment periods, respectively). MADR FEV₁ values were summarized with descriptive statistics by genotype and by visit. Genotype differences from an ANCOVA model, with terms for genotype, racial/ethnicity stratum and baseline, were presented as least square means and standard errors with the corresponding 95% confidence intervals for each visit. Baseline was defined as the pre-albuterol FEV₁ measure for each visit.

Other Evaluations: Other evaluations included within-group comparisons of lung function. Mean AM PEF over the last 4 weeks of the open-label albuterol treatment period was compared with mean AM PEF over the last 4 weeks of the open-label ipratropium period within each genotype. Within group t-tests were used to compare mean AM PEF values over the last 4 weeks of the 2 open-label treatment periods. PM PEF and percent of symptom-free days were compared in the same manner.

Since the randomization of subjects to blinded study drug was stratified based on their Arg16Gly genotype, for the primary efficacy measure of AM PEF mean change from baseline for the overall 16-week double-blind treatment period, Arg16Gly genotype was added as a covariate to the statistical models for the SNPs and poly-C repeat marker for exploratory purposes only. A separate statistical model included a term for Arg16Gly genotype with all main effects in the model (baseline, ethnicity stratum, sex, age and individual SNP or repeat marker) to explore the significance of the Arg16Gly genotype. No Arg16Gly term was found to be statistically significant at the 0.05 significance level for any of the individual SNPs or poly-c repeat marker and therefore, for the purpose of this report, Arg16Gly was not included as a covariate in the statistical models.

Single Marker Analysis: Each of the additional 12 markers was analyzed using an ANCOVA to determine significance between genotypes within each treatment. This

analysis also utilized baseline, age, gender, and racial/ethnicity stratum as covariates in the model. No correction was made for ascertainment bias (Arg16Gly genotype), with each SNP treated as an independent marker. There were no corrections for multiple comparisons. Markers at positions +491 (RS1800888) and +659 (RS3729943) had very low minor allele frequencies (<2%) and were not included in the analyses.

Assay Sensitivity: In order to assess assay sensitivity, mean change in FEV₁ at Endpoint from Screening FEV₁ was summarized and compared within each treatment group using within-group t-tests. Screening FEV₁ was measured at Visit 1 and Endpoint FEV₁ was defined as the last FEV₁ measure collected at a scheduled clinic visit during the 16-week double-blind treatment period.

5.8.9. Safety Analyses

Extent of Exposure

Extent of exposure to blinded study drug was calculated as the number of days between start of treatment and end of treatment for each subject and was summarized with descriptive statistics by treatment group and genotype.

Adverse Events

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) and were reported using the primary system organ class (SOC) and preferred term. Adverse event summaries reported the number (%) of subjects experiencing any adverse event, the number (%) of subjects with an adverse event by SOC, and the number (%) of subjects with an adverse event by preferred term within each SOC.

Adverse event summaries were provided for both the ITT and Open-Label Failure populations. Summaries were generated for adverse events occurring pre-treatment (during the screening and open-label treatment periods), during treatment (during the double-blind treatment period), and post-treatment (during the 2-week follow-up period). Summaries of most common (>3% of subjects in any genotype group) adverse events and drug-related adverse events during the double-blind treatment period were also provided for the ITT population.

Serious adverse events occurring during the double-blind treatment period were tabulated (by genotype by treatment group) for the ITT population. Subject listings were provided of all fatal serious adverse events and all non-fatal serious adverse events for the Total population. Adverse events leading to withdrawal from the study during the double-blind treatment period were tabulated by treatment group and genotype for the ITT population.

Pregnancies

Positive pregnancy tests reported during the study were presented in a subject listing.

Exacerbations

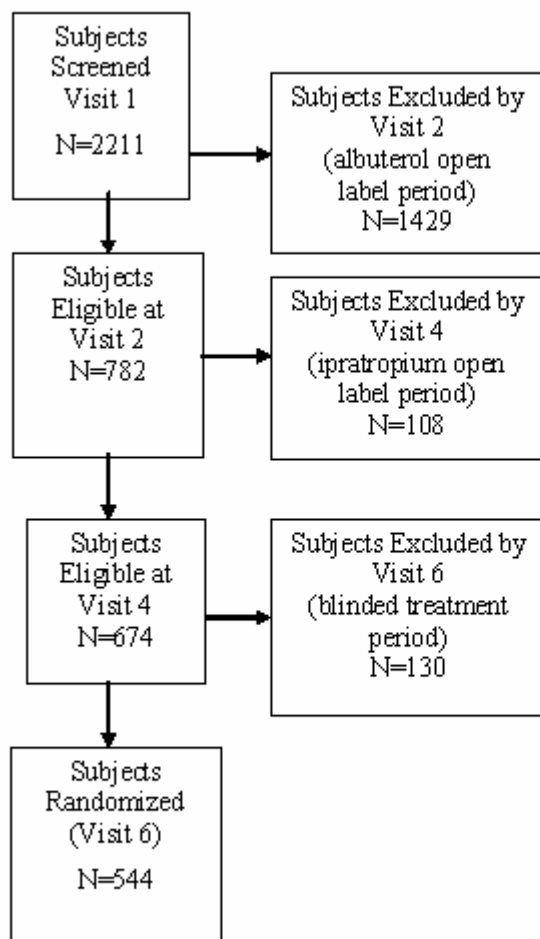
The proportion of subjects experiencing an exacerbation during the double-blind treatment period was summarized by treatment group and genotype for the ITT population. Exacerbations were further described by tabulating the number of exacerbations and the number (%) of exacerbations by suspected primary cause, outcome and severity. Exacerbations were also tabulated for the Open-Label Failure population by genotype.

6. STUDY POPULATION RESULTS

6.1. Disposition of Subjects

Disposition of Total Number of Subjects

The following flow chart describes the number of subjects eligible to continue at the screening visit, the two open-label periods, and the randomization period.



Screen Failures/Withdrawals

The total number of subjects (2211) screened was provided from data compiled by the Covance Interactive Voice Response System utilized for drug distribution in this study.

Table 6.1 presents the number of subjects who failed at the Screening Visit (Visit 1) or during the screening period between Visit 1 and Visit 2 and withdrew from the study, as well as the associated reasons for withdrawal. A summary of these data is shown in Table 1.

Table 1 Reason for Failure/Withdrawal - Screening Period (Visit 1-Visit 2)

Reason, n (%)	N (%)
Screen Failure/Withdrawal	1429
Adverse Event	7 (<1%)
Lost to follow-up	23 (2%)
Decided to withdraw	32 (2%)
Prohibited medication use	7 (<1%)
Did not fulfil eligibility	798 (56%)
Exacerbation	5 (<1%)
Genotype quota filled	533 (37%)
Did not fulfil continuation criteria	7 (<1%)
Other	14 (<1%)
No reason given	3 (<1%)

Source Data: [Table 6.1](#)

The most common reasons for excluding subjects (1429, 65% of 2211 subjects who were screened) from the study, either during the Screening Visit, the 2 weeks of the screening period, by Visit 2, the beginning of the albuterol open-label treatment period, were failure to fulfil eligibility criteria (798, 56% of the 1429 subjects) and filled genotype quota (533, 37% of the 1429 subject). Subjects remained on their usual beta₂ agonist therapy between the Screening Visit and Visit 2. Of these, 782 (35% of the 2211 subjects screened at Visit 1) subjects were eligible at Visit 2.

OPEN-LABEL TREATMENT FAILURES/WITHDRAWALS

[Table 6.2](#) presents the total number (108) of subjects by genotype, who withdrew from the albuterol open-label treatment period, as well as the associated reasons for withdrawal. A summary of these data is shown in [Table 2](#).

Table 2 Reason for Failure/Withdrawal during the Albuterol Open Label Treatment Period

Reason, n (%)	Arg/Arg N=37	Gly/Gly N=28	Arg/Gly N=43
Adverse Event	3 (8%)	2 (7%)	3 (7%)
Lost to follow-up	8 (22%)	0	5 (12%)
Decided to withdraw	8 (22%)	5 (18%)	6 (14%)
Prohibited medication use	1 (3%)	1 (4%)	2 (5%)
Did not fulfil eligibility	3 (8%)	0	2 (5%)
Exacerbation	1 (3%)	1 (4%)	2 (5%)
Genotype quota filled	1 (3)	11 (39%)	9 (21%)
Did not fulfil continuation criteria	7 (19%)	5 (18%)	11 (26%)
Other	5 (14%)	3 (11%)	3 (7%)

Source Data: [Table 6.2](#)

Of the 108 subjects who were withdrawn from the study during the albuterol open-label period, the most common reasons for withdrawal were: did not fulfil continuation criteria (23, 21%), genotype quota filled (21, 19%), and subject decided to withdraw (19, 18%). See Section 8.7 Asthma Exacerbations for details of genotype, primary cause, outcome and severity.

Note: The continuation criterion during the albuterol open-label period at Visit 2 was a best FEV₁ of $\geq 70\%$ of predicted. Continuation criteria at Visit 3 was a best FEV₁ of $\geq 70\%$ of predicted and < 56 puffs per week of medication.

Table 6.3 also presents the total number (130) of subjects by genotype, who withdrew from the ipratropium open-label treatment period, as well as the associated reasons for withdrawal. A summary of these data is shown in Table 3.

Table 3 Reason for Failure/Withdrawal during the Ipratropium Bromide Open Label Treatment Period

Reason, n (%)	Arg/Arg N=27	Gly/Gly N=41	Arg/Gly N=62
Adverse Event	4 (15%)	1 (2%)	1 (2%)
Lost to follow-up	3 (11%)	3 (7%)	5 (8%)
Decided to withdraw	8 (30%)	4 (10%)	2 (3%)
Prohibited medication use	0	3 (7%)	1 (2%)
Did not fulfil eligibility	0	0	1 (2%)
Exacerbation	1 (4%)	1 (2%)	2 (3%)
Genotype quota filled	0	19 (46%)	47 (76%)
Did not fulfil continuation criteria	6 (22%)	6 (15%)	2 (3%)
Other	5 (19%)	4 (10%)	1 (2%)

Source Data: Table 6.3

Of the 130 subjects who were withdrawn from the study during the ipratropium bromide open-label period, the most common reasons for withdrawal were: filled genotype quota (66, 51%), subject decided to withdraw (14, 11%), and did not fulfil continuation criteria (14 (11%). See Section 8.7 Asthma Exacerbations for details of genotype, primary cause, outcome and severity.

Note: Continuation criteria at Visits 4 and 5 were a best FEV₁ of $\geq 70\%$ of predicted and < 56 puffs per week of medication (ipratropium bromide as well as albuterol). These continuation criteria were also required at Visit 6, Day 1 of the double-blind treatment period.

ITT POPULATION

Double-blind Period

A total of 544 subjects were randomly assigned to one of the two double-blind study treatments at 58 investigational centers in the FSC 100/50mcg treatment group and 61

investigational centers in the SM 50mcg treatment group. [Table 6.4](#) presents the number of subjects enrolled by Investigator. In the 16 weeks of the double-blind treatment period, 83 subjects (15% the total for both treatment groups) were withdrawn early ([Table 6.5](#)).

The reasons for withdrawal after randomization during Weeks 1-16 are summarized in [Table 4](#) by genotype and each treatment group.

Table 4 Reason for Withdrawal during the Double-blind Treatment Period (Weeks 1-16)

	FSC 100/50mcg N=272	SM 50mcg N=272	Total N=544
Genotype, n			
Arg/Arg, n	89	90	179
Gly/Gly, n	91	92	183
Arg/Gly, n	92	90	182
Number (%) withdrawn	30 (11%)	53 (19%)	83 (15%)
Arg/Arg	10 (11%)	21 (23%)	
Gly/Gly	12 (13%)	16 (17%)	
Arg/Gly	8 (9%)	16 (18%)	
Reason for withdrawal			
Adverse event, n (%)	5 (2%)	10 (4%)	15 (3%)
Arg/Arg	3 (3%)	1 (1%)	
Gly/Gly	1 (1%)	3 (3%)	
Arg/Gly	1 (1%)	6 (7%)	

Table 4 continued

Source Data: [Table 6.5](#)

Table 4 (continued) Reason for Withdrawal during the Double-blind Treatment Period (Weeks 1-16)

	FSC 100/50mcg N=272	SM 50mcg N=272	Total N=544
Exacerbation, n (%)	2 (<1%)	7 (3%)	9 (2%)
Arg/Arg	1 (1%)	3 (3%)	
Gly/Gly	1 (1%)	3 (3%)	
Arg/Gly	0	1 (1%)	
Lost to follow-up, n (%)	4 (1%)	9 (3%)	13 (2%)
Arg/Arg	1 (1%)	4 (4%)	
Gly/Gly	3 (3%)	2 (2%)	
Arg/Gly	0	3 (3%)	
Protocol violation, n (%)	4 (1%)	8 (3%)	12 (2%)
Arg/Arg	1 (1%)	4 (4%)	
Gly/Gly	1 (1%)	3 (3%)	
Arg/Gly	2 (2%)	1 (1%)	
Consent withdrawn, n (%)	10 (4%)	12 (4%)	22 (4%)
Arg/Arg	0	6 (7%)	
Gly/Gly	6 (7%)	3 (3%)	
Arg/Gly	4 (4%)	3 (3%)	
Sponsor terminated study site, n (%)	0	1 (<1%)	1 (<1%)
Arg/Arg	0	1 (1%)	
Gly/Gly	0	0	
Arg/Gly	0	0	
Other, n (%)	5 (2%)	6 (2%)	11 (2%)
Arg/Arg	4 (4%)	2 (2%)	
Gly/Gly	0	2 (2%)	
Arg/Gly	1 (1%)	2 (2%)	

Source Data: [Table 6.5](#)

Overall, few subjects withdrew from the study. The percentages of subjects withdrawn from the study were similar in each genotype within each treatment group. None of the specific reasons for withdrawal after randomization affected more than 7% of subjects within each genotype in either treatment group. [Table 6.6](#) presents individual subjects who withdrew from the study after randomization. See Section [8.7](#) Asthma Exacerbations for details of genotype, primary cause, outcome and severity.

Washout Period

[Table 6.5](#) Summary of End of Study Record and [Table 5](#) present the primary reason for withdrawal of any subject during the washout period in each treatment group.

Table 5 Reasons for Withdrawal during the Washout Period (2 Weeks)

	FSC 100/50mcg N=272	SM 50mcg N=272	Total N=544
Number (%) withdrawn	3 (1%)	2 (<1%)	5 (<1%)
Arg/Arg	1 (1%)	1 (1%)	
Gly/Gly	0	0	
Arg/Gly	2 (2%)	1 (1%)	
Reason for withdrawal			
Adverse event, n (%)	1 (<1%)	0	1 (<1%)
Arg/Arg	0	0	
Gly/Gly	0	0	
Arg/Gly	1 (1%)	0	
Exacerbation, n (%)	1 (<1%)	0	1 (<1%)
Arg/Arg	1 (1%)	0	
Gly/Gly	0	0	
Arg/Gly	0	0	
Lost to follow-up, n (%)	0	0	0
Arg/Arg	0	0	
Gly/Gly	0	0	
Arg/Gly	0	0	
Protocol violation, n (%)	1 (<1%)	0	1 (<1%)
Arg/Arg	0	0	
Gly/Gly	0	0	
Arg/Gly	1 (1%)	0	
Consent withdrawn, n (%)	0	0	0
Arg/Arg	0	0	
Gly/Gly	0	0	
Arg/Gly	0	0	
Sponsor terminated study/site, n (%)	0	1 (<1%)	1 (<1%)
Arg/Arg	0	1 (1%)	
Gly/Gly	0	0	
Arg/Gly	0	0	
Other, n (%)	0	1 (<1%)	1 (<1%)
Arg/Arg	0	0	
Gly/Gly	0	0	
Arg/Gly	0	1 (1%)	

Source Data: [Table 6.5](#)

Overall, few subjects withdrew from the washout period of the study. The percentages of subjects withdrawn were similar between treatment groups. None of the specific reasons for withdrawal after randomization affected more than 1% of subjects within each genotype in either treatment group.

6.2. Protocol Deviations

Table 6.7 presents the number and percent of randomized subjects who deviated from at least one protocol criterion. The categories of major (i.e., the potential to affect efficacy) and minor protocol deviations were determined by the GSK clinical team while the database remained blinded. Table 6.8 presents the individual subjects and the associated deviations by treatment group and by Investigator. Table 6 presents the protocol deviations that occurred during the study.

Table 6 Protocol Deviations Attributed to Randomized Subjects

	FSC 100/50mcg N=272	SM 50mcg N=272
Genotype, n		
Arg/Arg, n	89	90
Gly/Gly, n	91	92
Arg/Gly, n	92	90
Number (%) Subjects with Protocol Violations	27 (10%)	23 (8%)
Arg/Arg	11 (12%)	9 (10%)
Gly/Gly	9 (10%)	5 (5%)
Arg/Gly	7 (8%)	9 (10%)
Inclusion criteria, n (%)	1 (<1%)	2 (<1%)
Arg/Arg	1 (1%)	2 (2%)
Gly/Gly	0	0
Arg/Gly	0	0
Exclusion criteria, n (%)	1 (<1%)	0
Arg/Arg	0	0
Gly/Gly	1 (1%)	0
Arg/Gly	0	0
Use of prohibited medication, n (%)	22 (8%)	16 (6%)
Arg/Arg	10 (11%)	6 (7%)
Gly/Gly	7 (8%)	5 (5%)
Arg/Gly	5 (5%)	5 (6%)
Dispensing incorrect blinded study drug†, n (%)	3 (1%)	5 (2%)
Arg/Arg	1 (1%)	2 (2%)
Gly/Gly	1 (1%)	0
Arg/Gly	1 (1%)	3 (3%)
Incorrect race/ethnicity stratification, n (%)	1 (<1%)	1 (<1%)
Arg/Arg	0	0
Gly/Gly	0	0
Arg/Gly	1 (1%)	1 (1%)

Source Data: Table 6.7-Table 6.10

† Site personnel error when dispensing blinded drug at a specific visit

The number and type of major and minor protocol violations were similar between treatment groups in the total population of subjects.

6.3. Populations Analyzed

The Intent-to-Treat population (N=544) was defined as all randomized subjects in the Reporting and Analysis Plan and Section 5.8 Analysis Populations. Analyses based on the Intent-to-Treat population included all available data for these subjects. This population formed the basis for all safety, background and demographic summaries as well as for analysis of the primary, secondary, and related efficacy measures. This population includes subjects randomized by Investigator [REDACTED]. All data from the 10 subjects randomized by Investigator [REDACTED] were excluded from any efficacy analyses due to administrative and study conduct deficiencies.

A Per-Protocol population (N=484) was also analyzed for the primary efficacy measure. [See Table 7.3 Summary of AM PEF (L/min) and Table 7.4 Analysis of AM PEF (L/min)]. This population was defined as all subjects in the ITT population, excluding subjects randomized by Investigator [REDACTED] who did not have a protocol deviation.

6.4. Demographics and Other Baseline Characteristics

Section 6.4.1. Screen Withdrawals at Visit 1, Section 6.4.2. Open-Label Period (Albuterol) - Withdrawals, Section 6.4.3. Open-Label Period (Ipratropium Bromide) - Withdrawals, Section 6.4.4. ITT Population, and referenced tables in each section demonstrate that subjects who were withdrawn during the screening and open-label periods were similar to the ITT population in terms of demographic characteristics, pulmonary function, asthma duration, and other baseline disease characteristics.

6.4.1. Screen Withdrawals at Visit 1

Table 6.24, Table 6.25, Table 6.26 and Table 7 present demographic and other baseline characteristics for those subjects who were screen failures at Visit 1.

Table 7 Demographic and Other Baseline Characteristics: Screen Failures/Withdrawals

	Total N=1429
Age (years), n	1428
Mean (SD)	34.1 (15.14)
Range	12-84
Sex, n (%)	1429
Male	535 (37%)
Female	894 (63%)
Race, n (%)	1429
White	861 (60%)
Black	471 (33%)
Other	97 (7%)
Ethnicity, n (%)	1429
Hispanic or Latino	268 (19%)
Other	1161(81%)
Asthma duration (years), n	1374
Mean (SD)	16.4 (12.90)
Range	0-73
≥15 years, n (%)	640 (47%)
Screening FEV ₁ , n	1344
L (SD)	2.71 (0.78)
% Predicted (SD)	82.9 (16.0)
% Reversibility, n	999
Screening Visit (SD)	14.0 (17.71)
% Reversibility, n	88
Historical (SD)	21.3 (10.45)

Source Data: [Table 6.24-Table 6.26](#)

Other baseline disease characteristics of the screen failure population presented in [Table 6.25](#) indicate that 297 (23%) subjects in this population were exposed to passive smoke.

[Table 6.27](#) presents all subjects identified as screen failures (859, 60% of a total of 1429 screened) who did not meet all inclusion and exclusion criteria: 463 (32%) did not meet inclusion criteria for reversibility criteria of $\geq 12\%$ of pre-dose FEV₁ and 200ml increase, 368 (26%) did not meet the inclusion criteria for FEV₁ of $\geq 70\%$ and $\leq 100\%$ of predicted at Visit 1.

6.4.2. Open-Label Period (Albuterol) – Withdrawals

[Table 6.28](#), [Table 6.29](#), [Table 6.30](#) and [Table 8](#) present demographic and other baseline characteristics related to subjects who withdrew during the albuterol open-label period.

Table 8 Demographic and Other Baseline Characteristics: Albuterol Open Label Period Withdrawals

	Arg/Arg N=37	Gly/Gly N=28	Arg/Gly N=43
Age (years), n			
Mean (SD)	31.7 (14.1)	34.7 (17.8)	34.9 (13.6)
Range	12-74	12-72	14-63
Sex, n (%)			
Male	16 (43%)	9 (32%)	16 (37%)
Female	21 (57%)	19 (68%)	27 (63%)
Race, n (%)			
White	16 (43%)	17 (61%)	21 (49%)
Black	13 (35%)	10 (36%)	17 (40%)
Other	8 (22%)	1 (4%)	5 (12%)
Ethnicity, n (%)			
Hispanic or Latino	8 (22%)	2 (7%)	8 (19%)
Not Hispanic or Latino	29 (78%)	26 (93%)	35 (81%)
Asthma duration (years), n	37	28	43
Mean (SD)	14.6 (11.6)	15.6 (14.0)	14.7 (12.2)
Range	1-46	1-49	1-48
≥15 years, n (%)	18 (49%)	10 (36%)	19 (44%)
Passive smoke exposure, n	37	28	43
Yes	5 (14%)	5 (18%)	8 (19%)
No	32 (86%)	23 (82%)	35 (81%)
Screening FEV ₁ n	37	28	43
Mean (SD), L	2.65 (0.67)	2.53 (0.61)	2.63 (0.64)
% Predicted (SD)	78.6 (8.9)	83.1 (7.9)	79.8 (9.6)
% Reversibility, n	36	28	43
Screening Visit			
Mean (SD)	20.9 (10.5)	20.4 (6.6)	17.0 (8.1)
% Reversibility, n	3	1	0
Historical			
Mean (SD)	25.3 (9.00)	16.0	N/A

Source Data: [Table 6.28-Table 6.30](#).

Demographic and baseline characteristics were similar across the three genotypes. See Section [6.1](#) Disposition of Subjects and [Table 2](#).

6.4.3. Open-Label Period (Ipratropium Bromide) – Withdrawals

[Table 6.31](#), [Table 6.32](#), [Table 6.33](#), and [Table 9](#) present demographic and other baseline characteristics related to subjects who withdrew during the albuterol open-label period.

Table 9 **Demographic and Other Baseline Characteristics: Ipratropium Bromide Open Label Period Withdrawals**

	Arg/Arg N=27	Gly/Gly N=41	Arg/Gly N=62
Age (years), n			
Mean (SD)	32.7 (17.7)	29.5 (9.90)	31.0 (12.7)
Range	12-77	13-63	11-65
Sex, n (%)			
Male	12 (44%)	14 (34%)	22 (36%)
Female	15 (56%)	27 (66%)	39 (64%)
Race, n (%)			
White	16 (59%)	24 (59%)	27 (44%)
Black	7 (26%)	10 (24%)	9 (15%)
Other	4 (15%)	7 (17%)	25 (41%)
Ethnicity, n (%)			
Hispanic or Latino	9 (33%)	13 (32%)	26 (43%)
Not Hispanic or Latino	18 (67%)	28 (68%)	35 (57%)
Asthma duration (years), n	27	41	62
Mean (SD)	15.9 (13.1)	14.4 (10.7)	14.4 (11.0)
Range	1-55	0-36	1-43
≥15 years, n (%)	9 (33%)	19 (46%)	25 (40%)
Passive smoke exposure, n	27	41	62
Yes	6 (22%)	9 (22%)	16 (26%)
No	21 (78%)	32 (78%)	46 (74%)
Screening FEV ₁ , n	27	41	62
Mean (SD), L	2.59 (0.66)	2.87 (0.48)	2.70 (0.70)
% Predicted (SD)	82.0 (7.9)	83.9 (8.1)	82.5 (8.1)
% Reversibility, n	24	38	59
Screening Visit			
Mean (SD)	18.0 (6.1)	19.5 (8.1)	20.8 (9.7)
% Reversibility, n	3	4	0
Historical			
Mean (SD)	16.4 (6.4)	21.7 (5.2)	N/A

Source Data: [Table 6.31-Table 6.33](#).

Demographic and baseline characteristics were similar across the three genotypes. See Section [6.1](#) Disposition of Subjects and [Table 3](#).

6.4.4. ITT Population

[Table 6.12](#), [Table 6.13](#), [Table 10](#) and [Table 11](#) present demographic and other baseline characteristics related to subjects in the ITT population in the FSC 100/50mcg group and in the SM 50mcg group. Also see [Table 6.14](#) Listing of Demographic Characteristics.

Table 10 Demographic Characteristics: ITT Population in the FSC 100/50mcg group

	Arg/Arg	Gly/Gly	Arg/Gly
Age (years), n	89	91	92
Mean (SD)	33.8 (13.31)	33.3 (14.33)	31.0 (14.40)
Range	12-73	12-68	12-69
Sex, n (%)	89	91	92
Male	27 (30%)	36 (40%)	33 (36%)
Female	62 (70%)	55 (60%)	59 (64%)
Race, n (%)	89	91	92
White	44 (49%)	59 (65%)	57 (62%)
Black	29 (33%)	18 (20%)	17 (18%)
Other	16 (18%)	14 (15%)	18 (20%)
Ethnicity, n (%)	89	91	92
Hispanic or Latino	28 (31%)	27 (30%)	28 (30%)
Not Hispanic or Latino	61 (69%)	64 (70%)	64 (70%)
Asthma duration (years), n	89	91	92
Mean (SD)	17.0 (10.98)	17.0 (12.05)	16.8 (11.25)
Range	0-52	0-63	1-50
≥15 years	50 (56%)	44 (48%)	47 (51%)
Passive smoke exposure, n	89	91	92
Yes	14 (16%)	21 (23%)	14 (15%)
No	75 (84%)	70 (77%)	78 (85%)

Source Data: [Table 6.12](#) and [Table 6.13](#)

Demographic and other baseline characteristics were similar across Arg/Arg subjects, Gly/Gly subjects, and Arg/Gly subjects.

Table 11 **Demographic Characteristics: ITT Population in the SM 50mcg group**

	Arg/Arg	Gly/Gly	Arg/Gly
Age (years), n	90	92	90
Mean (SD)	30.0 (12.02)	35.2 (16.34)	32.8 (14.17)
Range	12-62	12-74	12-63
Sex, n (%)	90	92	90
Male	33 (37%)	41 (45%)	32 (36%)
Female	57 (63%)	51 (55%)	58 (64%)
Race, n (%)	90	92	90
White	45 (50%)	57 (62%)	54 (60%)
Black	32 (36%)	19 (21%)	15 (17%)
Other	13 (14%)	16 (17%)	21 (23%)
Ethnicity, n (%)	90	92	90
Hispanic or Latino	26 (29%)	26 (28%)	29 (32%)
Not Hispanic or Latino	64 (71%)	66 (72%)	61 (68%)
Asthma duration (years), n	90	92	90
Mean (SD)	13.8 (10.21)	17.1 (12.01)	16.1 (12.52)
Range	1-41	1-68	1-60
≥15 years	36 (40%)	45 (49%)	40 (44%)
Passive smoke exposure, n	90	92	90
Yes	28 (31%)	13 (14%)	17 (19%)
No	62 (69%)	79 (86%)	73 (81%)

Source Data: [Table 6.12](#) and [Table 6.13](#)

Demographic and other baseline characteristics were similar across Arg/Arg subjects, Gly/Gly subjects, and Arg/Gly subjects.

Continuation Assessments

[Table 6.15](#), [Table 6.16](#), and [Table 6.17](#) present asthma status characteristics for subjects in the ITT population and continuation assessments. [Table 12](#) and [Table 13](#) summarize these asthma status characteristics and continuation assessments (pulmonary function measures and doses of medication) made at the first visit (Visit 2) of the albuterol open-label period and first visit (Visit 4) the ipratropium bromide open label period, as well as Visit 6 (randomization visit).

Table 12 Asthma Status Characteristics for ITT Population in the FSC100/50mcg Group

	Arg/Arg	Gly/Gly	Arg/Gly
Screening FEV ₁ , n	89	91	92
L (SD)	2.64 (0.63)	2.73 (0.62)	2.75 (0.63)
% Predicted (SD)	82.0 (7.74)	82.6 (7.70)	82.5 (7.78)
% Reversibility n	83	90	91 ^c
Screening (SD)	19.9 (11.47)	18.4 (9.11)	17.9 (6.19)
% Reversibility n	2	0	0
Historical (SD)	13.6 (0.35)	N/A	N/A
Open-Label Visit 2, n	89	91	92
% of subjects with FEV ₁ ≥70%	86 (97%)	88 (97%)	89 (97%)
% predicted (SD)	86.3 (12.76)	85.9 (10.51)	85.9 (10.34)
Open-Label Visit 4 ^a , n	89	91	92
% of subjects with FEV ₁ ≥70% & >56 puffs/wk albuterol	88 (99%)	90 (100%)	91 (99%)
% predicted (SD)	86.0 (10.64)	87.5 (11.05)	86.8 (9.93)
Visit 6 (Randomization) ^b , n	89	91	92
% of subjects with FEV ₁ ≥70% & ≤56 puffs/wk ipratropium (and albuterol) ^b	88 (99%)	91 (100%)	92 (100%)
% predicted (SD)	85 (10.04)	86.7 (10.93)	86.3 (10.46)

1. Baseline = Last week of albuterol open-label period

2. Final Week = Last week of ipratropium bromide open-label period

Source Data: [Table 6.15-Table 6.17](#)

These data show that subjects in the FSC 100/50mcg treatment group were appropriately randomized into the study by maintaining appropriate continuation assessments of FEV₁ and doses of medication that were required at Visit 2, the first visit of the albuterol open-label period and Visit 4, the first visit of the ipratropium bromide open-label period of this study, as well as at Visit 6 (randomization).

Table 13 Asthma Status Characteristics for ITT Population in the SM 50mcg Group

	Arg/Arg	Gly/Gly	Arg/Gly
Screening FEV ₁ , n	90	92	90
L (SD)	2.78 (0.68)	2.73 (0.66)	2.72 (0.70)
% Predicted (SD)	83.3 (8.23)	81.5 (8.44)	82.1 (8.15)
% Reversibility, n	86	88	85
Screening (SD)	19.5 (9.88)	20.2 (7.79)	20.9 (12.35)
% Reversibility, n	4	0	0
Historical (SD)	18.7 (6.77)	N/A	N/A
Open-Label Visit 2, n	90	92	90
% of subjects with FEV ₁ ≥70%	88 (98%)	88 (96%)	87 (97%)
% predicted (SD)	88.4 (11.35)	84.5 (10.73)	85.3 (10.05)
Open-Label Visit 4 ^a , n	90	92	90
% of subjects with FEV ₁ ≥70% & ≤56 puffs/wk albuterol	90 (100%)	92 (100%)	90 (100%)
% predicted (SD)	89.3 (12.72)	85.7 (10.51)	86.3 (10.23)
Visit 6 (Randomization) ^b , n	90	92	90
% of subjects with FEV ₁ ≥70% & ≤56 puffs/wk ipratropium (and albuterol) ^b	90 (100%)	90 (98%)	87 (97%)
% predicted (SD)	87.2 (11.31)	86.0 (11.06)	85.6 (11.44)

1. Baseline = Last week of albuterol open-label period

2. Final Week = Last week of ipratropium bromide open-label period

Source Data: [Table 6.15-Table 6.17](#)

These data show that subjects in the SM 50mcg treatment group were appropriately randomized into the study by maintaining appropriate FEV₁ and doses of medication continuation assessments that were required at Visit 2, the first visit of the albuterol open-label period and Visit 4, the first visit of the ipratropium bromide open-label period of this study, as well as at Visit 6 (randomization).

6.4.5. Other Current Medical Conditions

[Table 6.18](#) provides the concurrent medical conditions present at the Screening Visit.

A similar number of subjects in the FSC 100/50mcg treatment group (Arg/Arg 74%, Gly/Gly 79%, and Arg/Gly 73%) had at least one concurrent medical condition. The most common medical conditions were immune system disorders (26%, 29%, 27%), nervous system disorders (35%, 27%, 33%), and skin and subcutaneous tissue disorders (19%, 25%, 24%), across each of the genotypes, respectively.

A similar number of subjects in the SM 50mcg treatment group (Arg/Arg 73%, Gly/Gly 71%, and Arg/Gly 74%) also had at least one concurrent medical condition. The most common medical conditions were immune system disorders (18%, 26%, 20%), musculoskeletal and connective tissue disorders (20%, 24%, 20%), and nervous system disorders (23%, 26%, 29%), across each of the genotypes, respectively.

6.4.6. Previous Medications

Table 6.19 presents asthma medications taken prior to the Screening Visit. Any anti-asthma medication taken 4 weeks prior to Visit 1 in addition to short acting beta₂ agonist medications were recorded in the CRF.

All subjects were required to have used a short-acting β₂-agonist on a scheduled basis or as needed for at least 30 days prior to the Screening Visit (Section 5.3.1. Inclusion Criteria).

Prior to Amendment 02 of the SFA100062 protocol, subjects were permitted to use a long-acting β₂-agonist for at least 30 days prior to the Screening Visit.

Section 5.3.2 Exclusion Criteria 5 identifies time periods prior to the Screening Visit during which subjects were not permitted use of the asthma medications.

No subject in either treatment group was taken off of the asthma medication he/she was currently using during the 4 week period between Visit 1 and Visit 2.

6.5. Concomitant Medications

The CRF text for concurrent medications was coded using the GSK Drug dictionary and reported using the Medication Class and Dictionary Term. Concurrent medications were summarized and grouped by Medication Class and Dictionary Term within Medication Class. Results are displayed in the order of decreasing frequency.

6.5.1. Asthma Medications

Table 6.20 relates the Medication Class and Dictionary Term to the concurrent medication recorded in the CRF for the Intent-to-Treat populations. Table 6.21 presents the concurrent asthma medications reported in the CRF during the blinded treatment period. Daily ipratropium and albuterol use as rescue medication(s) was recorded by the subject in the diary card during the blinded treatment study period.

6.5.2. Non-Asthma Medications

Table 6.22 presents the concurrent non-asthma medications used by subjects in the FSC 100/50mcg group and in the SM 50mcg group during the blinded treatment period. All non-asthma medications are presented in Table 6.22 by SOC and genotypes (Arg/Arg, Gly/Gly, and Arg/Gly).

The majority of subjects across the three genotypes used concurrent non-asthma medications during the study (89%, 86%, 91%) in the FSC100/50mcg treatment group.

The medications reported by subjects, regardless of genotype, most frequently for use in non-asthma conditions were classified for the nervous system (e.g., paracetamol [44%], ibuprofen [40%], acetylsalicylic acid [11%]). Non-asthma medications were reported for the respiratory system (e.g., fexofenadine hydrochloride [13%], loratadine [12%],

benadryl [11%], pseudoephedrine hydrochloride [10%]), for the genito urinary system/sex hormone (e.g., ibuprofen [40%], naproxen sodium [11%]) and for the musculo-skeletal system (e.g. ibuprofen [40%], naproxen sodium [11%]).

The majority of subjects across three genotypes (Arg/Arg, Gly/Gly, and Arg/Gly) used concurrent non-asthma medications during the study (90%, 87%, 90%) in the SM 50mcg treatment group.

The medications reported by subjects, regardless of genotype, most frequently for use in non-asthma conditions were classified for the nervous system (e.g., ibuprofen [37%], paracetamol [36%], acetylsalicylic acid [10%]). Other non-asthma medications subjects most frequently reported were used for the respiratory system (e.g., loratadine [11%]), for the genito urinary system/sex hormones (e.g. ibuprofen [37%]), and for the musculo-skeletal system (e.g. ibuprofen [37%]).

6.6. Treatment Compliance

Treatment compliance was assessed according to the dose counter on the device and data recorded on diary cards by the subject.

Each subject recorded on their diary card the total number of doses of blinded study medication taken each day. Blinded study medication use was also recorded in the CRF. [Table 6.23](#) presents subject mean overall compliance with the dosing regimen during the double blind treatment period (Weeks 1-16) with 95.3% in the FSC 100/50mcg group and 97.2% in the SM 50mcg group.

7. EFFICACY RESULTS

The primary, secondary, and other related efficacy measures for each of the Intent-to-Treat populations are provided in Section 7.1 Primary Efficacy Results, Section 7.2 Secondary Efficacy Results and Section 7.3 Other Efficacy Results.

7.1. Primary Efficacy Results

The primary efficacy measure was the evaluation of AM PEF AUC relative to baseline (AUC [bl]) during the double-blind treatment period for subjects identified with a B16 Arg/Arg genotype compared to subjects identified with a B16 Gly/Gly genotype over 16 weeks of treatment with FSC 100/50mcg BID.

7.1.1. AM PEF

Summary statistics and treatment differences for the Arg/Arg, Gly/Gly, and Arg/Gly genotypes are presented in Table 7.1 and Table 7.2 and summarized in Table 14 and Table 15.

The overall AM PEF mean changes from baseline (AUC) for each genotype in the FSC 100/50mcg group and in the SM 50mcg group following the double blind treatment period are also displayed graphically in Figure 1.

FSC 100/50mcg Treatment Group

The overall mean changes from baseline in AM PEF following the double blind treatment period and the washout period are summarized in Table 14 and Table 15.

Table 14 AM PEF (Intent-to-Treat Population) in the FSC 100/50mcg group

AM PEF (L/min)	Arg/Arg	Gly/Gly	Arg/Gly
Subjects, n	87	90	91
Baseline [†] , n	84	89	91
Mean (SE)	352 (10.3)	371 (10.0)	373 (9.6)
Double-blind Period (Weeks 1-16), n	86	89	91
Mean (SE)	382.6 (10.1)	394.3 (9.7)	399.3 (11.1)
Mean change (SE)	32.6 (4.7)	24.9 (5.9)	25.9 (4.8)
Washout (2 Weeks), n	77	78	82
Mean (SE)	372 (10.3)	385 (10.6)	393 (11.3)
Mean change (SE)	27.2 (5.1)	9.1 (4.8)	17.0 (4.6)
Statistical Comparisons	Arg/Arg vs Gly/Gly	Arg/Gly vs Gly/Gly	Arg/Arg vs Arg/Gly
Double-blind Period (Weeks 1-16)			
LS means difference	7.9	0.8	7.1
95% Confidence Interval	-6.3, 22.1	-13.0, 14.6	-7.1, 21.3
p-value	0.276	0.910	0.325
Washout (2 Weeks)			
LS means difference	15.9	7.6	8.3
95% Confidence Interval	2.5, 29.2	-5.4, 20.5	-4.9, 21.5
p-value	0.020	0.250	0.218

Source Data: [Table 7.1](#) and [Table 7.2](#)[†]Baseline- calculated from diary data and defined as the average value for the 7 day period preceding randomization (Visit 6). Diary data was required for three (3) days to calculate a baseline for each subject.

The improvements overall in AM PEF for all genotypes were not statistically different in the FSC 100/50mcg double blind treatment period (Weeks 1-16). During the washout period, a statistically significant difference was observed in AM PEF for the Arg/Arg genotype compared to the Gly/Gly genotype (treatment difference 15.9 L/min, p=0.020).

Similar results in AM PEF were observed in the per-protocol population ([Table 7.3](#) Summary of AM PEF (L/min) and [Table 7.4](#) Analysis of AM PEF (L/min)).

SM 50mcg Treatment Group**Table 15 AM PEF (Intent-to-Treat Population) in the SM 50mcg Group**

AM PEF (L/min)	Arg/Arg	Gly/Gly	Arg/Gly
Subjects, n	86	91	89
Baseline†, n	80	91	86
Mean (SE)	387 (11.5)	373 (10.2)	362 (9.4)
Double-blind Period (Weeks 1-16), n	81	89	86
Mean (SE)	403.1 (11.9)	385.1 (9.8)	388.9 (11.0)
Mean change (SE)	19.4 (3.9)	12.4 (3.1)	24.6 (5.4)
Washout (2 Weeks), n	65	75	73
Overall Mean (SE)	394 (13.0)	375 (10.8)	378 (12.6)
Mean change (SE)	11.6 (5.2)	1.1 (3.8)	18.3 (7.7)
Statistical Comparisons	Arg/Arg vs Gly/Gly	Arg/Gly vs Gly/Gly	Arg/Arg vs Arg/Gly
Double-blind Period (Weeks 1-16)			
LS means difference	9.8	11.1	-1.2
95% Confidence Interval	-1.7, 21.4	-0.2, 22.3	-13.0, 10.6
p-value	0.095	0.054	0.836
Washout (2 Weeks)			
LS means difference	12.1	16.7	-4.6
95% Confidence Interval	-4.5, 28.7	0.7, 32.6	-21.6, 12.4
p-value	0.153	0.041	0.596

Source Data: [Table 7.1](#) and [Table 7.2](#)

†Baseline- calculated from diary data and defined as the average value for the 7 day period preceding randomization (Visit 6). Diary data was required for three (3) days to calculate a baseline for each subject.

Changes in AM PEF for all genotypes were not statistically significant in the SM 50mcg double blind treatment period (Weeks 1-16). During the washout period, a statistically significant difference was observed in AM PEF for the Arg/Gly genotype compared to the Gly/Gly genotype (treatment difference 16.7 L/min, $p=0.041$).

Similar results in AM PEF were observed in the per-protocol population ([Table 7.3](#) and [Table 7.4](#)).

7.2. Secondary Efficacy Results

Summary statistics and the analyses of secondary efficacy measures for the Intent-to-Treat population are provided in [Table 7.5-Table 7.12](#) and described in Section 5.6.2.2 Secondary efficacy endpoints.

7.2.1. PM PEF

Summary statistics and treatment differences for PM PEF are presented in [Table 7.5](#) and [Table 7.6](#).

FSC 100/50mcg Treatment Group

The changes from baseline overall at the end of the double blind treatment period and the washout period in PM PEF are summarized in [Table 16](#).

Table 16 PM PEF (Intent-to-Treat Population) in the FSC 100/50mcg Group

PM PEF (L/min)	Arg/Arg	Gly/Gly	Arg/Gly
Subjects, n	87	90	91
Baseline [†] , n	84	89	91
Mean (SE)	370 (10.6)	380 (10.0)	381 (9.8)
Double-blind Period (Weeks 1-16), n	86	89	91
Mean (SE)	394.7 (10.5)	400.2 (9.7)	405.8 (11.2)
Mean change (SE)	26.8 (4.8)	22.4 (5.8)	25.0 (4.6)
Washout (2 Weeks), n	77	78	82
Overall Mean (SE)	386 (10.5)	391 (10.9)	398 (11.2)
Mean change (SE)	21.5 (5.7)	6.4 (4.9)	15.1 (4.6)
Statistical Comparisons	Arg/Arg vs Gly/Gly	Arg/Gly vs Gly/Gly	Arg/Arg vs Arg/Gly
Double-blind Period (Weeks 1-16)			
LS means difference	5.6	2.5	3.0
95% Confidence Interval	-8.4, 19.6	-11.1, 16.1	-10.9, 17.0
p-value	0.433	0.714	0.667
Washout (2 Weeks)			
LS means difference	13.9	8.1	5.8
95% Confidence Interval	0.0, 27.8	-5.3, 21.6	-7.9, 19.5
p-value	0.049	0.235	0.406

Source Data: [Table 7.5](#) and [Table 7.6](#)

[†]Baseline- calculated from diary data and defined as the average value for the 7 day period preceding randomization (Visit 6). Diary data was required for three (3) days to calculate a baseline for each subject.

The improvements overall in PM PEF for all genotypes were not statistically different in the FSC 100/50mcg double blind treatment period (Weeks 1-16). During the washout period, a statistically significant difference was observed in PM PEF for the Arg/Arg genotype compared to the Gly/Gly genotype (treatment difference 13.9 L/min, p=0.049).

SM 50mcg Group

The changes from baseline overall at the end of the double blind treatment period and the washout period in PM PEF are summarized in [Table 17](#).

Table 17 PM PEF (Intent-to-Treat Population) in the SM 50mcg Group

PM PEF (L/min)	Arg/Arg	Gly/Gly	Arg/Gly
Subjects in Treatment, n	86	91	89
Baseline [†] , n	80	90	87
Mean (SE)	398 (12.6)	386 (10.7)	373 (10.2)
Double-blind Period (Weeks 1-16), n	81	89	86
Mean (SE)	414.1 (13.0)	395.7 (10.1)	399.6 (11.6)
Mean change (SE)	19.3 (3.9)	10.5 (3.2)	26.2 (5.9)
PM PEF (L/min)	Arg/Arg	Gly/Gly	Arg/Gly
Washout (2 Weeks), n	65	75	72
Overall Mean (SE)	403 (13.9)	387 (11.0)	392 (13.0)
Mean change (SE)	9.8 (5.1)	1.1 (4.7)	22.8 (8.6)
Statistical Comparisons	Arg/Arg vs Gly/Gly	Arg/Gly vs Gly/Gly	Arg/Arg vs Arg/Gly
Double-blind Period (Weeks 1-16)			
LS means difference	11.7	14.6	-2.9
95% Confidence Interval	-0.6, 24.0	2.7, 26.5	-15.4, 9.6
p-value	0.062	0.017	0.648
Washout (2 Weeks)			
LS means difference	10.7	20.5	-9.8
95% Confidence Interval	-7.5, 29.0	3.0, 38.1	-28.4, 8.8
p-value	0.248	0.022	0.301

Source Data: [Table 7.5](#) and [Table 7.6](#)

[†]Baseline- calculated from diary data and defined as the average value for the 7 day period preceding randomization (Visit 6). Diary data was required for three (3) days to calculate a baseline for each subject.

Improvements overall in PM PEF were statistically significant in the SM 50mcg double blind treatment period (Weeks 1-16) for Arg/Gly subjects versus Gly/Gly subjects (LS mean difference 14.6 L/min, p=0.017). During the washout period, a statistically significant difference was also observed in PM PEF for the Arg/Gly genotype compared to the Gly/Gly genotype (treatment difference 20.5 L/min, p=0.022).

7.2.2. Pre-Dose FEV₁

Summary statistics and treatment differences for pre-dose FEV₁ are presented in [Table 7.7](#) and in [Table 7.8](#).

FSC 100/50mcg

The changes from baseline overall during the double blind treatment period and the washout period in FEV₁ are summarized in [Table 18](#).

Table 18 Pre-Dose FEV₁ (Intent-to-Treat Population) in the FSC 100/50mcg Group

Pre-Dose FEV ₁ (L)	Arg/Arg	Gly/Gly	Arg/Gly
Albuterol Open-Label Visit 2, n	87	90	91
Mean (SE)	2.77 (0.07)	2.84 (0.07)	2.86 (0.07)
Ipratropium Open Label Visit 4, n	87	90	91
Mean (SE)	2.78 (0.08)	2.88 (0.06)	2.89 (0.07)
Baseline [†] , n	87	90	91
Mean (SE)	2.76 (0.08)	2.86 (0.07)	2.87 (0.07)
Double-blind Period (Weeks 1-16), n	81	88	89
Mean (SE)	2.95 (0.08)	3.05 (0.08)	3.09 (0.08)
Mean change (SE)	0.22 (0.03)	0.21 (0.03)	0.22 (0.03)
Washout (2 Weeks), n	76	79	82
Mean (SE)	2.76 (0.09)	2.94 (0.08)	2.89 (0.08)
Mean change (SE)	0.03 (0.03)	0.12 (0.04)	0.02 (0.03)
Statistical Comparisons	Arg/Arg vs Gly/Gly	Arg/Gly vs Gly/Gly	Arg/Arg vs Arg/Gly
Double-blind Period (Weeks 1-16)			
LS means difference (L)	0.02	0.02	0.00
95% Confidence Interval	-0.07, 0.10	-0.07, 0.10	-0.08, 0.09
p-value	0.679	0.714	0.953
Wash-out (2 Weeks)			
LS means difference (L)	-0.08	-0.09	0.01
95% Confidence Interval	-0.17, 0.01	-0.18, 0.00	-0.08, 0.10
p-value	0.094	0.051	0.814

Source Data: [Table 7.7](#) and [Table 7.8](#)

[†] Baseline – Visit 6, Day 1 of double-blind period

Changes over baseline in pre-dose FEV₁ were similar for all genotypes in the FSC 100/50mcg in the double blind treatment period overall (Weeks 1-16).

SM 50mcg

The changes from baseline overall during the double blind treatment period and the washout period in FEV₁ are summarized in [Table 19](#).

Table 19 Pre-Dose FEV₁ (Intent-to-Treat Population) in the SM 50mcg Group

Pre-Dose FEV ₁ (L)	Arg/Arg	Gly/Gly	Arg/Gly
Albuterol Open-Label Visit 2, n	86	91	89
Mean (SE)	2.94 (0.08)	2.82 (0.07)	2.81 (0.07)
Ipratropium Open Label Visit 4, n	86	91	89
Mean (SE)	2.95 (0.08)	2.87 (0.08)	2.85 (0.08)
Baseline [†] , n	86	91	89
Mean (SE)	2.89 (0.08)	2.88 (0.08)	2.84 (0.08)
Double-blind Period (Weeks 1-16), n	79	84	84
Mean (SE)	3.07 (0.09)	2.97 (0.09)	3.00 (0.08)
Mean change (SE)	0.21 (0.03)	0.08 (0.03)	0.13 (0.03)
Washout (2 Weeks), n	65	75	72
Mean (SE)	2.90 (0.09)	2.81 (0.09)	2.85 (0.08)
Mean change (SE)	0.01 (0.04)	-0.06 (0.04)	0.03 (0.04)
Statistical Comparisons	Arg/Arg vs Gly/Gly	Arg/Gly vs Gly/Gly	Arg/Arg vs Arg/Gly
Double-blind Period (Weeks 1-16)			
LS means difference (L)	0.13	0.05	0.08
95% Confidence Interval	0.04, 0.21	-0.03, 0.13	-0.01, 0.16
p-value	0.003	0.218	0.076
Wash-out (2 Weeks)			
LS means difference (L)	0.05	0.09	-0.03
95% Confidence Interval	-0.05, 0.16	-0.02, 0.19	-0.14, 0.08
p-value	0.323	0.094	0.539

Source Data: [Table 7.7](#) and [Table 7.8](#)

[†] Baseline – Visit 6, Day 1 of double-blind period

Changes in pre-dose FEV₁ for Arg/Arg subjects compared to Gly/Gly subjects were statistically significant overall in the double blind treatment period (Weeks 1-16) were 0.13 L/min, p=0.003.

7.2.3. Percent of Symptom Free Days

Summary statistics and treatment differences for percent of symptom free days are presented in [Table 7.9](#) and [Table 7.10](#), respectively.

FSC 100/50mcg Group

Changes from baseline overall during the double blind treatment period and the washout period in percent of symptom free days are summarized in [Table 20](#).

Table 20 Percent of Symptom Free Days (Intent-to-Treat Population) in the FSC 100/50mcg Group

Symptom Free Days (%)	Arg/Arg	Gly/Gly	Arg/Gly
Subjects, n	87	90	91
Baseline [†] , n	81	89	90
Mean (SE)	31.5 (4.63)	32.2 (3.70)	34.6 (4.39)
Double-blind Period (Weeks 1-16), n	86	89	91
Mean (SE)	43.5 (4.41)	50.6 (4.20)	48.6 (4.21)
Mean change (SE)	9.9 (2.83)	18.2 (2.88)	14.6 (3.19)
Washout (2 Weeks), n	77	76	82
Mean (SE)	41.4 (4.92)	42.8 (4.78)	38.7 (4.41)
Mean change (SE)	7.5 (3.31)	9.5 (2.91)	6.5 (2.96)
Statistical Comparisons	Arg/Arg vs Gly/Gly	Arg/Gly vs Gly/Gly	Arg/Arg vs Arg/Gly
Double-blind Period (Weeks 1-16)			
LS means difference	-7.7	-3.2	-4.5
95% Confidence Interval	-15.8, 0.4	-11.0, 4.6	-12.6, 3.6
p-value	0.061	0.419	0.271
Wash-out (2 Weeks)			
LS means difference	-1.7	-3.3	1.6
95% Confidence Interval	-10.1, 6.8	-11.5, 4.9	-6.7, 9.9
p-value	0.697	0.428	0.702

Source Data: [Table 7.9](#) and [Table 7.10](#)

[†]Baseline- calculated from diary data and defined as the average value for the 7 day period preceding randomization (Visit 6). Diary data was required for three (3) days to calculate a baseline for each subject.

No statistically significant differences were observed overall during the double blind treatment period in percent of symptom free days between the genotypes in the FSC 100/50mcg treatment group.

SM 50mcg Group

Changes from baseline overall during the double blind treatment period and the washout period in percent of symptom free days are summarized in [Table 21](#).

Table 21 Percent of Symptom Free Days (Intent-to-Treat Population) in the SM 50mcg Group

Symptom Free Days (%)	Arg/Arg	Gly/Gly	Arg/Gly
Subjects, n	86	91	89
Baseline [†] , n	80	90	87
Mean (SE)	34.4 (4.63)	36.1 (4.31)	35.4 (4.31)
Double-blind Period (Weeks 1-16), n	81	89	86
Mean (SE)	44.9 (4.14)	43.6 (4.18)	44.9 (4.31)
Mean change (SE)	9.6 (3.21)	8.2 (2.69)	9.1 (2.69)
Washout (2 Weeks), n	64	75	72
Mean (SE)	42.4 (4.96)	37.1 (4.80)	40.7 (5.12)
Mean change (SE)	4.2 (3.97)	4.6 (3.58)	3.2 (2.63)
Statistical Comparisons	Arg/Arg vs Gly/Gly	Arg/Gly vs Gly/Gly	Arg/Arg vs Arg/Gly
Double-blind Period (Weeks 1-16)			
LS means difference	2.1	1.0	1.1
95% Confidence Interval	-5.4, 9.5	-6.3, 8.2	-6.4, 8.6
p-value	0.583	0.795	0.768
Wash-out (2 Weeks)			
LS means difference	1.3	-0.6	1.9
95% Confidence Interval	-7.9, 10.5	-9.4, 8.2	-7.4, 11.2
p-value	0.782	0.889	0.687

Source Data: [Table 7.9](#) and [Table 7.10](#)

[†]Baseline- calculated from diary data and defined as the average value for the 7 day period preceding randomization (Visit 6). Diary data was required for three (3) days to calculate a baseline for each subject.

No statistically significant differences were observed overall during the double blind treatment period in percent of symptom free days between the genotypes in the SM 50mcg treatment group.

7.2.4. Supplemental Ipratropium Bromide Use

Summary statistics and treatment differences for supplemental ipratroium bromide use are presented in [Table 7.11](#) and [Table 7.12](#), respectively.

When required, subjects were allowed to use *prn* albuterol if ipratropium bromide was not sufficient to resolve symptoms. Albuterol use is reported in Section 7.3 Other Efficacy Results. Summary statistics may be found in Section 7.3.3. Percent of Subjects Requiring Albuterol and in Section 7.3.4. Supplemental Albuterol Use (puffs/day) .

FSC 100/50mcg Group

Changes from baseline overall in the double blind treatment period and the washout period in ipratropium bromide use are summarized in [Table 22](#).

Table 22 Supplemental Ipratropium Bromide Use (Intent-to-Treat Population) in the FSC 100/50mcg Group

Supplemental Ipratropium Use (puffs/day)	Arg/Arg	Gly/Gly	Arg/Gly
Subjects, n	87	90	91
Ipratropium Open-Label Period, n			
Overall, n	86	90	90
Mean (SE)	1.04 (0.10)	1.13 (0.10)	1.18 (0.13)
Baseline [†] , n	82	87	87
Mean (SE)	0.98 (0.12)	1.15 (0.13)	1.15 (0.14)
Double-blind Period (Weeks 1-16), n	86	89	89
Mean (SE)	0.51 (0.07)	0.57 (0.07)	0.56 (0.07)
Mean change (SE)	-0.49 (0.11)	-0.60 (0.12)	-0.63 (0.11)
Washout (2 Weeks), n	77	75	81
Mean (SE)	0.64 (0.10)	0.74 (0.11)	0.75 (0.10)
Mean change (SE)	-0.42 (0.11)	-0.39 (0.10)	-0.50 (0.13)
Statistical Comparisons	Arg/Arg vs Gly/Gly	Arg/Gly vs Gly/Gly	Arg/Arg vs Arg/Gly
Double-blind Period (Weeks 1-16)			
LS means difference	-0.04	-0.03	-0.01
95% Confidence Interval	-0.22, 0.14	-0.21, 0.14	-0.19, 0.17
p-value	0.637	0.697	0.926
Wash-out (2 Weeks)			
LS means difference	-0.13	-0.07	-0.05
95% Confidence Interval	-0.36, 0.11	-0.30, 0.16	-0.29, 0.18
p-value	0.296	0.541	0.646

Source Data: [Table 7.11](#) and [Table 7.12](#)

[†]Baseline- calculated from diary data and defined as the average value for the 7 day period preceding randomization (Visit 6). Diary data was required for three (3) days to calculate a baseline for each subject.

No statistically significant differences were observed overall during the open-label, double-blind treatment period or washout period in supplement ipratropium bromide use between the genotypes in the FSC 100/50mcg treatment group.

SM 50mcg Group

Changes from baseline overall in the double blind treatment period and the washout period in supplemental ipratropium bromide use are summarized in [Table 23](#).

Table 23 Supplemental Ipratropium Bromide Use (Intent-to-Treat Population) in the SM 50mcg Group

Supplemental Ipratropium Use (puffs/day)	Arg/Arg	Gly/Gly	Arg/Gly
Subjects, n	86	91	89
Ipratropium Open-Label Period, n			
Overall, n	84	91	87
Mean (SE)	1.09 (0.10)	1.10 (0.11)	1.13 (0.12)
Baseline [†] , n	80	86	86
Mean (SE)	1.04 (0.12)	1.09 (0.13)	1.15 (0.14)
Double-blind Period (Weeks 1-16), n	81	89	85
Mean (SE)	0.66 (0.08)	0.71 (0.09)	0.68 (0.08)
Mean change (SE)	-0.36 (0.10)	-0.35 (0.08)	-0.45 (0.12)
Washout (2 Weeks), n	65	75	72
Mean (SE)	0.68 (0.10)	0.85 (0.11)	0.86 (0.14)
Mean change (SE)	-0.29 (0.13)	-0.23 (0.11)	-0.29 (0.11)
Statistical Comparisons	Arg/Arg vs Gly/Gly	Arg/Gly vs Gly/Gly	Arg/Arg vs Arg/Gly
Double-blind Period (Weeks 1-16)			
LS means difference	-0.09	-0.08	-0.01
95% Confidence Interval	-0.26, 0.09	-0.25, 0.10	-0.19, 0.17
p-value	0.347	0.391	0.914
Wash-out (2 Weeks)			
LS means difference	-0.15	-0.04	-0.10
95% Confidence Interval	-0.42, 0.13	-0.30, 0.22	-0.37, 0.17
p-value	0.292	0.751	0.452

Source Data: [Table 7.11](#) and [Table 7.12](#)

[†]Baseline- calculated from diary data and defined as the average value for the 7 day period preceding randomization (Visit 6). Diary data was required for three (3) days to calculate a baseline for each subject.

No statistically significant differences were observed overall during the open label period, double-blind treatment period or washout period in supplement ipratropium bromide use between the genotypes in the SM 50mcg treatment group.

7.3. Other Efficacy Results

Summary statistics and the analyses of other efficacy measures for the Intent-to-Treat population are provided in [Table 7.13](#) through [Table 7.112](#) and described in Section [5.6.2.3](#). Other efficacy endpoints and Section [5.8.8.3](#). Other efficacy measure(s).

7.3.1. AM PEF during Open-label Treatment with *prn* Albuterol and *prn* Ipratropium Bromide by Genotype

AM PEF was collected daily during each open label treatment period. Statistical comparisons of interest, the last 4 weeks of each open-label treatment period, are presented in [Table 7.13](#) and [Table 7.14](#) and summarized in [Table 24](#).

Table 24 AM PEF during Open-label Treatment with Albuterol and with Ipratropium Bromide by Genotype (Last 4 weeks of Each Open-Label Period)

AM PEF (L/min) - Arg/Arg Genotype	Albuterol Period	Ipratropium Period	
Weeks 1-4, n	171	170	
Mean (SE)	361.6 (7.4)	369.0 (7.8)	
Weeks 5-8, n	171	169	
Mean	367.6 (7.6)	368.2 (7.6)	
Overall, n	171	170	
Mean (SE)	364.7 (7.4)	368.3 (7.6)	
AM PEF (L/min) - Gly/Gly Genotype	Open-label Albuterol	Open-label Ipratropium	
Weeks 1-4, n	181	181	
Mean (SE)	368.5 (6.8)	369.3 (7.1)	
Weeks 5-8, n	179	181	
Mean (SE)	370.5 (6.7)	369.6 (7.0)	
Overall, n	181	181	
Mean (SE)	369.2 (6.6)	369.4 (7.0)	
AM PEF (L/min) - Arg/Gly Genotype	Open-label Albuterol	Open-label Ipratropium	
Weeks 1-4, n	178	176	
Mean (SE)	367.6 (6.8)	366.0 (6.6)	
Weeks 5-8, n	178	178	
Mean (SE)	368.6 (6.9)	370.1(6.6)	
Overall, n	178	178	
Mean (SE)	368.3 (6.8)	367.9 (6.5)	
Statistical Comparisons of Interest	Arg/Arg Alb vs IP	Gly/Gly Alb vs IP	Arg/Gly Alb vs IP
Weeks 5-8			
LS means difference	-0.4	0.4	-1.5
95% Confidence Interval	-4.8, 4.0	-4.0, 4.9	-6.1, 3.2
p-value	0.858	0.848	0.538

Source Data: [Table 7.13](#) and [Table 7.14](#)

No statistically significant differences in AM PEF measures for the Arg/Arg, Gly/Gly, or Arg/Gly genotypes were observed during the last four weeks (Weeks 5-8) of the albuterol open-label period compared to the last four weeks (Weeks 5-8) of the ipratropium bromide open-label period.

No statistically significant mean differences were observed in the last four weeks for the albuterol open-label period in PM PEF measures compared to the last four weeks of the open-label ipratropium bromide period. See [Table 7.15](#) Summary of Open-Label

Treatment Period PM PEF (L/min) and [Table 7.16](#), Analysis of Open-Label Treatment Period PM PEF (L/min) by Genotype.

7.3.2. Symptom free Days during Open-label Treatment with *prn* Albuterol and Open-label *prn* Ipratropium Bromide by Genotype

Symptom-free days during the open-label treatment with *prn* albuterol and open-label *prn* ipratropium bromide by genotype were collected daily during each open label treatment period. The statistical comparisons of interest, the last 4 weeks of each open-label treatment period, are presented in [Table 7.17](#) and [Table 7.18](#) and summarized in [Table 25](#).

Table 25 Symptom free Days during Open-label Treatment with *prn* Albuterol and Open-label *prn* Ipratropium Bromide by Genotype

Symptom free Days (%) - Arg/Arg Genotype	Open-label Albuterol		Open-label Ipratropium
Weeks 1-4, n	171		169
Mean (SE)	28.0 (2.57)		31.2 (2.83)
Weeks 5-8, n	171		166
Mean (SE)	30.1 (2.79)		31.7 (2.82)
Overall, n	171		170
Mean (SE)	29.2 (2.61)		31.3 (2.73)
Symptom free Days (%) - Gly/Gly Genotype	Open-label Albuterol		Open-label Ipratropium
Weeks 1-4, n	180		181
Mean (SE)	29.2 (2.41)		33.3 (2.70)
Weeks 5-8, n	180		181
Mean (SE)	32.7 (2.63)		33.9 (2.73)
Overall, n	181		181
Mean (SE)	31.1 (2.42)		33.6 (2.65)
Symptom free Days (%) - Arg/Gly Genotype	Open-label Albuterol		Open-label Ipratropium
Weeks 1-4, n	178		176
Mean (SE)	28.1 (2.44)		33.5 (2.82)
Weeks 5-8, n	178		177
Mean (SE)	33.0 (2.69)		33.7 (2.78)
Overall, n	178		178
Mean (SE)	30.5 (2.47)		33.8 (2.72)
Statistical Comparisons of Interest	Arg/Arg Alb vs IP	Gly/Gly Alb vs IP	Arg/Gly Alb vs IP
Weeks 5-8			
LS means difference	-1.4	-1.2	-1.1
95% Confidence Interval	-4.2, 1.4	-3.9, 1.6	-4.0, 1.9
p-value	0.327	0.405	0.481

Source Data: [Table 7.17](#) and [Table 7.18](#)

No statistically significant mean differences between the Arg/Arg, Gly/Gly, or Arg/Gly genotypes in symptom free days were observed during the last four weeks (Weeks 5-8) of

the albuterol open-label period when compared to the last four weeks (Weeks 5-8) of the ipratropium bromide open-label period.

7.3.3. Percent of Subjects Requiring Albuterol

When required, subjects were allowed to use *prn* albuterol if ipratropium bromide was not sufficient to resolve symptoms.

In this context of use, summary statistics and treatment differences for the percent of subjects requiring albuterol during the albuterol and ipratropium bromide open-label periods, the double blind treatment period, and wash-period are presented in [Table 7.19](#) and [Table 7.20](#), respectively and are summarized in [Table 26](#) and [Table 27](#).

FSC 100/50mcg Group

Table 26 Percent of Subjects Requiring Albuterol (Intent-to-Treat Population) in the FSC 100/50mcg Group

Percent of Subject Requiring Albuterol	Arg/Arg	Gly/Gly	Arg/Gly
Albuterol Open-Label Period, n	87	90	91
Overall, n (%)	85 (98%)	89 (99%)	89 (98%)
Ipratropium Open-Label Period, n	87	90	91
Overall, n (%)	72 (86%)	73 (83%)	76 (84%)
Baseline [†] , n	80	85	86
Subjects (%)	38 (48%)	49 (58%)	45 (52%)
Double-blind Period (Weeks 1-16), n	86	88	91
Subjects, n (%)	63 (73%)	67 (76%)	72 (79%)
Washout (2 Weeks), n	77	77	82
Subjects, n (%)	46 (60%)	42 (55%)	57 (70%)
Statistical Comparisons	Arg/Arg vs Gly/Gly	Arg/Gly vs Gly/Gly	Arg/Arg vs Arg/Gly
Double-blind Period (Weeks 1-16)			
Relative risk	0.95	1.04	0.91
95% Confidence Interval	0.80, 1.13	0.89, 1.21	0.77, 1.07
p-value	0.567	0.644	0.248

Source Data: [Table 7.19](#) and [Table 7.20](#)

[†]Baseline- calculated from diary data and defined as the average value for the 7 day period preceding randomization (Visit 6). Diary data was required for three (3) days to calculate a baseline for each subject.

The percent of subjects requiring albuterol during the albuterol open-label period, the ipratropium bromide open-label period, the double blind treatment period, and the wash-out period were similar for all genotypes.

SM 50mcg Group**Table 27 Percent of Subjects Requiring Albuterol (Intent-to-Treat Population) in the SM 100/50mcg Group**

Percent of Subject Requiring Albuterol	Arg/Arg	Gly/Gly	Arg/Gly
Albuterol Open-Label Period, n	84	90	87
Overall, n (%)	82 (98%)	86 (96%)	82 (94%)
Ipratropium Open-Label Period, n	84	91	87
Overall, n (%)	68 (81%)	66 (73%)	70 (80%)
Baseline†, n	79	85	85
Subjects, n (%)	36 (46%)	46 (54%)	48 (56%)
Double-blind (Weeks 1-16), n	81	89	85
Subjects, n (%)	60 (74%)	71 (80%)	66 (78%)
Washout (2 Weeks), n	65	75	72
Subjects, n (%)	34 (52%)	46 (61%)	46 (64%)
Statistical Comparisons	Arg/Arg vs Gly/Gly	Arg/Gly vs Gly/Gly	Arg/Arg vs Arg/Gly
Double-blind Period (Weeks 1-16)			
Relative risk	0.93	0.97	0.98
95% Confidence Interval	0.79, 1.09	0.83, 1.14	0.82, 1.16
p-value	0.392	0.729	0.780

Source Data: [Table 7.19](#) and [Table 7.20](#)

†Baseline- calculated from diary data and defined as the average value for the 7 day period preceding randomization (Visit 6). Diary data was required for three (3) days to calculate a baseline for each subject.

The percent of subjects requiring albuterol during the albuterol open-label period, the ipratropium bromide open-label period, the double blind treatment period, and the wash-out period were similar for all genotypes.

7.3.4. Supplemental Albuterol Use (puffs/day)

A post hoc analysis was performed for supplemental albuterol use (puffs/day) during the albuterol and ipratropium bromide open-label periods, double blind period, and the washout period. Summary statistics and treatment differences for puffs per day of supplemental albuterol use by subjects requiring albuterol during the open-label periods, the double blind treatment period, and the wash-period are presented in [Table 7.21](#) and are summarized in [Table 28](#) and [Table 29](#).

FSC 100/50mcg**Table 28 Supplemental Albuterol Use (puffs/day) in the FSC 100/50mcg group**

Supplemental Albuterol Use (puffs/day)	Arg/Arg	Gly/Gly	Arg/Gly
Albuterol Open-Label Period, n	87	90	91
Mean (SE)	1.35 (0.14)	1.42 (0.11)	1.34 (0.13)
Ipratropium Open-Label Period, n	84	88	90
Mean (SE)	0.67(0.10)	0.67 (0.09)	0.81 (0.11)
Baseline [†] , n	80	85	86
Mean (SE)	0.60 (0.10)	0.62 (0.09)	0.81 (0.14)
Double-blind Period (Weeks 1-16), n	86	88	91
Mean (SE)	0.38 (0.06)	0.37 (0.06)	0.50 (0.09)
Mean change ^{††} (SE)	-0.21 (0.08)	-0.24 (0.08)	-0.36 (0.13)
Washout (2 Weeks), n	77	77	82
Mean (SE)	0.66 (0.11)	0.69 (0.13)	0.80 (0.11)
Mean change ^{††} (SE)	0.03 (0.10)	0.04 (0.09)	-0.08 (0.12)

Source Data: [Table 7.21](#)[†]Baseline- calculated from diary data and defined as the average value for the 7 day period preceding randomization (Visit 6). Diary data was required for three (3) days to calculate a baseline for each subject.^{††}Mean change from baseline

Supplemental albuterol use during the open-label periods, the double blind treatment period, and the wash-out period was similar for all genotype in the FSC 100/50mcg group.

SM 50mcg**Table 29 Supplemental Albuterol Use (puffs/day) in the SM 50mcg group**

Supplemental Albuterol Use (puffs/day)	Arg/Arg	Gly/Gly	Arg/Gly
Albuterol Open-Label Period, n	84	90	87
Mean (SE)	1.44 (0.13)	1.55 (0.15)	1.63 (0.17)
Ipratropium Open-Label Period, n	84	91	87
Mean (SE)	0.73 (0.10)	0.92 (0.12)	0.79 (0.12)
Baseline [†] , n	79	85	85
Mean (SE)	0.64 (0.11)	0.88 (0.14)	0.78 (0.13)
Double-blind Period (Weeks 1-16), n	81	89	85
Mean (SE)	0.50 (0.08)	0.68 (0.10)	0.59 (0.09)
Mean change ^{††} (SE)	-0.14 (0.08)	-0.21 (0.07)	-0.19 (0.10)
Washout (2 Weeks), n	65	75	72
Mean (SE)	0.45 (0.09)	0.96 (0.15)	0.87 (0.16)
Mean change ^{††} (SE)	-0.11 (0.11)	0.09 (0.11)	0.06 (0.10)

Source Data: [Table 7.21](#)[†]Baseline- calculated from diary data and defined as the average value for the 7 day period preceding randomization (Visit 6). Diary data was required for three (3) days to calculate a baseline for each subject.^{††}Mean change from baseline

Supplemental albuterol use during the open-label periods, the double blind treatment period, and the wash-out period was similar for all genotype in the SM 50mcg group.

7.3.5. Maximum Albuterol Dose Response (MADR)

Section 5.6.3. Assessment of pulmonary function describes the rationale to measure the maximum albuterol dose response (MADR) for each subject at Visit 4 (the beginning of the open-label ipratropium period, Visit 6 (randomization visit), and Visit 10 (end of blinded treatment period). Summary statistics and treatment differences for the maximum albuterol dose response are presented in [Table 7.22](#) and [Table 7.23](#), respectively and summarized below in [Table 30](#) and [Table 31](#).

FSC 100/50mcg

FEV₁ response to a maximum albuterol dose at Visit 4, Visit 6, and Visit 10 is summarized in [Table 30](#).

Table 30 Maximum Albuterol Dose Response (FEV₁) (Intent-to-Treat Population) in the FSC 100/50mcg Group

MADR (FEV ₁) (L)	Arg/Arg	Gly/Gly	Arg/Gly
Visit 4 (Open-label Ipratropium), n	87	90	91
Baseline mean (SE)	2.78 (0.08)	2.88 (0.06)	2.89 (0.07)
Max FEV ₁ post albuterol (SE)	3.08 (0.08)	3.21 (0.08)	3.20 (0.08)
Max change (%)	11.4 (0.93)	11.3 (0.96)	10.9 (0.80)
Visit 6-Double-blind Day 1, n	87	90	91
Baseline mean (SE)	2.76 (0.08)	2.86 (0.07)	2.87 (0.07)
Max FEV ₁ post albuterol (SE)	3.06 (0.08)	3.20 (0.08)	3.18 (0.08)
Max change (%) (SE)	11.7 (0.97)	12.0 (0.98)	11.0 (0.96)
Visit 10-Double-blind Period, n	77	79	83
Baseline mean (SE)	2.95 (0.08)	3.04 (0.09)	3.09 (0.09)
Max FEV ₁ post albuterol (SE)	3.12 (0.09)	3.22 (0.09)	3.23 (0.09)
Max Change (%) (SE)	6.2 (0.78)	6.1 (0.71)	4.9 (0.59)
Statistical Comparisons	Arg/Arg vs Gly/Gly	Arg/Gly vs Gly/Gly	Arg/Arg vs Arg/Gly
Visit 4 (Open-label Ipratropium)			
LS means difference (%)	0.1	-0.4	0.5
95% Confidence Interval	-2.4, 2.7	-2.9, 2.1	-2.0, 3.0
p-value	0.920	0.765	0.695
Visit 6-Double-blind Day 1			
LS means difference (%)	-0.1	-1.0	0.8
95% Confidence Interval	-2.8, 2.6	-3.6, 1.7	-1.9, 3.5
p-value	0.919	0.469	0.544
Visit 10-Double-blind Week 16			
LS means difference (%)	-0.0	-1.1	1.1
95% Confidence Interval	-1.9, 1.9	-3.0, 0.8	-0.8, 3.0
p-value	0.997	0.242	0.250

Source Data: [Table 7.22](#) and [Table 7.23](#)

No statistically significant differences were observed in the FEV₁ response to a maximum albuterol dose between any of the genotypes at Visit 4 (the beginning of the open-label ipratropium bromide period, Visit 6 (randomization visit), and Visit 10 (end of double-blind treatment period) in the FSC 100/50mcg treatment group.

SM 50mcg

FEV₁ response to a maximum albuterol dose at Visit 4, Visit 6, and Visit 10 is summarized in [Table 31](#).

Table 31 Maximum Albuterol Dose Response (FEV₁) (Intent-to-Treat Population) in the SM Group

MADR (FEV ₁) (L)	Arg/Arg	Gly/Gly	Arg/Gly
Visit 4 (Open-label Ipratropium), n	86	91	89
Baseline mean (SE)	2.95 (0.08)	2.87 (0.08)	2.85 (0.08)
Max FEV ₁ post albuterol (SE)	3.28 (0.09)	3.24 (0.09)	3.21 (0.09)
Max change (%)(SE)	11.0 (0.88)	13.5 (1.13)	12.8 (0.98)
Visit 6-Double-blind Day 1, n	86	91	89
Baseline mean (SE)	2.89 (0.08)	2.88 (0.08)	2.84 (0.08)
Max FEV ₁ post albuterol (SE)	3.21 (0.09)	3.24 (0.09)	3.17 (0.09)
Max change (%)(SE)	11.6 (0.95)	13.0 (1.12)	12.3 (1.06)
Visit 10-Double-blind Week 16, n	66	75	73
Baseline mean (SE)	3.12 (0.10)	2.91 (0.09)	2.92 (0.08)
Max FEV ₁ post albuterol (SE)	3.25 (0.10)	3.17 (0.09)	3.16 (0.09)
Max Change (%)(SE)	5.1 (0.89)	9.7 (1.05)	8.3 (0.99)
Statistical Comparisons	Arg/Arg vs Gly/Gly	Arg/Gly vs Gly/Gly	Arg/Arg vs Arg/Gly
Visit 4 (Open-label Ipratropium)			
LS means difference (%)	-2.2	-0.7	-1.5
95% Confidence Interval	-5.1, 0.6	-3.5, 2.0	-4.4, 1.3
p-value	0.121	0.607	0.298
Visit 6-Double-blind Day 1			
LS means difference (%)	-1.4	-0.8	-0.7
95% Confidence Interval	-4.4, 1.5	-3.6, 2.1	-3.6, 2.3
p-value	0.336	0.596	0.661
Visit 10-Double-blind Week 16			
LS means difference (%)	-3.8	-1.3	-2.4
95% Confidence Interval	-6.5, -1.0	-4.0, 1.3	-5.2, 0.4
p-value	0.008	0.317	0.087

Source Data: [Table 7.2](#) and [Table 7.23](#)

No statistically significant differences were observed in the FEV₁ response to a maximum albuterol dose between any of the genotypes at Visit 4 (the beginning of the open-label ipratropium bromide period or Visit 6 (randomization visit). A statistically significant difference in FEV₁ response to a maximum albuterol dose for Arg/Arg subjects compared to the Gly/Gly subjects was observed at Visit 10 (end of double-blind treatment period) in the SM 50mcg treatment group (LS mean difference -3.8%, p=0.008).

7.3.6. Additional *ADRB2* SNPs - Associations/Comparisons

The *ADRB2* gene is very polymorphic and it has been speculated that other SNPs within this gene may be associated with an attenuated response to beta agonist bronchodilators. In addition to the B16Arg/Gly SNP, we genotyped eleven SNPs and a poly-C repeat in the 3' region across the *ADRB2* as described by Hawkins, et al [[Hawkins, 2006](#)].

An evaluation of lung function as assessed by AM PEF AUC(bl), FEV₁, symptom free days, and supplemental ipratropium bromide use, with other *ADRB2* SNPs in the SM and FSC treatment groups over 16 weeks of treatment are presented in [Table 7.24–Table 7.111](#) and summarized in [Table 32](#). Eleven SNPs and a poly-C repeat in the 3' region were genotyped across the *ADRB2* as described by Hawkins, et al [[Hawkins, 2006](#)].

The 11 SNPs were genotyped by Flow Accelerated SNP Typing (FAST) and Fluorescence Resonance Energy Transfer (FRET) based assays. There was a 100% internal concordance for all of the 11 FAST and FRET assays. All polymorphisms were classified as class III. For the poly-C region, genotyping was completed by five prime-carboxyfluorescein (5'-FAM) labeled polymerase chain reaction (PCR) fragment analysis in conjunction with standard sequencing analysis. Details of the assays and assay performance are on file in the Pharmacogenetics Division at GSK.

There were 486 subjects from SFA100062 and 270 subjects from Internal Validation Plate 4 (IVP4) were added to this study as controls for Custom Genotyping. All subjects were subjected to the 6% duplicate standards. One subject failed the genotyping, and 7 subjects the sequencing. Fifty-five samples from the 544 randomized were not genotyped because of lack of informed consent for additional genotyping, lost samples during shipping, subject requested sample destruction and assay failure.

Single marker results by genotype and treatment group are presented in [Table 7.24–Table 7.111](#) and summarized in [Table 32](#) as the lowest p-value for each marker during the treatment and washout periods.

Table 32 Single Marker Analysis by Genotype and Treatment Group - Lowest p-values

Position	+46	-3459	-2387	-1818	-468	-47	+79	+523	+1053
FSC									
AM PEF Overall	0.168	0.027	0.256	0.095	0.093	0.086	0.093	0.637	0.800
AM PEF Washout	0.012	0.055	0.232	0.013	0.056	0.045	0.056	0.123	0.285
SM									
AM PEF Overall	0.096	0.260	0.428	0.082	0.513	0.462	0.516	0.122	0.043
AM PEF Washout	0.097	0.232	0.638	0.247	0.770	0.768	0.772	0.380	0.317
FSC									
FEV ₁ Overall	0.507	0.563	0.386	0.357	0.419	0.429	0.419	0.585	0.409
FEV ₁ Washout	0.037	0.278	0.661	0.112	0.531	0.362	0.531	0.064	0.040
SM									
FEV ₁ Overall	0.015	0.298	0.620	0.020	0.145	0.207	0.142	0.049	0.354
FEV ₁ Washout	0.181	0.230	0.023	0.234	0.148	0.160	0.151	0.182	0.025
FSC									
Symptom-free days – Overall	0.175	0.332	0.188	0.733	0.639	0.628	0.639	0.086	0.209
Symptom-free days - Washout	0.474	0.895	0.423	0.255	0.925	0.891	0.925	0.614	0.706
SM									
Symptom-free days – Overall	0.758	0.258	0.507	0.634	0.418	0.324	0.434	0.468	0.258
Symptom-free days - Washout	0.578	0.249	0.174	0.707	0.248	0.208	0.243	0.130	0.100
FSC									
Supplemental Ipratropium use – Overall	0.597	0.256	0.388	0.192	0.422	0.350	0.422	0.162	0.735
Supplemental Ipratropium use – Washout	0.200	0.300	0.416	0.146	0.251	0.233	0.251	0.033	0.053
SM									
Supplemental Ipratropium use – Overall	0.595	0.062	0.006	0.393	0.080	0.104	0.088	0.118	0.135
Supplemental Ipratropium use – Washout	0.587	0.384	0.023	0.810	0.271	0.308	0.268	0.020	0.026

Source Data: [Table 7.24](#) to [Table 7.111](#)

Values reported are the lowest p-values obtained across all genotypes

Markers: +46 (RS1042713), -3459 (RS9325122 T/C), -2387 ((RS1432623 T/C), -1818 (RS17778257 A/T), -468 (RS11168070), -47 (RS1042711 C/T), +79 (RS1042714), +523 (RS1042718 A/C), +1053 (RS1042719 G/C)

Markers with significant p-values

Results for the markers with significant p-values are detailed below. There were no statistically significant results for markers -468(RS1168070) or +79 (RS1042714) across any of the efficacy parameters.

Marker +46 (RS1042713) Arg/Gly: These results for the Arg16Gly marker were genotyped by GSK. At the end of the washout period, all three genotypes in the FSC 100/50mcg treatment group were above baseline; the Arg/Arg group was 29.3 L/min and the Gly/Gly group 10.3 L/min above baseline ($p = 0.012$). FEV₁ for the washout period in the FSC treatment was also significant. The Gly/Gly genotype was still 0.12 L above baseline versus the Arg/Gly group that was 0.02 L above ($p=0.037$). The overall increase in FEV₁ for SM 50mcg during treatment was 0.2 L, 0.14 L and 0.08 L for the Arg/Arg, Arg/Gly and Gly/Gly genotypes respectively (Arg/Arg versus Gly/Gly $p=0.015$). There were no significant differences in the percent symptom free days or supplemental ipratropium use for this marker.

Marker -3459 (RS9325122 T/C) Promoter Region: An overall increase of 18.5, 23.2 and 30.4 L/min for the C/C, C/T and T/T genotypes respectively ($p=0.027$), C/C versus T/T, was observed for the FSC treatment group in AM PEF. This genotype difference was not seen in FEV₁ measures which increased 0.22, 0.20 and 0.21 L for the C/C, C/T and T/T genotypes respectively. There were no significant differences found in symptom free days or supplemental ipratropium use. No significant differences for any efficacy parameter were observed in the salmeterol treatment group.

Marker -2387 (RS1432623 T/C) Promoter Region: There was a significant difference in the washout period for FEV₁ of the SM treatment group (C/C versus T/T $p=0.023$). All genotypes were above baseline at the end of the washout period. The C/C genotype was -0.10 L versus 0.04 for the T/T genotype. During treatment with SM, the C/T group reduced ipratropium use by 0.53 puffs/day as compared with the T/T genotype that decreased 0.26 puffs/day ($p=0.006$). Similarly at the end of the washout period the C/T group was still 0.39 puffs/day less than at baseline compared with the T/T group which was 0.15 puffs/day below baseline ($p=0.023$).

Marker -1818 (RS17778257 A/T) Promoter Region: The AM PEF for all genotypes in the FSC treatment group were still above baseline at the end of the washout period. The A/A, A/T and T/T were 14.1, 15.8 and 33.1 L/min above baseline resulting in significant p-values of 0.013 and 0.019 for the A/A versus T/T and A/T versus T/T genotypes respectively. No other significances were identified for this marker across genotypes, efficacy parameters or treatment with FSC 100/50mcg or SM 50mcg.

Marker -47 (RS1042711 C/T) Beta Upstream Peptide: The AM PEF for all genotypes in the FSC treatment group was still above baseline at the end of the 2 week washout period. The C/C, C/T and T/T were 8.6, 14.7 and 22.6 L/min above baseline resulting in a significant p-value of 0.045 for the CC versus T/T genotypes. No other significant differences were identified for this marker across genotypes, efficacy parameters or treatment with FSC 100/50mcg or SM 50mcg.

Marker +523 (RS1042718 A/C) Arg/Arg Coding: The overall increase in FEV₁ measures for the SM treatment group was 0.08 L versus 0.17 L for the A/A and C/C genotypes, respectively (p=0.049). In the FSC group, there was a statistically significant difference between the A/A and the C/C genotypes in ipratropium use during the washout phase (p=0.033). In the SM washout, ipratropium use for the A/A, A/C and C/C genotypes were 0.05, 0.34 and 0.23 puffs/day below baseline use resulting in a significant difference comparing the A/A versus A/C and the A/A versus C/C (p= 0.039 and 0.020, respectively)

Marker +1053 (RS1042719 G/C) Gly/Gly Coding: In the SM treatment group, the overall change from baseline in AM PEF in the 3 genotypes, C/C, C/G and G/G was 23.9, 13.7 and 23.2 L/min respectively. This resulted in a significant difference between the C/G and G/G genotypes (p=0.043). The washout for FEV₁ in both the FSC and SM treatments demonstrated significant differences. In the FSC group, the C/C, C/G and G/G genotypes were 0.16, 0.04 and 0.05 L above baseline respectively at the end of the washout period. Only the C/C versus C/G comparison was significant (p=0.04). In the SM treatment group, the FEV₁ in the G/G genotype was 0.05 L below baseline at the end of the washout period, resulting in a significant difference (p=0.025) between the G/G and C/G genotype which was 0.04 L above baseline. Also in the washout period ipratropium use for the SM group was below baseline use for all genotypes. The G/G genotype was 0.26 puffs/day below baseline versus the C/C genotype which was 0.18 puffs/day below baseline. The difference between these genotypes was significant (p=0.026).

Poly-C Repeat

In the 3' region of the *ADRB2* gene at approximately +1279 from the start site is a poly-C region which ranges from 7-14 repeats. The length of the poly-C region may influence lung function, especially, in African-American individuals with 13 repeats (Hawkins, 2006). The genotype frequency of the poly-C repeat region is presented in [Table 33](#).

Table 33 **Frequency for Poly-C Genotypes**

Genotype	Frequency	Percent
10, 11	91	19.00
10, 12	3	0.63
10, 13	1	0.21
10,14	4	0.84
10, 9	23	4.80
11, 12	68	14.20
11, 13	16	3.34
11, 14	3	0.63
12, 8	4	0.84
12, 9	29	6.05
13, 8	24	5.01
13, 9	125	26.10
14, 9	4	0.84
7, 8	1	0.21
8, 9	83	17.33

Source Data: [Table 7.112](#)

The table above demonstrates the distribution of the poly-C genotypes, and that there were significant numbers of individuals with large repeating units (≥ 12). For statistical comparisons we divided the subjects into those with < 12 repeats and those ≥ 12 repeats. This is based on the reported bimodal distribution around 12 repeats. There were no significant differences observed for any of the efficacy parameters in either treatment group. No statistical analyses were completed on the individual groupings of the poly-C region. See [Table 7.112](#).

Haplotype Analyses

A haplotype is a specific combination of closely linked single nucleotide polymorphisms (SNPs) on the same chromosome of an individual. Using SNP-based haplotypes may yield more powerful tests of genetic association than using individual SNPs, especially when the causal variants are unknown or not measured, or when there are interactions between mutations on the same chromosome. Determining the haplotypes is not easily obtained with current genotyping technology. Several methods exist to infer haplotypes or estimate haplotype frequencies from unphased genotype data. The majority of these tools assume that the sample is in Hardy-Weinberg equilibrium (HWE). Any deviation from HWE may adversely affect the validity of the estimation, and therefore any significance derived. No haplotype analyses were completed since this study recruited specific numbers of genotypes it is not in HWE which could lead to biased estimates of genetic effects and even less control of type I error rates.

7.3.7. Evaluation of Assay Sensitivity

Comparisons of the change from the screening FEV₁ to the endpoint FEV₁ made for each genotype within each treatment group are presented in [Table 7.113](#) and [Table 7.114](#) and summarized in [Table 34](#).

Table 34 Evaluation of Assay Sensitivity

FEV ₁ (L)	FSC 100/50mcg	SM 50mcg
Screening (Visit 1), n	268	266
Mean (SE)	2.71 (0.04)	2.74 (0.04)
Visit 10 Double-blind Period (Week 16), n	239	214
Mean (SE)	3.03 (0.05)	2.98 (0.05)
Mean change from Screening (SE)	0.33 (0.02)	0.25 (0.03)
Endpoint, n	258	247
Mean (SE)	3.03 (0.05)	2.99 (0.05)
Mean change from Screening (SE)	0.33 (0.02)	0.25 (0.02)
Statistical Comparisons	FSC 100/50mcg	SM 50mcg
Endpoint		
Mean difference (L)	0.33	0.25
95% Confidence Interval	0.29, 0.38	0.20, 0.30
p-value	<0.001	<0.001

Source Data: [Table 7.113](#) and [Table 7.114](#)

Assay sensitivity with FEV₁ was demonstrated to be statistically significant at endpoint in each treatment group for subjects across each genotype: FSC 100/50mcg (mean difference [L] 0.33, p<0.001) and SM 50mcg (mean difference [L] 0.25, p<0.001).

7.3.8. Efficacy in the Albuterol Open-label Failure Population and in the Ipratropium Bromide Open-Label Failure Population

Albuterol Open-Label Period

The albuterol open-label period of 8 weeks was comprised of 2 visits. AM PEF, FEV₁, percent of symptom free days, and albuterol use (puffs/day) are presented in [Table 7.115](#) through [Table 7.118](#). Overall measures of AM PEF, pre-dose FEV₁, percent of symptom free days, and albuterol use (puffs per day) were similar across the Arg/Arg, Gly/Gly, and Arg/Gly genotypes. Limited sample size and subjects discontinuation from the open label period did not allow statistical comparisons and interpretations between the subjects in the albuterol open-label failure population and those subjects who continued into the double-blind treatment period.

See Section 6.1 Disposition of Subjects and [Table 2](#). Twenty three (10%) subjects withdrew due to an inability to fulfil the continuation criteria (FEV₁ ≥70% of predicted and <56 puffs per week of medication.). Twenty one (9%) subjects withdrew due to the genotype quota being filled and 19 (8%) decided to withdraw.

Ipratropium Bromide Open-Label Period

The ipratropium bromide open-label period of 8 weeks was comprised of 2 visits. AM PEF, FEV₁, percent of symptom-free days, and albuterol use, and ipratropium use (puffs/day) are presented in Table 7.119 through Table 7.123. Overall measures of AM and PM PEF, pre-dose FEV₁, percent of symptom-free days, MADR, albuterol and ipratropium use (puffs per day) were similar across all genotypes. Limited sample size and subjects discontinuation from the open label period did not allow statistical comparisons and interpretations between the subjects in the ipratropium bromide open-label failure population and those subjects who continued into the double-blind treatment groups.

See Section 6.1 Disposition of Subjects and Table 3. Sixty six (28%) withdrew due to the genotype quota being filled and 14 (6%) decided to withdraw. Fourteen (6%) subjects withdrew due to an inability to fulfill the continuation criteria (FEV₁ ≥ 70% of predicted and < 56 puffs per week of medication).

7.4. Efficacy Conclusions

Primary Endpoint

Changes overall in AM PEF (AUC) for the Arg/Arg, Gly/Gly, and Arg/Gly genotypes were not statistically different in the FSC 100/50mcg treatment group or in the SM 50mcg treatment group of the double blind treatment period.

Secondary Endpoints

- Changes over the double-blind treatment period in PM PEF for the three genotypes were not statistically significant in the FSC 100/50mcg treatment group of the double blind treatment period. Changes over the double-blind treatment period in PM PEF were statistically significant in the SM 50mcg treatment group for Arg/Gly subjects compared to Gly/Gly subjects (LS means difference 14.6 L/min, p=0.017). No statistically significant differences were observed in PM PEF for Arg/Arg subjects compared to Arg/Gly subjects or for Arg/Arg subjects compared to Gly/Gly subjects.
- Changes in pre-dose FEV₁ were similar in the FSC 100/50mcg treatment arm of the double blind treatment period overall (Weeks 1-16) in all genotypes. Changes in pre-dose FEV₁ for Arg/Arg subjects compared to Gly/Gly subjects were statistically significant in the SM 50mcg treatment group at endpoint and overall in the double-blind treatment period (Weeks 1-16, LS means difference 0.13 L/min, p=0.003). No statistically significant differences were observed in pre-dose FEV₁ for Arg/Gly subjects compared to Gly/Gly subjects or for Arg/Arg subjects compared to Arg/Gly subjects.
- Percent of symptom free days was not statistically significant different overall during the double blind treatment period between any of the genotypes in the FSC 100/50mcg treatment group or in the SM 50mcg treatment group.

- Supplemental ipratropium use was not statistically significant different overall during the double blind treatment period between any of the genotypes in the FSC 100/50mcg treatment group or in the SM 50mcg treatment group.

Other Efficacy Endpoints of Interest

- AM PEF during the last four weeks of Open-Label treatment with *prn* albuterol compared to the last four weeks of the Open-Label treatment period with *prn* ipratropium was not statistically significant different overall between any of the genotypes for AM PEF.
- Symptom-free days during the last four weeks of Open-Label treatment with *prn* albuterol compared to the last four weeks of the Open-Label treatment period with *prn* ipratropium bromide were not statistically significant different between the genotypes in the FSC 100/50mcg treatment group or in the SM 50mcg treatment group.
- The percent of subjects requiring supplemental albuterol demonstrated no differences during the open-label periods, double blind treatment period, or washout period between the genotypes in the FSC 100/50mcg treatment group or in the SM 50mcg treatment group. *Post hoc* analyses demonstrated no differences in the supplemental use of albuterol (puffs/day) during the open-label periods, double blind treatment period, or washout period between the genotypes in the FSC 100/50mcg treatment group or in the SM 50mcg treatment group.
- The FEV₁ response to a maximum albuterol dose (MADR) demonstrated no statistically significant differences between any of the genotypes at Visit 4 (the beginning of the open-label ipratropium bromide period, Visit 6 (randomization visit), and Visit 10 (end of double-blind treatment period), in the FSC 100/50mcg treatment group. No statistically significant effects were observed in the FEV₁ response to a maximum albuterol dose between any of the genotypes at Visit 4 (the beginning of the open-label ipratropium period or Visit 6 (randomization visit). A statistically significant difference in FEV₁ response to a maximum albuterol dose for the Arg/Arg genotype compared to the Gly/Gly genotype was observed at Visit 10 (end of double-blind treatment period) in the SM 50mcg treatment group (LS means difference -3.8%, p=0.008).
- Observations from analyses of additional *ADRB2* SNPS were as follows:
 - For FSC 100/50mcg, there was only one significant SNP (-3459) during the double-blind period for AM PEF. There were no significant differences found in FEV₁, symptom free days or supplemental ipratropium bromide use. Significant differences were observed during the washout period between markers -1818, -47, +46 (Arg16Gly), +1053 for AM PEF and FEV₁. No significant differences occurred in symptom free days. One marker, +523, was significant for ipratropium use. There were no consistent patterns between endpoints, and markers would not reach significance if adjusted for multiple comparisons.

- For SM 50mcg, marker +1053 was significant for AM PEF. Marker +46 (Arg16Gly), +523, and -1818 were significant for FEV₁ during the double-blind period. Marker -2387 was significant for ipratropium bromide use overall. There were no significant effects for symptom free days. During the washout, there were no significance genotypes in AM PEF. Markers -2387 and +1053 were significant for FEV₁ washout. No significant genotypes were observed for symptom free days, but markers -2387, +523 and +1053 were significant for ipratropium use. There were no consistent patterns between endpoints, and markers would not reach significance if adjusted for multiple comparisons.

8. SAFETY RESULTS

8.1. Extent of Exposure

Table 8.1, Table 8.2 and Table 35 present the duration of exposure (days) to double-blind study medication by genotype in the FSC 100/50mcg treatment group and the SM 50mcg treatment group for all randomized subjects in the Intent-to-Treat population.

Table 35 Extent of Exposure: ITT Population – FSC 100/50mcg and SM 50mcg

FSC 100/50mcg	Arg/Arg	Gly/Gly	Arg/Gly
Subjects in treatment n	89	91	92
Double-Blind Period Weeks 1-16			
Mean (days), SD	108.9 (21.26)	108.9 (19.83)	108.2 (18.85)
SM 50mcg			
Subjects in treatment n	90	92	90
Double-Blind Period Weeks 1-16			
Mean (days), SD	104.7 (22.94)	104.2 (26.72)	103.1 (26.91)

Source Data: Table 8.1 and Table 8.2

The mean duration of exposure was similar within treatment groups and genotypes for the double-blind treatment period. No overdose was reported during this study. See Section 6.1 Disposition of Subjects and Table 4.

8.2. Adverse Events

The CRF text for adverse events was coded using the MedDRA dictionary and reported using the primary System Organ Class (SOC) and Preferred Term. Adverse events were summarized and grouped by primary SOC and by adverse event (i.e., Preferred Term) within the primary SOC. Results were displayed in the order of decreasing frequency, both across the primary SOC and within the primary SOC.

8.2.1. All Adverse Events

Adverse events reported in the open-label albuterol and ipratropium periods by subjects who continued into the Intent-to-Treat population are presented in Table 8.3 and Table 8.4.

Adverse events reported in the Intent-to-Treat population in the FSC 100/50mcg group and in the SM 50mcg group during the blinded treatment period are presented in Table 8.5 and Table 8.6.

Adverse events reported in the Intent-to-Treat population in the FSC 100/50mcg group and in the SM 50mcg group during the washout period following the double-blind treatment are presented in Table 8.7.

Table 8.8 is a by-subject listing of adverse events that occurred and were reported during the screening period, the open-label periods, the double-blind treatment period and during the washout period. Table 8.9 is a record of subject numbers for each adverse event by the ITT treatment group and genotype group. Table 8.10 describes the relationship of the adverse event SOC, preferred term and verbatim text.

FSC 100/50mcg

Adverse events reported by subjects during the open-label albuterol and ipratropium periods are presented in Table 8.3 and Table 8.4. These subjects were also in the Intent-to-Treat population in the FSC 100/50mcg treatment group. Adverse events reported for these subjects are summarized in Table 36 and Table 37.

Open-Label Albuterol Period

Table 36 Most Common Adverse Events (3% or Greater Incidence) for Subjects Randomized into the FSC 100/50mcg ITT Population

Adverse Event	Arg/Arg N=89	Gly/Gly N=91	Arg/Gly N=92	Total N=272
Number (%) of subjects with any adverse event	43 (48%)	41 (45%)	30 (33%)	114 (42%)
Nervous system disorders Headache	16 (18%)	10 (11%)	9 (10%)	35 (13%)
Infections and infestations Nasopharyngitis	5 (6%)	3 (3%)	5 (5%)	13 (5%)
Respiratory, thoracic, & mediastinal disorders Pharyngolaryngeal pain Cough	6 (7%) 2(2%)	4 (4%) 3(3%)	3(3%) 3 (3%)	13 (5%) 8 (3%)
Musculoskeletal & connective tissue disorders Myalgia	2 (2%)	4 (4%)	1 (1%)	7 (3%)

Source Data: Table 8.3

The overall incidence of adverse events was generally similar across the open-label albuterol period for the three genotypes. Adverse events reported with an incidence of $\geq 3\%$ for the treatment group were generally similar across the genotype groups. The most commonly affected SOC was nervous system disorders with headache the most commonly reported adverse event within that SOC (Arg/Arg 18%, Gly/Gly 11%, and Arg/Gly 10% of subjects in each genotype).

Open-Label Ipratropium Bromide Period**Table 37 Most Common Adverse Events (3% or Greater Incidence) for Subjects Randomized into the FSC 100/50mcg ITT Population**

Adverse Event	Arg/Arg N=89	Gly/Gly N=91	Arg/Gly N=92	Total N=272
Number (%) of subjects with any adverse event	26 (29%)	41 (45%)	32 (35%)	99 (36%)
Nervous system disorders Headache	11 (12%)	13 (14%)	11 (12%)	35 (13%)
Gastrointestinal Toothache	1 (1%)	6 (7%)	3 (3%)	10 (4%)
Respiratory, thoracic and mediastinal disorders Pharyngolaryngeal pain	3 (3%)	3 (3%)	3 (3%)	9 (3%)
Cough	3 (3%)	3 (3%)	1 (1%)	7 (3%)

Source Data: [Table 8.4](#)

The overall incidence of adverse events was generally similar across the open-label ipratropium period for the three genotypes. Adverse events reported with an incidence of $\geq 3\%$ for the treatment group were generally similar across the genotypes. The most commonly affected SOC was nervous system disorders with headache the most commonly reported adverse event within that SOC (Arg/Arg 12%, Gly/Gly 14%, and Arg/Gly 12% of subjects in each genotype).

Double-blind Treatment Period – FSC 100/50mcg

Adverse events reported in the Intent-to-Treat population in the FSC 100/50mcg treatment group during the blinded treatment period are presented in [Table 8.5](#) and [Table 8.6](#) and are summarized in [Table 38](#).

Table 38 Most Common Adverse Events (3% or Greater) Incidence in the FSC 100/50mcg Treatment Group (Intent-to-Treat Population)

Adverse Event	Arg/Arg N=89	Gly/Gly N=91	Arg/Gly N=92	Total N= 272
Number (%) of subjects with any adverse event	43 (48%)	45 (49%)	44 (48%)	132 (49%)
Nervous system disorders Headache	8 (9%)	9 (10%)	19 (21%)	36 (13%)
Infections and infestations Nasopharyngitis	3 (3%)	12 (13%)	6 (7%)	21 (8%)
Upper respiratory tract infection	1 (1%)	4 (4%)	3 (3%)	8 (3%)
Respiratory, thoracic, and mediastinal disorders Pharyngolaryngeal pain	5 (6%)	2 (2%)	4(4%)	11 (4%)
Cough	1(1%)	1(1%)	6(7%)	8 (3%)

Source Data: [Table 8.5](#) and [Table 8.6](#)

The overall incidence of adverse events was generally similar across the FSC 100/50mcg treatment group for the three genotypes. Adverse events reported with an incidence of $\geq 3\%$ for the treatment group were generally similar across the genotypes. The most commonly affected SOC was nervous system disorders with headache the most commonly reported adverse event within that SOC (Arg/Arg 9%, Gly/Gly 10%, and Arg/Gly 21% of subjects in each genotype).

SM 50mcg

Adverse events presented in [Table 8.3](#) and [Table 8.4](#) were reported by subjects during the open-label albuterol and ipratropium periods. These subjects were also in the Intent-to-Treat population in the SM 50mcg treatment group. Adverse events reported for these subjects are summarized in [Table 39](#) and [Table 40](#).

Open-Label Albuterol Treatment Period

Table 39 Most Common Adverse Events (3% or Greater Incidence) for Subjects Randomized into the SM 50mcg ITT Population

Adverse Event	Arg/Arg N=90	Gly/Gly N=92	Arg/Gly N=90	Total N=272
Number (%) of subjects with any adverse event	33 (37%)	36 (39%)	38 (42%)	107 (39%)
Nervous system disorders Headache	11 (12%)	17 (18%)	15 (17%)	43 (16%)
Infections and infestations Nasopharyngitis	4 (4%)	2 (2%)	4 (4%)	10 (4%)
Respiratory, thoracic, & mediastinal disorders Pharyngolaryngeal pain	2 (2%)	5 (5%)	5 (6%)	12 (4%)
Gastrointestinal disorders Abdominal pain upper	4 (4%)	2 (2%)	2 (2%)	8 (3%)

Source Data: [Table 8.3](#)

The overall incidence of adverse events was generally similar across the open-label albuterol period for the three genotypes. Adverse events reported with an incidence of $\geq 3\%$ for the treatment group were generally similar across the genotypes. The most commonly affected SOC was nervous system disorders with headache the most commonly reported adverse event within that SOC (Arg/Arg 12%, Gly/Gly 18%, and Arg/Gly 17% of subjects in each genotype).

Open-Label Ipratropium Bromide Period**Table 40 Most Common Adverse Events (3% or Greater Incidence) for Subjects Randomized into the SM 50mcg ITT Population**

Adverse Event	Arg/Arg N=90	Gly/Gly N=92	Arg/Gly N=90	Total N=272
Number (%) of subjects with any adverse event	22 (24%)	36 (39%)	24 (27%)	82 (30%)
Nervous system disorders Headache	6 (7%)	11 (12%)	9 (10%)	26 (10%)
Infections and infestations Nasopharyngitis	2 (2%)	4 (4%)	1 (1%)	7 (3%)
Respiratory, thoracic, & mediastinal disorders Pharyngolaryngeal pain	2 (2%)	4 (4%)	3 (3%)	9 (3%)

Source Data: [Table 8.4](#)

The overall incidence of adverse events was generally similar across the ipratropium bromide period for the three genotypes. Adverse events reported with an incidence of $\geq 3\%$ for the treatment group were generally similar across the genotypes. The most commonly affected SOC was nervous system disorders with headache the most commonly reported adverse event within that SOC (Arg/Arg 7%, Gly/Gly 12%, and Arg/Gly 10% of subjects in each genotype).

Double-blind Treatment Period – SM 50mcg

Adverse events reported in the Intent-to-Treat population in the SM 50mcg treatment group during the blinded treatment period are presented in [Table 8.5](#) and [Table 8.6](#) and are summarized in [Table 41](#).

Table 41 Most Common Adverse Events (3% or Greater Incidence in the SM 50mcg Treatment Group (Intent-to-Treat Population))

Adverse Event	Arg/Arg N=90	Gly/Gly N=92	Arg/Gly N=90	Total N=272
Number (%) of subjects with any adverse event	39 (43%)	44 (48%)	37 (41%)	120 (44%)
Nervous system disorders Headache	6 (7%)	12 (13%)	12 (13%)	30 (11%)
Infections and infestations Nasopharyngitis	6 (7%)	9 (10%)	3 (3%)	18 (7%)
Upper respiratory tract infection	7 (8%)	3 (3%)	2 (2%)	12 (4%)
Sinusitis	6 (7%)	2 (2%)	0	8 (3%)
Respiratory, thoracic, and mediastinal disorders Pharyngolaryngeal pain	1 (1%)	3 (3%)	3 (3%)	7 (3%)
Musculoskeletal & connective tissue disorders Back pain	0	6 (7%)	1 (1%)	7 (3%)

Source Data: [Table 8.5](#) and [Table 8.6](#)

The overall incidence of adverse events was generally similar across the SM 50mcg treatment group for the three genotypes. Adverse events reported for the treatment group with an incidence of $\geq 3\%$ were generally similar across the genotypes. The most commonly affected SOC was nervous system disorders with headache the most commonly reported adverse event within that SOC (Arg/Arg 7%, Gly/Gly 13%, and Arg/Gly 13% of subjects in each genotype).

Washout Period

Table 8.7 presents adverse events reported during the washout period in the FSC 100/50mcg treatment group and in the SM 50mcg treatment group. There were no adverse events reported in any SOC by $\geq 3\%$ of subjects in either of the two treatment groups. There were 30 (11%) adverse events reported by subjects from the FSC 100/50mcg treatment group and 28 (10%) reported by subjects from the SM 50mcg treatment group with the highest incidence in the Arg/Gly genotype in each treatment group (FSC 100/50mcg 14, 15% and SM 50mcg 14, 16%).

8.2.2. Drug-Related Adverse Events

Drug-related adverse events were adverse events considered by the investigator to be possibly related to study drug. Drug-related adverse events for the Intent-to-Treat population in the FSC 100/50mcg treatment group and the SM 50mcg treatment group occurring during the treatment period are presented in Table 8.11 and in Table 42 and Table 43.

FSC 100/50mcg

Table 42 Drug-Related Adverse Events in the FSC 100/50mcg group (Intent-to-Treat Population)

Adverse Event	Arg/Arg N=89	Gly/Gly N=91	Arg/Gly N=92	Total N=272
Number (%) of subjects with any adverse event	43 (48%)	45 (49%)	44 (32%)	139 (49%)
Number (%) of subjects with any drug-related adverse event	6 (7%)	2 (2%)	5 (5%)	13 (5%)
Nervous system disorders	1 (1%)	1 (1%)	2 (2%)	4 (1%)
Infections and infestations	2 (2%)	1 (1%)	2 (2%)	5 (2%)
Respiratory, thoracic, and mediastinal disorders	3 (3%)	1 (1%)	0	4 (1%)
Gastrointestinal disorders	2 (2%)	0	2 (2%)	4 (1%)
Ear & labyrinth disorders	0	1 (1%)	0	1 (<1%)
Musculoskeletal & connective tissue disorders	1 (1%)	1 (1%)	0	2 (<1%)

Source Data: Table 8.5 and Table 8.11

Overall, the incidence of adverse events having a reasonable possibility of being drug-related was small and generally similar across the genotypes in the FSC 100/50mcg treatment group, affecting 6 (7%), 2 (2%), and 5 (5%) subjects across the three

genotypes. No drug-related adverse events were reported in any SOC by >3% of subjects in any of the genotypes. In the Arg/Arg genotype 4 adverse events in the respiratory, thoracic and mediastinal disorders SOC, were reported by 3 (3%) subjects. Cough was reported by 1 (1%) subject, dry throat was reported by 1 (1%) subject, pharyngolaryngeal pain was reported by 1 (1%) subject, and sinus congestion was reported by 1 (1%) subject.

SM 50mcg

Table 43 Drug-Related Adverse Events in the SM 50mcg Group (Intent-to-Treat Population)

Adverse Event	Arg/Arg N=90	Gly/Gly N=92	Arg/Gly N=90	Total N=272
Number (%) of subjects with any adverse event	39 (43%)	44 (48%)	37 (41%)	120 (44%)
Number (%) of subjects with any drug-related adverse event	1 (1%)	5 (5%)	4 (4%)	10 (4%)
Nervous system disorders	0	3 (3%)	2 (2%)	5 (2%)
Infections and infestations	0	1 (1%)	1 (1%)	2 (<1%)
Respiratory, thoracic, and mediastinal disorders	1 (1%)	1 (1%)	1 (1%)	3 (1%)
Ear & labyrinth disorders	0	1 (1%)	0	1 (<1%)
Psychiatric disorders	0	1 (1%)	1 (1%)	2 (<1%)
Cardiac disorders	0	0	1 (1%)	1 (<1%)
General disorders	0	1 (1%)	0	1 (<1%)
Investigations	0	0	1 (1%)	1 (<1%)

Source Data: [Table 8.5](#) and [Table 8.11](#)

Overall, the incidence of adverse events having a reasonable possibility of being drug-related was small, affecting 1 (1%), 5 (5%), and 4 (4%) subjects across the three genotypes. No drug-related adverse events were reported in any SOC by >3% of subjects in any of the genotypes. In the Gly/Gly genotype, 4 adverse events in the nervous system disorders SOC were reported by 3 (3%) subjects. Headache was reported by 1 (1%) subject, tremor was reported by 2 (2%) subjects, and sinus headache was reported by 1 (1%) subject.

8.3. Serious Adverse Events

8.3.1. Deaths

There was one death in this study.

The exacerbation was considered not related to the study medication by the investigator ([Table 8.12](#) Summary of Serious Adverse Events During Double-Blind Treatment, Section 12 Case Narratives and [Table 8.13](#), Listing of Fatal Adverse Events).

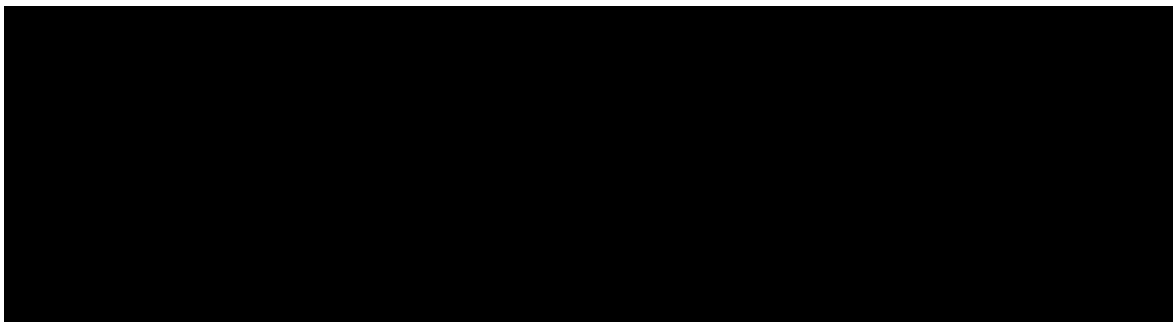
8.3.2. Non-Fatal Serious Adverse Events

[Table 8.14](#) presents the non-fatal SAEs by SOC and provides the individual subject SAE information. Narratives are provided in [Section 12](#) Case Narratives.

Screening Period

Serious adverse events that occurred during the screening period are summarized in [Table 44](#).

Table 44 Non-Fatal Serious Adverse Events during the Screening Period

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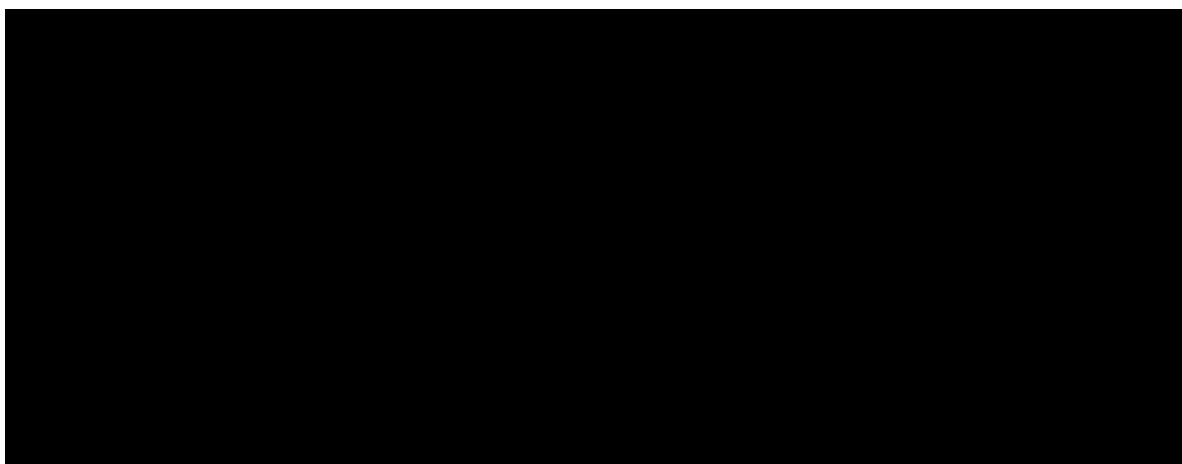
Source Data: [Table 8.14](#)

No subject randomized into the double blind treatment period of the study experienced a serious adverse event during the screening period.

Open-Label Periods

Serious adverse events are reported in [Table 8.14](#) and are summarized in [Table 45](#) and [Table 46](#).

Table 45 Non-Fatal Serious Adverse Events in the Open-Label Albuterol Period

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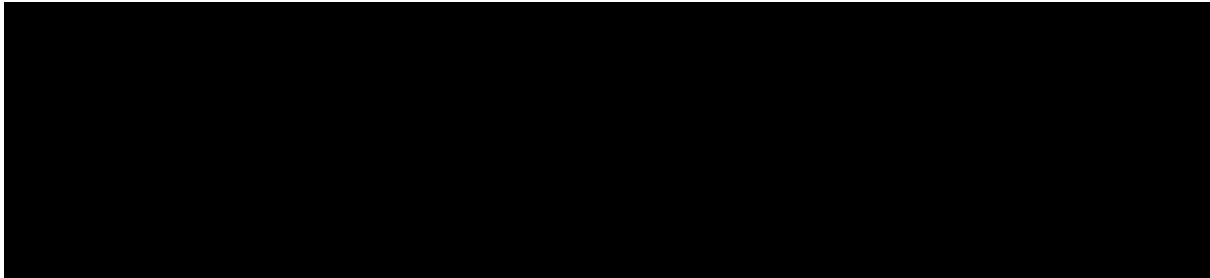
Source Data: [Table 8.14](#)

†Albuterol *prn*

During the open-label albuterol period, three Arg/Arg subjects and one Gly/Gly subject experienced serious adverse events. Each of these subjects withdrew prior to randomization. No Arg/Gly subject reported a serious adverse event during the open-label albuterol period.

Open-Label Ipratropium Period

Table 46 Non-Fatal Serious Adverse Events in the Open-Label Ipratropium Bromide Period



† Ipratropium *pm*

 Both subjects were randomized into the FSC 100/50mcg double blind treatment period and completed the study. No subjects in the Gly/Gly or Arg/Gly genotypes reported a serious adverse event during the open-label ipratropium bromide period.

FSC 100/50mcg and SM 50mcg Treatment Periods

[Table 8.12](#) presents the non-fatal SAEs by the SOC and preferred term. [Table 8.14](#) provides the individual subject SAE information. Case narratives are provided in [Section 12 Case Narratives](#).

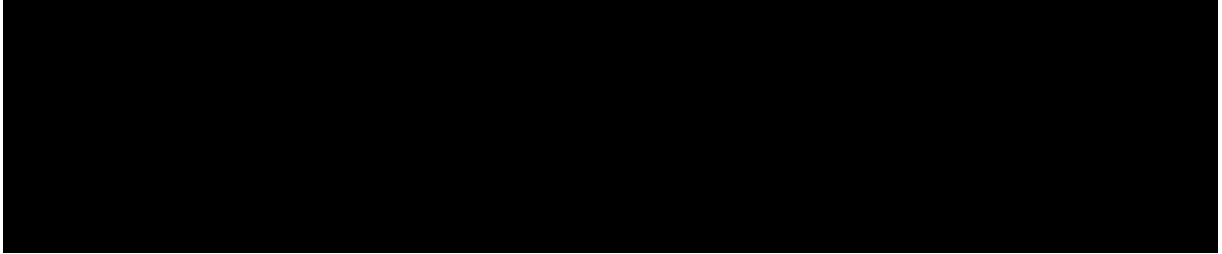
FSC 100/50mcg

There were no serious adverse events reported by subjects in the FSC 100/50mcg treatment period.

SM 50mcg

No serious adverse events were reported for Arg/Arg subjects or Gly/Gly subjects in the SM 50mcg treatment period. [Table 47](#) summarizes the non-fatal serious adverse event that was reported for an Arg/Gly subject in the SM 50mcg group.

Table 47 Non-Fatal Serious Adverse Events in the SM 50mcg group (Intent-to-Treat Population)

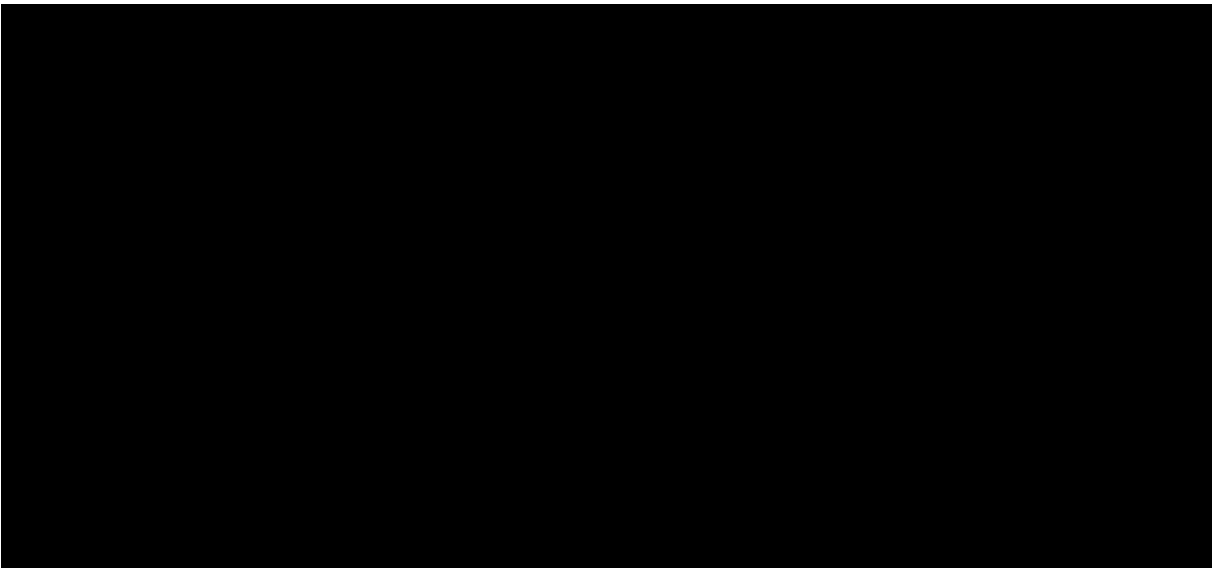


8.4. Adverse Events Leading to Premature Discontinuation of Investigational Product and/or Study

Adverse events experienced by subjects in the FSC 100/50mcg treatment group and by subjects in the SM 50mcg treatment group that led to withdrawal from the study are presented in [Table 8.15](#) and in [Table 48](#) and [Table 49](#). [Table 8.16](#) presents the individual subject adverse event information. [Table 8.10](#) presents the relationship of the adverse event by the SOC and preferred term and verbatim text. Narratives for subjects withdrawn due to adverse events are provided in [Section 12](#) Case Narratives.

FSC 100/50mcg

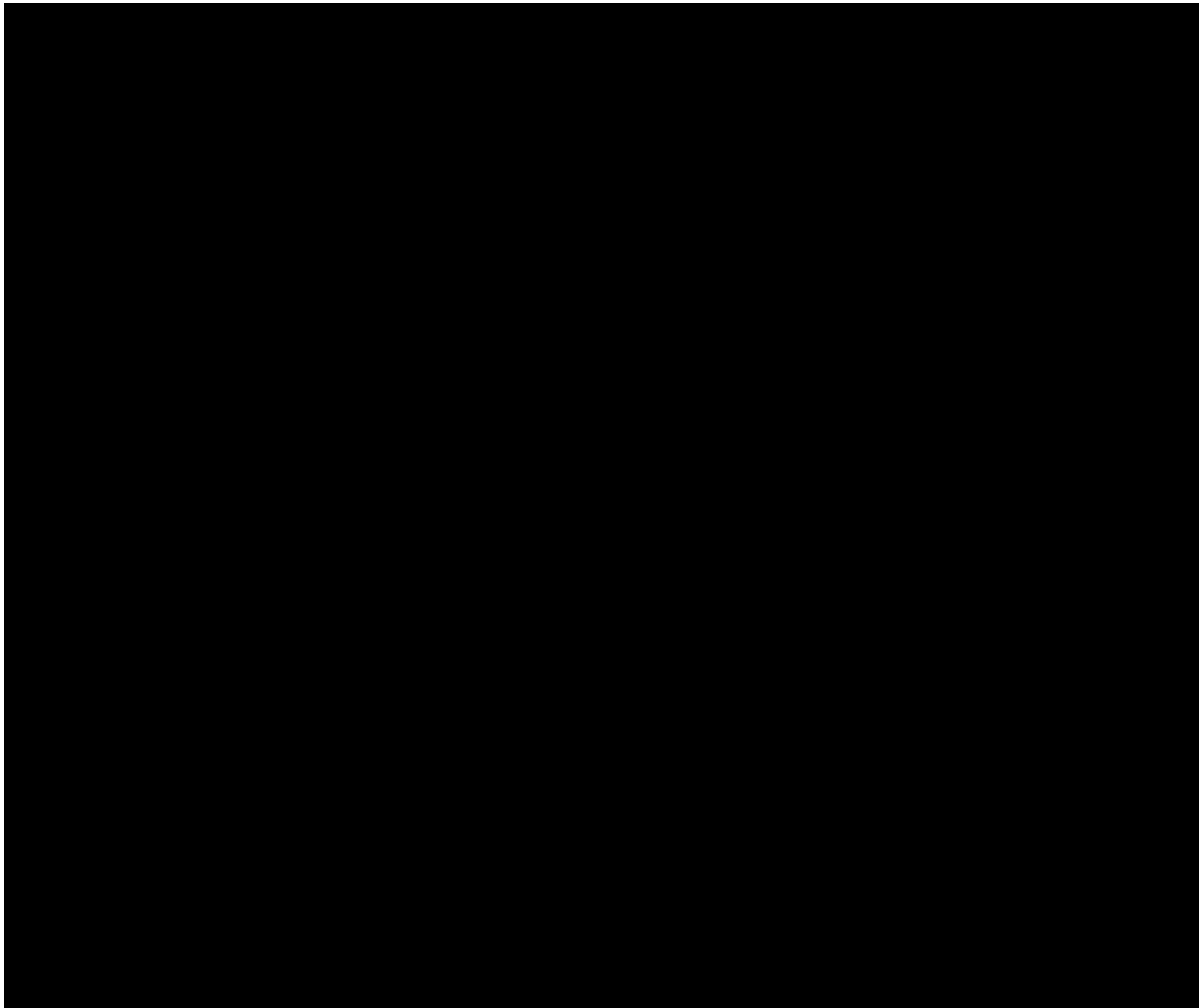
Table 48 Adverse Events Leading to Withdrawal in the FSC 100/50mcg Group (Intent-to-Treat Population)



Five subjects reported 6 adverse events that led to withdrawal in the FSC 100/50mcg treatment group. [REDACTED]

SM 50mcg

**Table 49 Adverse Events Leading to Withdrawal in the SM 50mcg Group
(Intent-to-Treat Population)**



[REDACTED]

[REDACTED] The exacerbation was
considered not-related to the study medication by the investigator. [REDACTED]

[REDACTED]

8.5. Other Relevant Adverse Events

Adverse events experienced by the open-label failure population are presented in [Table 8.17](#) and summarized in [Table 50](#)

Table 50 Adverse Events (3% or greater Incidence) – Open-Label Failure Population

Adverse Event	Arg/Arg N=64	Gly/Gly N=69	Arg/Gly N=105
Number (%) of subjects with any adverse event	27 (42%)	30 (43%)	53 (50%)
Infections and infestations	17 (27%)	13 (19%)	24 (23%)
Nasopharyngitis	2 (3%)	2 (3%)	7 (7%)
Sinusitis	3 (5%)	1 (1%)	5 (5%)
Upper respiratory tract infection	2 (3%)	3 (4%)	4 (4%)
Influenza	2 (3%)	1 (1%)	1 (<1%)
Viral upper respiratory tract infection	2 (3%)	2 (3%)	0
Nervous system disorders	7 (11%)	11 (16%)	20 (19%)
Headache	5 (8%)	10 (14%)	17 (16%)
Dizziness	1 (2%)	0	3 (3%)
Respiratory, thoracic, and mediastinal disorders	10 (16%)	8 (12%)	9 (9%)
Pharyngolaryngeal pain	6 (9%)	4 (6%)	3 (3%)
Cough	3 (5%)	0	2 (2%)
Rhinitis allergic	0	3 (4%)	1 (<1%)
Nasal congestion	2 (3%)	1 (1%)	1 (<1%)
Gastrointestinal disorders	5 (8%)	7 (10%)	10 (10%)
Abdominal pain upper	1 (2%)	2 (3%)	2 (2%)
Abdominal pain	2 (3%)	0	1 (<1%)
Diarrhoea	3 (5%)	0	0
Nausea	3 (5%)	1 (1%)	1 (<1%)
Toothache	0	0	5 (5%)

Source Data: [Table 8.17](#)

The overall incidence of adverse events was generally similar across the open-label failure population. The most commonly affected SOC was infections and infestations with nasopharyngitis the most commonly reported adverse event within that SOC (Arg/Arg 3%, Gly/Gly 3%, and Arg/Gly 7%). Headache in the nervous system disorders SOC was reported by 8% of subjects in the Arg/Arg genotype, 14% in the Gly/Gly genotype, and 16% in the Arg/Gly genotype.

8.6. Pregnancies

Narratives for pregnancies are presented in Section 12 Case Narratives. Also see [Table 8.18](#) Listing of Positive Pregnancy Testing. Pregnancy testing was required to be performed on all female subjects at Visit 2 and Visit 4 (first visits of each open-label

treatment period), and at Visit 6 (randomization visit), Visit 8, Visit 10 (last visit in the blinded treatment period, Visit 11 (last visit of washout period), or at a Premature Discontinuation Visit.

There was one pregnancy during the double-blind treatment period. This Arg/Arg subject was in the SM 50mcg group. There were 6 pregnancies reported in the open-label treatment periods. None of these subjects were exposed to double blind study drug. Three subjects were in the Arg/Arg genotype group, two subjects were in the Gly/Gly genotype group, and one subject was in the Arg/Gly genotype group.

All pregnant subjects were withdrawn from the study. The outcome was normal birth for four of the pregnancies. An elected abortion was performed for non-medical reasons for two of the pregnancies. One pregnancy ended with a spontaneous abortion.

8.7. Asthma Exacerbations

Asthma exacerbations reported in the FSC 100/50mcg treatment group and in the SM 0mcg treatment group during the double-blind treatment period are presented in [Table 8.19](#). The number of subjects who experienced an asthma exacerbation and the number of subjects who were withdrawn due to an asthma exacerbation were recorded on the Asthma Exacerbation CRF page and are summarized in [Table 6.5](#) and [Table 8.19](#).

8.7.1. Albuterol and Ipratropium Bromide Open-Label Periods

Subjects who experienced an exacerbation during one of the open-label periods and were randomized into the FSC 100/50mcg or SM 50mcg double blind treatment groups are presented in [Table 8.20](#) and in [Table 51](#). (See Section [5.6.4.7](#) Asthma exacerbation).

Table 51 Summary of Asthma Exacerbations during the Albuterol and Ipratropium Bromide Open-Label Periods

Albuterol Open-Label Period (Weeks 1-8)	Arg/Arg	Gly/Gly	Arg/Gly
Number of subjects experiencing an asthma exacerbation	7	2	0
Race and Ethnicity			
Caucasian or other	4 (57%)	1 (50%)	0
Black	3 (43%)	1 (50%)	0
Hispanic or Latino	0	0	0
Primary Cause, n (%)			
Upper respiratory infection	4 (57%)	1 (50%)	0
Unknown etiology	2 (29%)	0	0
Exercise	1 (14%)	0	0
Allergy	0	1 (50%)	0
Outcome, n (%)			
Resolved	7 (100%)	2 (100%)	0
Fatal	0	0	0
Not resolved	0	0	0
Severity, n (%)			
Mild	1 (14%)	0	0
Moderate	6 (86%)	2 (100%)	0
Severe	0	0	0
Ipratropium Open-Label Period (Weeks 1-8)	Arg/Arg	Gly/Gly	Arg/Gly
Number of subjects experiencing an asthma exacerbation	3	0	0
Race and Ethnicity			
Caucasian or other	0	0	0
Black	2 (67%)	0	0
Hispanic or Latino	1 (33%)	0	0
Primary Cause, n (%)			
Allergy	1 (33%)		
Other	2 (67%)	0	0
Outcome, n (%)			
Resolved	3 (100%)	0	0
Fatal	0	0	0
Not resolved	0	0	0
Severity, n (%)			
Mild	0	0	0
Moderate	3 (100%)	0	0
Severe	0	0	0

Source Data: [Table 8.20](#) and [Table 8.21](#)

Exacerbations experienced by Arg/Arg subjects in the albuterol and ipratropium bromide open-label periods were considered mild (1) to moderate (9), all of which were resolved. Gly/Gly subjects (2) experienced exacerbations that were considered moderate in severity and resolved. Medications dispensed for treatment of each exacerbation are reported in [Table 8.22](#). No Arg/Gly subject experienced an exacerbation during the two open-label periods.

8.7.2. Double-blind treatment period

Incidents of asthma exacerbations reported in the FSC 100/50mcg group and in the SM 50mcg group during the double-blind treatment period are presented in the tables below. The number of subjects who experienced an asthma exacerbation and the number of subjects who were withdrawn due to an asthma exacerbation were recorded on the Asthma Exacerbation CRF page and presented in [Table 8.19](#) and [Table 8.21](#) and summarized in [Table 52](#) and [Table 53](#).

FSC 100/50mcg

Table 52 Summary of Asthma Exacerbations in the FSC 100/50mcg Group (Intent-to-Treat Population)

Double-blind Period	Arg/Arg N=89	Gly/Gly N=91	Arg/Gly N=92
Number (%) of subjects experiencing an asthma exacerbation – Total <1%	0	1 (1%)	0
Race and Ethnicity			
Caucasian or other	0	1(100%)	0
Black	0	0	0
Hispanic or Latino	0	0	0
Primary Cause, n (%)			
Cold air/Cold weather	0	1	0
Outcome, n (%)			
Resolved	0	1 (100%)	0
Fatal	0	0	0
Not resolved	0	0	0
Severity, n (%)			
Mild	0	0	0
Moderate	0	0	0
Severe	0	1 (100%)	0
Subjects, n (%) withdrawn due to an asthma exacerbation	0	1 (100%)	0

Source Data: [Table 6.6](#), [Table 8.19](#) and [Table 8.21](#)

The incidents of asthma exacerbations reported during the FSC 100/50mcg treatment period was low (1, <1%) across the genotypes. Only one subject (Gly/Gly) experienced a severe exacerbation during the FSC 100/50mcg treatment period. The exacerbation resolved and the subject was withdrawn.

SM 100/50mcg**Table 53 Summary of Asthma Exacerbations in the SM 50mcg Group (Intent-to-Treat Population)**

Double-blind Period	Arg/Arg N=90	Gly/Gly N=92	Arg/Gly N=90
Number (%) of subjects experiencing an asthma exacerbation – Total 10 (4%)	3 (3%)	4 (4%)	3 (3%)
Race and Ethnicity			
Caucasian or other	1 (33%)	1 (25%)	1 (33%)
Black	2 (67%)	1 (25%)	0
Hispanic or Latino	0	2 (50%)	2 (67%)
Primary Cause, n (%)			
Cold air/Cold weather	0	2 (50%)	0
Unknown etiology	1 (33%)	0	1 (33%)
Upper respiratory infection	2 (67%)	1 (25%)	1 (33%)
Other	0	1 (25%)	0
Missing	0	0	1 (33%)
Outcome, n (%)			
Resolved	3 (100%)	3 (75%)	2 (67%)
Fatal	0	0	1 (33%)
Not resolved	0	1 (25%)	0
Severity, n (%)			
Mild	0	2 (50%)	0
Moderate	3 (100%)	1 (25%)	2 (67%)*
Severe	0	1 (25%)	1 (33%)
Subjects, n (%) withdrawn due to an asthma exacerbation*	3 (100%)	4 (100%)	2 (67%)

*One subject (805) was not withdrawn

Source Data: [Table 6.6](#), [Table 8.19](#) and [Table 8.21](#)

The total number of asthma exacerbations reported during the SM 50mcg treatment period was low (10, 4%) and were distributed similarly across the three genotypes.

Exacerbations experienced by Arg/Arg subjects were moderate (3). Exacerbations experienced by Gly/Gly subjects were mild (2), moderate (1), and severe (1). Two exacerbations experienced by Arg/Gly subjects were considered moderate. [REDACTED]

[REDACTED] The death was not attributed to the investigational product. (See Section [12.1](#). Fatal Events for additional details.)

[REDACTED] All other subjects were withdrawn who experienced an exacerbation during the double-blind treatment period.

8.7.3. Washout Period

Incidents of asthma exacerbation reported during the washout period following the 16 week blinded treatment period are presented in [Table 8.21](#) and are summarized in [Table 54](#).

Table 54 Asthma Exacerbations in the FSC 100/50mcg and SM 50mcg Treatment Groups

FSC 100/50mcg Treatment Group	Arg/Arg	Gly/Gly	Arg/Gly
Number (%) of subjects experiencing an asthma exacerbation – Total <1%	1	0	0
Race and Ethnicity			
Caucasian or other	1 (100%)	0	0
Black	0	0	0
Hispanic or Latino	0	0	0
Primary Cause, n			
Unknown etiology	1	0	0
Outcome, n (%)			
Resolved	1 (100%)	0	0
Fatal	0	0	0
Not resolved	0	0	0
Severity, n (%)			
Mild	0	0	0
Moderate	1 (100%)	0	0
Severe	0	0	0
Subjects, n (%) withdrawn due to an asthma exacerbation	1 (100%)	0	0
SM 50mcg Treatment Group	Arg/Arg	Gly/Gly	Arg/Gly
Number (%) of subjects experiencing an asthma exacerbation – Total <1%	0	0	1†
Race and Ethnicity			
Caucasian or other			0
Black			1 (100%)
Hispanic or Latino			0
Primary Cause, n (%)			
Unknown etiology	0	0	1 (100%)
Outcome, n (%)			
Resolved	0	0	1 (100%)
Fatal	0	0	0
Not resolved	0	0	0
Severity, n (%)			
Mild	0	0	1 (100%)
Moderate	0	0	0
Severe	0	0	0
Subjects, n (%) withdrawn due to an asthma exacerbation†	0	0	0

Source Data: [Table 8.21](#)

†Subject (941) was not withdrawn

The other exacerbation in an Arg/Arg subject was reported in the FSC treatment group. No exacerbations were reported for Gly/Gly subjects during the washout period.

8.7.4. Asthma Exacerbations – Screen Failures (Visit 1- Visit 2)

A total of 1429 subjects (65% of 2211 subjects screened) were screen failures. During the screening period (Visit 1 – Visit 2), 5 (<1%) of the screen failure subjects experienced an exacerbation. Genotypes were not known at the time of these exacerbations. Details of these exacerbations were recorded in source documents at investigative sites; no data was captured in a CRF.

Asthma Exacerbations - Open-Label Failure Population

Incidents of asthma exacerbations reported for subjects who withdrew during the two open-label period are presented in [Table 8.23](#) and are summarized in [Table 55](#).

Table 55 Asthma Exacerbations in the Open-Label Failure Population

Open-Label Failure Population	Arg/Arg N=64	Gly/Gly N=69	Arg/Gly N=105
Number (%) of subjects experiencing an asthma exacerbation – Total 23 (10%)	8 (13%)	5 (7%)	10 (10%)
Primary Cause, n (%)			
Cold air/Cold weather	0	0	1(10%)
Withholding/reducing asthma medication	0	1 (20%)	0
Unknown etiology	2 (25%)	0	3 (30%)
Lower respiratory infection	1 (13%)	0	1(10%)
Upper respiratory infection	4 (50%)	1 (20%)	2 (20%)
Air pollution	0	1 (20%)	0
Allergy	1 (13%)	1 (20%)	3 (30%)
Outcome, n (%)			
Resolved	7 (88%)	5 (100%)	10 (100%)
Fatal	0	0	0
Not resolved	1 (13%)	0	0
Severity, n (%)			
Mild	1 (13%)	1 (20%)	3 (30%)
Moderate	6 (75%)	4 (80%)	6 (60%)
Severe	1 (13%)	0	1 (10%)

Source Data: [Table 8.23](#)

During the open-label treatment periods, 23 (10%) of subjects who failed/withdrew experienced an exacerbation. The exacerbations experienced by subjects were low in number and generally considered moderate in severity across the three genotypes (Arg/Arg 8, 13%; Gly/Gly 5, 7%; Arg/Gly 10, 10%).

8.8. 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.

8.9. Safety Conclusion(s)

- The frequency and type of adverse events reported by subjects were generally similar across the genotypes during the albuterol and ipratropium open-label periods.
- The frequency and type of adverse events reported by subjects were generally similar across the genotypes in each of the treatment groups.
- The frequency and type of drug-related adverse events were generally similar and low across the genotypes in each of the treatment groups.

Serious Adverse Events

- During the albuterol open-label period, 3 Arg/Arg subjects reported SAEs and one Gly/Gly subject. None of the SAEs were considered to be drug-related. These subjects were withdrawn from the study. No SAEs were reported in Arg/Gly subjects.
- During the ipratropium bromide open-label period, 2 Arg/Arg subjects reported SAEs. None of the SAEs were considered to be drug-related. These subjects remained in the study. No SAEs were reported by Gly/Gly subjects or by Arg/Gly subjects.
- During the double-blind treatment period, no SAEs were reported by subjects in the FSC 100/50mcg treatment group.
- In the SM 50mcg treatment group, one Arg/Gly subject reported a non fatal SAE not attributed to study medication. The subject remained in the study. One death was reported. An Arg/Gly subject in the SM 50mcg treatment group experienced a severe exacerbation. The death was not attributed to the investigational product. No SAEs were reported by Arg/Arg subjects or by Gly/Gly subjects.

Adverse Events Leading to Premature Discontinuation

- Five subjects in the FSC 100/50mcg treatment group reported six adverse events that led to withdrawal: 2 Arg/Arg subjects, 1 Gly/Gly subject, and 2 Arg/Gly subjects. One event reported by 1 Arg/Gly subject was considered by the investigator to be related to study medication.

- Ten subjects in the SM 50mcg treatment group reported 17 adverse events that led to withdrawal: 1 Arg/Arg subject, 3 Gly/Gly subjects, and six Arg/Gly subjects. The event reported for the Arg/Arg subject was considered by the investigator to be related to study medication. Three events reported for 1 Gly/Gly subject were considered drug-related by the investigator, and 3 events reported for 2 Arg/Gly subjects were also considered drug-related by the investigator.

Asthma Exacerbations

- Exacerbations experienced during the albuterol open-label period were more prevalent (7) in the Arg/Arg group. Two additional exacerbations were reported during this period in the Gly/Gly group. During the ipratropium bromide open-label period (3) Arg/Arg exacerbations were reported. No exacerbations were reported among the other genotypes. None of the exacerbations were judged by the investigators to be severe.
- The incidence of asthma exacerbations reported in the FSC 100/50mcg treatment group was low (1, 1% Gly/Gly subject). The exacerbation was severe and resolved. The incidents of asthma exacerbations reported in the SM 50mcg treatment group were similar across the genotypes (Arg/Arg 3, 3%, Gly/Gly 4, 4%, Arg/Gly 3, 3%). One exacerbation (severe) experienced by an Arg/Gly subject occurred in the SM 50mcg treatment group and was fatal.
- One (<1%) exacerbation was reported during the washout period was moderate and resolved (Arg/Arg subject) in the FSC 100/50mcg treatment group. One Arg/Gly subject in the SM 50mcg treatment group experienced a mild asthma exacerbation (<1%) that was resolved during the washout period.

9. DISCUSSION AND CONCLUSIONS

9.1. Discussion

The prevalence of asthma is common; however, the etiology of the disease remains unknown. The incidence of asthma may be altered through gene-by-environment interactions; however the genetic susceptibility relationships of this polygenic disease are not well understood. Studies have identified over 35 genes that may predispose the development of asthma and suggest that ethnicity and other factors may influence this outcome [Drysedale, 2000; Liggett, 2002].

Not only may the development of asthma be associated with an individual genetic profile, but the clinical response to asthma medications may also be genetically linked. The variability of response to corticosteroid and bronchodilator medications has been associated with specific gene variations [Huizenga, 1998; Tantisira, 2004; Dishy, 2001; Barnes, 2001; Larj, 2002; Hawkins, 2006]. Further, the β 2-adrenergic receptor gene (*ADRB2*) has been extensively genotyped and SNPs associated with altered responses to beta-agonist proposed. The *ADRB2* SNP most often linked with poor clinical outcomes during treatment with beta-agonists is located at codon 16. This SNP is characterized by the substitution of glycine for arginine, producing a homozygous Arg/Arg genotype. This Arg/Arg polymorphism is common, occurring in approximately 17% of Caucasians and in 22% of African Americans [Weir, 1998].

Both retrospective and prospective studies have shown that β 16-Arg/Arg homozygotes may experience a small decline in lung function when receiving four times daily albuterol [Taylor, 2000; Israel, 2000; Israel, 2001; Israel, 2004]. In addition, one retrospective study has suggested that similar responses in lung function may occur in subjects receiving long-acting beta-agonists [Wechsler, 2006]; however, larger studies have not confirmed this observation [Taylor, 2005; Bleecker, 2006].

For patients who remain symptomatic on low dose ICS, asthma control is best achieved by adding long-acting beta-agonists as compared with increasing the dose of ICS or adding a leukotriene modifier (LTM) [Durchame, 2006]. However, if genetic variation of the beta-receptor modulates the response to long-acting beta-agonists, this effect must be identified in prospective well-controlled studies. This study explored whether polymorphisms in *ABRD2* contribute to heterogeneity in response to salmeterol and salmeterol co-administered with fluticasone propionate.

The primary treatment comparison in this study was between the Arg/Arg and the Gly/Gly genotype (codon 16) in the FSC treatment group. The primary endpoint was overall change in AM PEF. There were no significant differences between the homozygote genotypes in AM PEF following 16 weeks of FSC treatment. Further, there were no significant differences between study subjects with the homozygote genotypes and those with the heterozygote genotype (Arg/Gly) in AM PEF.

Secondary and other endpoints included PM PEF, FEV₁ (clinic visits only), symptom-free days, rescue bronchodilator (ipratropium bromide and albuterol) use. An additional endpoint included maximum albuterol dose response (MADR) following 16 weeks of

double-blind treatment, and also preceding double-blind treatment after 8 weeks of run-in on *prn* albuterol followed by 8 weeks on *prn* ipratropium bromide.

During FSC treatment, there were no significant differences by genotype for secondary endpoints including PM PEF, FEV₁, symptom free-days, rescue ipratropium bromide use, rescue albuterol use, or MADR. During the washout period (2-week *prn* ipratropium only treatment) following FSC treatment a gradual decline in AM PEF toward baseline was observed in the Arg/Arg and other genotypes. A significant difference was observed between Arg/Arg versus Gly/Gly genotypes; although neither fell below baseline, no significant differences were observed for all other secondary and other endpoints between genotypes.

Subjects treated with salmeterol (SM) during the double-blind treatment period showed similar results to those treated with FSC, only the magnitude of treatment response by genotype(s) was generally lower. For the primary comparison, there were no significant differences between the homozygote genotypes in AM PEF following 16 weeks of SAL treatment. Further, there were no significant differences between the β 16-Arg homozygous subjects and the heterozygous (Arg/Gly) subjects in AM PEF.

During SM treatment, there were generally no significant differences by genotype for PM PEF, FEV₁ (except Arg/Arg vs Gly/Gly subgroups), symptom-free days, rescue ipratropium bromide use, rescue albuterol use, or MADR (except Arg/Arg vs Gly/Gly subgroups). Where significant differences were noted, a positive treatment response was observed for each genotype and the clinical relevance to the statistical finding is unknown. During the washout period (2-week *prn* ipratropium treatment only) following SM treatment, a gradual decline in AM PEF toward baseline was observed in the Arg/Arg and other genotypes. A significant difference was observed between subjects with the Arg/Gly vs. Gly/Gly genotypes, although neither fell below baseline. No significant differences were observed for all other secondary and other endpoints between genotypes.

One exacerbation was reported for FSC (Gly/Gly) compared with 10 for SM (3 Arg/Arg; 4 Gly/Gly; 3 Arg/Gly) during double-blind treatment. During washout following double blind treatment, there was 1 exacerbation in a subject washing out of FSC (Arg/Arg), and 1 exacerbation in a subject washing out of SM (Arg/Gly). Prior to double blind treatment, there were 9 exacerbations in the open-label *prn* albuterol period (7 Arg/Arg; 2 Gly/Gly) and 3 exacerbations in the subsequent open label *prn* ipratropium bromide period (2 Arg/Arg). Adverse events profiles were unremarkable and similar between treatments.

9.2. Conclusions

There is no evidence that any single SNP in *ADRB2* is associated with either a poor response to FSC or SM, or loss of response, as evaluated by pulmonary function and subject derived variables such as symptoms and rescue beta-agonist use. Nor does a comparison of the albuterol and ipratropium bromide open-label periods suggest that the Arg/Arg genotype, or the Gly/Gly or Arg/Gly genotypes, respond better to a non-beta-agonist bronchodilator such as ipratropium.

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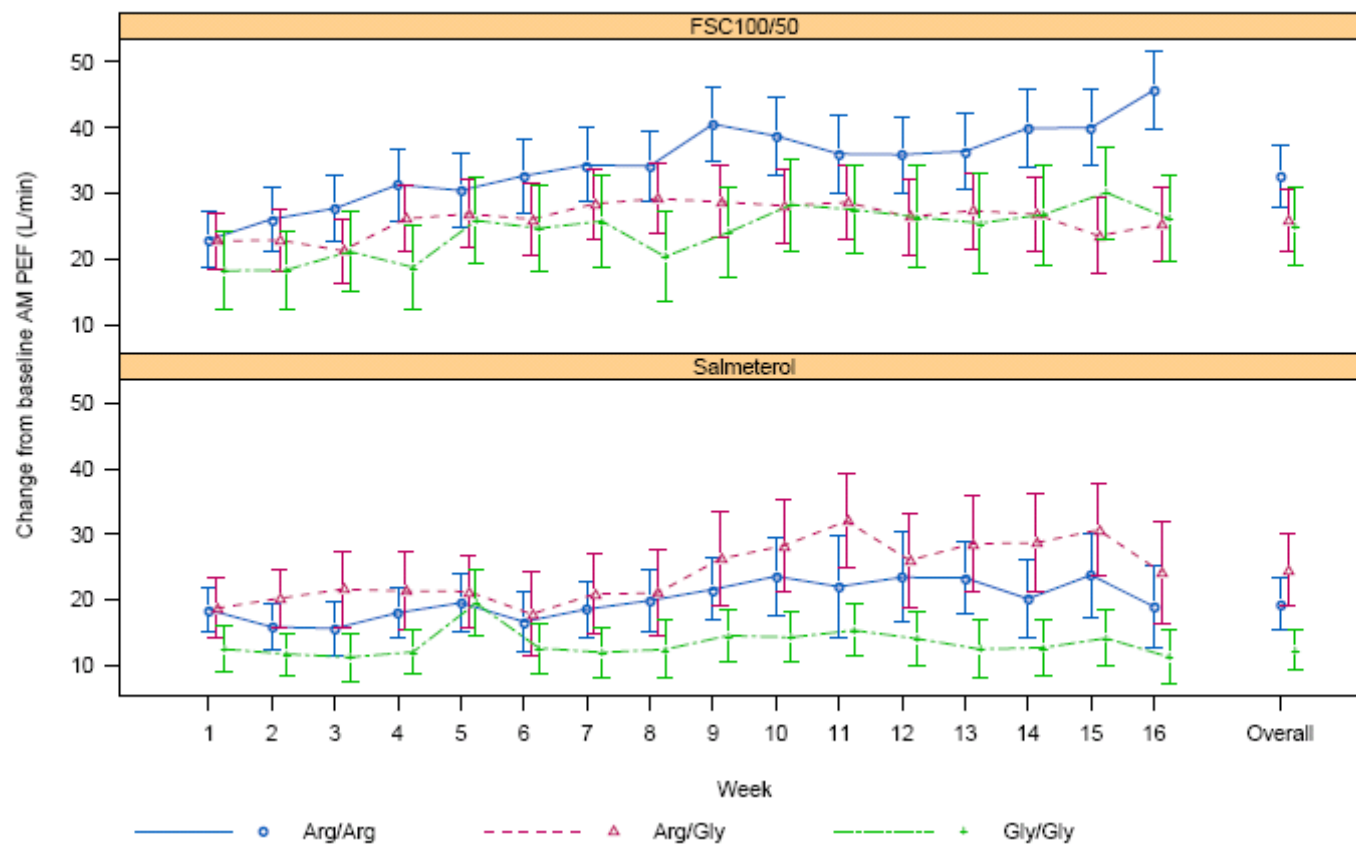
11. FIGURE

Figure 1 Overall AM PEF Mean Changes

Protocol: SFA100062

Population: ITT Excluding Investigator [REDACTED]

Change from Baseline AM PEF (L/min)



*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**.*

13. TIME AND EVENTS TABLE

Screening, Open-label, and Blinded Treatment Periods	Screen	Open-label	Open-label	Open-label	Open-label	Blinded	Blinded	Blinded	Blinded	Blinded	Washout	Premature Dis.
Visit	1	2	3	4	5	6	7	8	9	10	11	
Week		-16	-12	-8	-4	0	4	8	12	16	18	
Number of Days from Visit 6						0	28±2	56±2	84±2	112±2	126±2	
Informed consent	X ^a											
Medical history	X											
Physical exam	X									X		X
Adverse event assessment	X ^b	X ^b	X	X	X	X	X	X	X	X	X	X
Concomitant medication assessment	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X									X		X
Venipuncture	X ^c											
Urinalysis for pregnancy		X		X		X		X		X	X	X
Clinic FEV ₁	X ^d	X	X ^f	X ^f	X ^f	X ^f	X	X	X	X	X	X
Reversibility	X ^e											
Maximum Albuterol Dose Response assessment (MADR)				X ^g		X ^g				X ^g		
Dispense Peak Flow Meter		X										
Dispense Study medication (rescue, open-label, blinded)		X	X	X	X	X	X	X	X	X		
Collect study medication (rescue, open-label, blinded)			X	X	X	X	X	X	X	X	X	X
Dispense Diary Card		X	X	X	X	X	X	X	X	X		
Collect/review diary data			X	X	X	X	X	X	X	X	X	X

- Consent must be signed prior to the withholding of any medication
- Study participation events only
- Take 2 tubes of blood at Visit 1, one for genotyping and one for pharmacogenetics
- Visit 1 FEV₁ percent predicted assessment
- If reversibility assessment is failed twice, site can perform methacholine challenge testing
- Continuation assessment
- Take vital signs before MADR and at least once after each dose of albuterol is administered

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Table 6.1
Summary of Analysis Populations

		Total (N=2211)

Total population		2211
Screen failure population		1429 (65%)
Reason for screen failure	No reason given	3 (<1%)
	Adverse event	7 (<1%)
	Lost to follow-up	23 (2%)
	Subject decided to withdraw from study	32 (2%)
	Prohibited medication use	7 (<1%)
	Did not fulfil eligibility criteria	798 (56%)
	Exacerbation	5 (<1%)
	Genotype quota filled	533 (37%)
	Did not fulfil continuation criteria	7 (<1%)
	Other	14 (<1%)
Open-label failure population		238 (11%)
Reason for open-label albuterol failure	No reason given	0
	Adverse event	8 (3%)
	Lost to follow-up	13 (5%)
	Subject decided to withdraw from study	19 (8%)
	Prohibited medication use	4 (2%)
	Did not fulfil eligibility criteria	5 (2%)
	Exacerbation	4 (2%)
	Genotype quota filled	21 (9%)
	Did not fulfil continuation criteria	23 (10%)
	Other	11 (5%)

Note: Percentages for screen failure reasons are based on the Screen failure population.
Percentages for open-label failure reasons are based on the Open-label failure population.
All other percentages are based on the Total population.

Table 6.1
Summary of Analysis Populations

	Total (N=2211)
Reason for open-label ipratropium bromide failure	
No reason given	0
Adverse event	6 (3%)
Lost to follow-up	11 (5%)
Subject decided to withdraw from study	14 (6%)
Prohibited medication use	4 (2%)
Did not fulfil eligibility criteria	1 (<1%)
Exacerbation	4 (2%)
Genotype quota filled	66 (28%)
Did not fulfil continuation criteria	14 (6%)
Other	10 (4%)
Intent-to-Treat population	544 (25%)
Per protocol population	484 (22%)

Note: Percentages for screen failure reasons are based on the Screen failure population.
Percentages for open-label failure reasons are based on the Open-label failure population.
All other percentages are based on the Total population.

Table 6.2
Summary of Open-Label Failure Reason (Open-Label Albuterol Failure Population)

	Arg/Arg (N=37)	Arg/Gly (N=43)	Gly/Gly (N=28)	Total (N=108)
Reason for open-label albuterol failure				
No reason given	0	0	0	0
Adverse event	3 (8%)	3 (7%)	2 (7%)	8 (7%)
Did not fulfil continuation criteria	7 (19%)	11 (26%)	5 (18%)	23 (21%)
Lost to follow-up	8 (22%)	5 (12%)	0	13 (12%)
Subject decided to withdraw from study	8 (22%)	6 (14%)	5 (18%)	19 (18%)
Prohibited medication use	1 (3%)	2 (5%)	1 (4%)	4 (4%)
Did not fulfil eligibility criteria	3 (8%)	2 (5%)	0	5 (5%)
Exacerbation	1 (3%)	2 (5%)	1 (4%)	4 (4%)
Genotype quota filled	1 (3%)	9 (21%)	11 (39%)	21 (19%)
Other	5 (14%)	3 (7%)	3 (11%)	11 (10%)

Table 6.3
Summary of Open-Label Failure Reason (Open-Label Ipratropium Failure Population)

	Arg/Arg (N=27)	Arg/Gly (N=62)	Gly/Gly (N=41)	Total (N=130)

Reason for open-label ipratropium bromide failure				
No reason given	0	0	0	0
Adverse event	4 (15%)	1 (2%)	1 (2%)	6 (5%)
Did not fulfil continuation criteria	6 (22%)	2 (3%)	6 (15%)	14 (11%)
Lost to follow-up	3 (11%)	5 (8%)	3 (7%)	11 (8%)
Subject decided to withdraw from study	8 (30%)	2 (3%)	4 (10%)	14 (11%)
Prohibited medication use	0	1 (2%)	3 (7%)	4 (3%)
Did not fulfil eligibility criteria	0	1 (2%)	0	1 (<1%)
Exacerbation	1 (4%)	2 (3%)	1 (2%)	4 (3%)
Genotype quota filled	0	47 (76%)	19 (46%)	66 (51%)
Other	5 (19%)	1 (2%)	4 (10%)	10 (8%)

Table 6.4
Summary of Enrollment by Investigator

Treatment: FSC100/50

Country/ Investigator Name (ID)	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Subjects in treatment group	89	92	91	272
Kenya				
All investigators	7 (8%)	0	5 (5%)	12 (4%)
[REDACTED]	5 (6%)	0	2 (2%)	7 (3%)
[REDACTED]	2 (2%)	0	3 (3%)	5 (2%)
Peru				
All investigators	8 (9%)	11 (12%)	11 (12%)	30 (11%)
[REDACTED]	2 (2%)	0	2 (2%)	4 (1%)
[REDACTED]	6 (7%)	11 (12%)	9 (10%)	26 (10%)
United States				
All investigators	74 (83%)	81 (88%)	75 (82%)	230 (85%)
[REDACTED]	1 (1%)	1 (1%)	0	2 (<1%)
[REDACTED]	1 (1%)	0	0	1 (<1%)
[REDACTED]	0	0	0	0
[REDACTED]	0	1 (1%)	2 (2%)	3 (1%)
[REDACTED]	1 (1%)	4 (4%)	5 (5%)	10 (4%)
[REDACTED]	3 (3%)	3 (3%)	0	6 (2%)
[REDACTED]	2 (2%)	2 (2%)	1 (1%)	5 (2%)
[REDACTED]	2 (2%)	0	3 (3%)	5 (2%)
[REDACTED]	0	0	0	0
[REDACTED]	1 (1%)	1 (1%)	2 (2%)	4 (1%)
[REDACTED]	1 (1%)	5 (5%)	5 (5%)	11 (4%)
[REDACTED]	0	0	0	0
[REDACTED]	0	0	0	0
[REDACTED]	0	0	0	0
[REDACTED]	3 (3%)	2 (2%)	1 (1%)	6 (2%)
[REDACTED]	1 (1%)	0	0	1 (<1%)
[REDACTED]	1 (1%)	2 (2%)	1 (1%)	4 (1%)
[REDACTED]	1 (1%)	1 (1%)	0	2 (<1%)

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Table 6.4
Summary of Enrollment by Investigator

Treatment: FSC100/50

Country/ Investigator Name (ID)	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
	1 (1%)	0	0	1 (<1%)
	0	0	0	0
	3 (3%)	0	0	3 (1%)
	0	2 (2%)	3 (3%)	5 (2%)
	1 (1%)	4 (4%)	1 (1%)	6 (2%)
	0	0	1 (1%)	1 (<1%)
	0	4 (4%)	2 (2%)	6 (2%)
	2 (2%)	0	1 (1%)	3 (1%)
	6 (7%)	3 (3%)	3 (3%)	12 (4%)
	1 (1%)	0	0	1 (<1%)
	0	0	0	0
	0	2 (2%)	0	2 (<1%)
	2 (2%)	1 (1%)	2 (2%)	5 (2%)
	0	3 (3%)	2 (2%)	5 (2%)
	0	4 (4%)	4 (4%)	8 (3%)
	1 (1%)	3 (3%)	1 (1%)	5 (2%)
	3 (3%)	2 (2%)	1 (1%)	6 (2%)
	0	0	0	0
	1 (1%)	0	1 (1%)	2 (<1%)
	0	1 (1%)	0	1 (<1%)
	2 (2%)	0	2 (2%)	4 (1%)
	1 (1%)	0	0	1 (<1%)
	3 (3%)	6 (7%)	6 (7%)	15 (6%)
	0	0	2 (2%)	2 (<1%)
	1 (1%)	1 (1%)	0	2 (<1%)
	0	0	0	0
	5 (6%)	2 (2%)	3 (3%)	10 (4%)
	2 (2%)	1 (1%)	1 (1%)	4 (1%)
	2 (2%)	0	1 (1%)	3 (1%)
	0	0	3 (3%)	3 (1%)
	1 (1%)	0	0	1 (<1%)
	1 (1%)	0	1 (1%)	2 (<1%)

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Table 6.4
Summary of Enrollment by Investigator

Treatment: FSC100/50

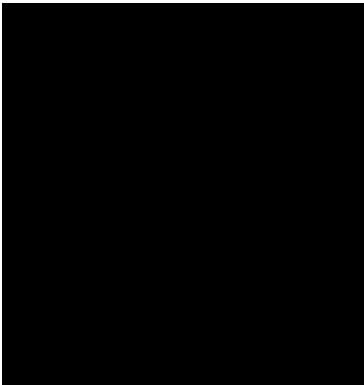
Country/ Investigator Name (ID)	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
	0	1 (1%)	1 (1%)	2 (<1%)
	2 (2%)	2 (2%)	2 (2%)	6 (2%)
	3 (3%)	0	0	3 (1%)
	2 (2%)	0	0	2 (<1%)
	1 (1%)	2 (2%)	1 (1%)	4 (1%)
	3 (3%)	0	0	3 (1%)
	1 (1%)	0	1 (1%)	2 (<1%)
	2 (2%)	2 (2%)	4 (4%)	8 (3%)
	1 (1%)	4 (4%)	2 (2%)	7 (3%)
	0	1 (1%)	0	1 (<1%)
	1 (1%)	4 (4%)	1 (1%)	6 (2%)
	0	4 (4%)	0	4 (1%)
	1 (1%)	0	2 (2%)	3 (1%)

Table 6.4
Summary of Enrollment by Investigator

Treatment: Salmeterol

Country/ Investigator Name (ID)	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Subjects in treatment group	90	90	92	272
Kenya				
All investigators	12 (13%)	3 (3%)	1 (1%)	16 (6%)
[REDACTED]	10 (11%)	2 (2%)	0	12 (4%)
	2 (2%)	1 (1%)	1 (1%)	4 (1%)
Peru				
All investigators	9 (10%)	15 (17%)	13 (14%)	37 (14%)
[REDACTED]	3 (3%)	1 (1%)	1 (1%)	5 (2%)
	6 (7%)	14 (16%)	12 (13%)	32 (12%)
United States				
All investigators	69 (77%)	72 (80%)	78 (85%)	219 (81%)
[REDACTED]	2 (2%)	1 (1%)	0	3 (1%)
	0	0	0	0
	1 (1%)	0	0	1 (<1%)
	0	0	1 (1%)	1 (<1%)
	0	4 (4%)	3 (3%)	7 (3%)
	1 (1%)	4 (4%)	2 (2%)	7 (3%)
	1 (1%)	2 (2%)	2 (2%)	5 (2%)
	0	2 (2%)	1 (1%)	3 (1%)
	1 (1%)	0	0	1 (<1%)
	0	3 (3%)	2 (2%)	5 (2%)
	3 (3%)	3 (3%)	2 (2%)	8 (3%)
	1 (1%)	0	0	1 (<1%)
	1 (1%)	0	0	1 (<1%)
	0	1 (1%)	1 (1%)	2 (<1%)
	1 (1%)	1 (1%)	0	2 (<1%)
	2 (2%)	0	0	2 (<1%)
	1 (1%)	1 (1%)	2 (2%)	4 (1%)
	0	0	3 (3%)	3 (1%)

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Table 6.4
Summary of Enrollment by Investigator

Treatment: Salmeterol

Country/ Investigator Name (ID)	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
	1 (1%)	0	0	1 (<1%)
	2 (2%)	0	0	2 (<1%)
	0	0	0	0
	2 (2%)	1 (1%)	1 (1%)	4 (1%)
	1 (1%)	3 (3%)	4 (4%)	8 (3%)
	0	0	0	0
	0	0	3 (3%)	3 (1%)
	1 (1%)	1 (1%)	0	2 (<1%)
	4 (4%)	4 (4%)	7 (8%)	15 (6%)
	1 (1%)	0	0	1 (<1%)
	0	0	1 (1%)	1 (<1%)
	2 (2%)	3 (3%)	2 (2%)	7 (3%)
	1 (1%)	0	3 (3%)	4 (1%)
	0	5 (6%)	2 (2%)	7 (3%)
	2 (2%)	2 (2%)	2 (2%)	6 (2%)
	5 (6%)	3 (3%)	3 (3%)	11 (4%)
	3 (3%)	0	0	3 (1%)
	1 (1%)	0	0	1 (<1%)
	0	1 (1%)	0	1 (<1%)
	1 (1%)	3 (3%)	1 (1%)	5 (2%)
	2 (2%)	0	3 (3%)	5 (2%)
	0	0	0	0
	2 (2%)	5 (6%)	1 (1%)	8 (3%)
	1 (1%)	0	0	1 (<1%)
	0	0	2 (2%)	2 (<1%)
	1 (1%)	0	0	1 (<1%)
	1 (1%)	2 (2%)	1 (1%)	4 (1%)
	4 (4%)	1 (1%)	1 (1%)	6 (2%)
	1 (1%)	3 (3%)	3 (3%)	7 (3%)
	3 (3%)	1 (1%)	2 (2%)	6 (2%)
	0	0	0	0
	0	1 (1%)	1 (1%)	2 (<1%)

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Table 6.4
Summary of Enrollment by Investigator

Treatment: Salmeterol

Country/ Investigator Name (ID)	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
	0	0	0	0
	1 (1%)	1 (1%)	0	2 (<1%)
	2 (2%)	0	0	2 (<1%)
	0	2 (2%)	2 (2%)	4 (1%)
	0	0	2 (2%)	2 (<1%)
	5 (6%)	0	0	5 (2%)
	2 (2%)	0	0	2 (<1%)
	0	3 (3%)	5 (5%)	8 (3%)
	1 (1%)	1 (1%)	1 (1%)	3 (1%)
	0	0	3 (3%)	3 (1%)
	0	1 (1%)	0	1 (<1%)
	1 (1%)	1 (1%)	0	2 (<1%)
	0	2 (2%)	3 (3%)	5 (2%)

Table 6.5
Summary of End of Study Record

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Subjects in treatment group	89	92	91	272
Completion status				
Completed study	78 (88%)	82 (89%)	79 (87%)	239 (88%)
Prematurely withdrawn	11 (12%)	10 (11%)	12 (13%)	33 (12%)
Primary Reason for Withdrawal During Double-blind Treatment				
Any reason	10 (11%)	8 (9%)	12 (13%)	30 (11%)
Adverse event	3 (3%)	1 (1%)	1 (1%)	5 (2%)
Exacerbation	1 (1%)	0	1 (1%)	2 (<1%)
Lost to follow-up	1 (1%)	0	3 (3%)	4 (1%)
Protocol violation	1 (1%)	2 (2%)	1 (1%)	4 (1%)
Subject decided to withdraw from the study	0	4 (4%)	6 (7%)	10 (4%)
Sponsor terminated study	0	0	0	0
Other	4 (4%)	1 (1%)	0	5 (2%)
Primary Reason for Withdrawal During Wash-out Period				
Any reason	1 (1%)	2 (2%)	0	3 (1%)
Adverse event	0	1 (1%)	0	1 (<1%)
Exacerbation	1 (1%)	0	0	1 (<1%)
Lost to follow-up	0	0	0	0
Protocol violation	0	1 (1%)	0	1 (<1%)
Subject decided to withdraw from the study	0	0	0	0
Sponsor terminated study	0	0	0	0
Other	0	0	0	0

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Table 6.5
Summary of End of Study Record

Treatment: Salmeterol

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Subjects in treatment group	90	90	92	272
Completion status				
Completed study	68 (76%)	73 (81%)	76 (83%)	217 (80%)
Prematurely withdrawn	22 (24%)	17 (19%)	16 (17%)	55 (20%)
Primary Reason for Withdrawal During Double-blind Treatment				
Any reason	21 (23%)	16 (18%)	16 (17%)	53 (19%)
Adverse event	1 (1%)	6 (7%)	3 (3%)	10 (4%)
Exacerbation	3 (3%)	1 (1%)	3 (3%)	7 (3%)
Lost to follow-up	4 (4%)	3 (3%)	2 (2%)	9 (3%)
Protocol violation	4 (4%)	1 (1%)	3 (3%)	8 (3%)
Subject decided to withdraw from the study	6 (7%)	3 (3%)	3 (3%)	12 (4%)
Sponsor terminated study	1 (1%)	0	0	1 (<1%)
Other	2 (2%)	2 (2%)	2 (2%)	6 (2%)
Primary Reason for Withdrawal During Wash-out Period				
Any reason	1 (1%)	1 (1%)	0	2 (<1%)
Adverse event	0	0	0	0
Exacerbation	0	0	0	0
Lost to follow-up	0	0	0	0
Protocol violation	0	0	0	0
Subject decided to withdraw from the study	0	0	0	0
Sponsor terminated study	1 (1%)	0	0	1 (<1%)
Other	0	1 (1%)	0	1 (<1%)

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Table 6.6
Listing of End of Study Record

Trt	Arg16Gly genotype	Inv.	Subj.	Date of Premature Withdrawal	Period	Day within Period	Reason for Premature Withdrawal

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.

Table 6.7
Summary of Protocol Deviations

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Subjects in treatment group	89	92	91	272
Protocol deviation				
Any protocol deviation	11 (12%)	7 (8%)	9 (10%)	27 (10%)
Inclusion criteria violation	1 (1%)	0	0	1 (<1%)
Exclusion criteria violation	0	0	1 (1%)	1 (<1%)
Use of prohibited medication	10 (11%)	5 (5%)	7 (8%)	22 (8%)
Dispensing incorrect blinded study drug	1 (1%)	1 (1%)	1 (1%)	3 (1%)
Mis-stratification	0	1 (1%)	0	1 (<1%)

Note: Subjects may have had more than one protocol deviation.

Table 6.7
Summary of Protocol Deviations

Treatment: Salmeterol

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Subjects in treatment group	90	90	92	272
Protocol deviation				
Any protocol deviation	9 (10%)	9 (10%)	5 (5%)	23 (8%)
Inclusion criteria violation	2 (2%)	0	0	2 (<1%)
Exclusion criteria violation	0	0	0	0
Use of prohibited medication	6 (7%)	5 (6%)	5 (5%)	16 (6%)
Dispensing incorrect blinded study drug	2 (2%)	3 (3%)	0	5 (2%)
Mis-stratification	0	1 (1%)	0	1 (<1%)

Note: Subjects may have had more than one protocol deviation.

Table 6.8
Listing of Protocol Deviations

Trt	Arg16Gly genotype	Inv.	Subj.	Protocol deviation

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.

Table 6.9
Summary of Inclusion/Exclusion Criteria Deviations

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)

Subjects in treatment group	89	92	91	272
Any criteria deviations	1 (1%)	0	1 (1%)	2 (<1%)
Inclusion criteria				
FEV1 >=70% and <=100% of predicted normal at Visit 1	1 (1%)	0	0	1 (<1%)
Exclusion criteria				
Use of prohibited anti-asthma medications	0	0	1 (1%)	1 (<1%)

Table 6.9
Summary of Inclusion/Exclusion Criteria Deviations

Treatment: Salmeterol

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)

Subjects in treatment group	90	90	92	272
Any criteria deviations	2 (2%)	0	0	2 (<1%)
Inclusion criteria				
FEV1 >=70% and <=100% of predicted normal at Visit 1	2 (2%)	0	0	2 (<1%)

Table 6.10
Listing of Subjects with Inclusion/Exclusion Criteria Deviations

Trt	Arg16Gly genotype	Inv.	Subj.	Type	Criterion
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.					

Table 6.11
Listing of Subjects for Whom the Treatment Blind was Broken

No data to report

Table 6.12
Summary of Demographic Characteristics (ITT Population)

Treatment: FSC100/50

		Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Subjects in treatment group		89	92	91	272
Age at screening (y)	n	89	92	91	272
	Mean	33.8	31.0	33.3	32.7
	SD	13.31	14.40	14.33	14.03
	Median	31.0	29.5	32.0	30.5
	Min.	12	12	12	12
	Max.	73	69	68	73
Sex	n	89	92	91	272
	Female	62 (70%)	59 (64%)	55 (60%)	176 (65%)
	Male	27 (30%)	33 (36%)	36 (40%)	96 (35%)
Ethnicity	n	89	92	91	272
	Hispanic or Latino	28 (31%)	28 (30%)	27 (30%)	83 (31%)
	Not Hispanic or Latino	61 (69%)	64 (70%)	64 (70%)	189 (69%)
Race	n	89	92	91	272
	Arabic/North African	1 (1%)	0	0	1 (<1%)
	Black	29 (33%)	17 (18%)	18 (20%)	64 (24%)
	African American	23 (79%)	16 (94%)	12 (67%)	51 (80%)
	African Heritage	6 (21%)	1 (6%)	6 (33%)	13 (20%)
	East & South East Asian	0	0	0	0
	Japanese	0	1 (1%)	1 (1%)	2 (<1%)
	South Asian	0	1 (1%)	2 (2%)	3 (1%)
	White/Caucasian	44 (49%)	57 (62%)	59 (65%)	160 (59%)
	Other	15 (17%)	16 (17%)	11 (12%)	42 (15%)
	Native Hawaiian	0	0	0	0
	Other Pacific Islander	1 (7%)	2 (13%)	0	3 (7%)
	American Indian	10 (67%)	12 (75%)	11 (100%)	33 (79%)
	Alaska Native	0	0	0	0

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Table 6.12
Summary of Demographic Characteristics (ITT Population)

Treatment: Salmeterol

		Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Subjects in treatment group		90	90	92	272
Age at screening (y)	n	90	90	92	272
	Mean	30.0	32.8	35.2	32.7
	SD	12.02	14.17	16.34	14.41
	Median	28.0	31.0	34.5	30.0
	Min.	12	12	12	12
	Max.	62	63	74	74
Sex	n	90	90	92	272
	Female	57 (63%)	58 (64%)	51 (55%)	166 (61%)
	Male	33 (37%)	32 (36%)	41 (45%)	106 (39%)
Ethnicity	n	90	90	92	272
	Hispanic or Latino	26 (29%)	29 (32%)	26 (28%)	81 (30%)
	Not Hispanic or Latino	64 (71%)	61 (68%)	66 (72%)	191 (70%)
Race	n	90	90	92	272
	Arabic/North African	0	0	0	0
	Black	32 (36%)	15 (17%)	19 (21%)	66 (24%)
	African American	18 (56%)	11 (73%)	16 (84%)	45 (68%)
	African Heritage	14 (44%)	4 (27%)	3 (16%)	21 (32%)
	East & South East Asian	1 (1%)	3 (3%)	2 (2%)	6 (2%)
	Japanese	0	0	0	0
	South Asian	0	2 (2%)	0	2 (<1%)
	White/Caucasian	45 (50%)	54 (60%)	57 (62%)	156 (57%)
	Other	12 (13%)	16 (18%)	14 (15%)	42 (15%)
	Native Hawaiian	0	0	0	0
	Other Pacific Islander	0	0	0	0
	American Indian	10 (83%)	15 (94%)	12 (86%)	37 (88%)
	Alaska Native	0	0	0	0

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Table 6.13
Summary of Disease Characteristics (ITT Population)

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Subjects in treatment group	89	92	91	272
Asthma duration (years)				
n	89	92	91	272
Mean	17.0	16.8	17.0	16.9
SD	10.98	11.25	12.05	11.40
Median	16.0	15.0	13.0	15.0
Min.	0	1	0	0
Max.	52	50	63	63
Duration in categories				
n	89	92	91	272
<6 months	1 (1%)	0	1 (1%)	2 (<1%)
>=6 months to <1 year	1 (1%)	1 (1%)	0	2 (<1%)
>=1 year to <5 years	10 (11%)	11 (12%)	9 (10%)	30 (11%)
>=5 years to <10 years	13 (15%)	14 (15%)	18 (20%)	45 (17%)
>=10 years to <15 years	14 (16%)	19 (21%)	19 (21%)	52 (19%)
>=15 years	50 (56%)	47 (51%)	44 (48%)	141 (52%)
Is the subject exposed to passive smoke?				
n	89	92	91	272
Yes	14 (16%)	14 (15%)	21 (23%)	49 (18%)
No	75 (84%)	78 (85%)	70 (77%)	223 (82%)
Is the subject exposed to pets?				
n	88	92	91	271
Yes	38 (43%)	41 (45%)	48 (53%)	127 (47%)
No	50 (57%)	51 (55%)	43 (47%)	144 (53%)

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Table 6.13
Summary of Disease Characteristics (ITT Population)

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Does the subject attend school?				
n	89	92	91	272
Yes	23 (26%)	40 (43%)	26 (29%)	89 (33%)
No	66 (74%)	52 (57%)	65 (71%)	183 (67%)
Biological relatives with asthma history				
Father	12 (13%)	19 (21%)	14 (15%)	45 (17%)
Maternal grandparents	9 (10%)	7 (8%)	14 (15%)	30 (11%)
Mother	14 (16%)	31 (34%)	18 (20%)	63 (23%)
Paternal grandparents	4 (4%)	8 (9%)	6 (7%)	18 (7%)
Sibling	26 (29%)	32 (35%)	22 (24%)	80 (29%)
Subject	89 (100%)	92 (100%)	88 (97%)	269 (99%)
Biological relatives with croup history				
Father	1 (1%)	0	2 (2%)	3 (1%)
Maternal grandparents	0	0	0	0
Mother	1 (1%)	2 (2%)	3 (3%)	6 (2%)
Paternal grandparents	1 (1%)	0	0	1 (<1%)
Sibling	3 (3%)	4 (4%)	3 (3%)	10 (4%)
Subject	5 (6%)	7 (8%)	4 (4%)	16 (6%)
Biological relatives with eczema history				
Father	6 (7%)	7 (8%)	4 (4%)	17 (6%)
Maternal grandparents	2 (2%)	1 (1%)	2 (2%)	5 (2%)
Mother	5 (6%)	7 (8%)	4 (4%)	16 (6%)
Paternal grandparents	1 (1%)	1 (1%)	2 (2%)	4 (1%)
Sibling	9 (10%)	9 (10%)	9 (10%)	27 (10%)
Subject	16 (18%)	17 (18%)	13 (14%)	46 (17%)

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Table 6.13
Summary of Disease Characteristics (ITT Population)

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Biological relatives with food allergy history				
Father	3 (3%)	5 (5%)	5 (5%)	13 (5%)
Maternal grandparents	0	1 (1%)	3 (3%)	4 (1%)
Mother	5 (6%)	9 (10%)	7 (8%)	21 (8%)
Paternal grandparents	2 (2%)	1 (1%)	0	3 (1%)
Sibling	8 (9%)	8 (9%)	12 (13%)	28 (10%)
Subject	14 (16%)	12 (13%)	19 (21%)	45 (17%)
Biological relatives with hives history				
Father	2 (2%)	3 (3%)	1 (1%)	6 (2%)
Maternal grandparents	0	0	0	0
Mother	9 (10%)	4 (4%)	5 (5%)	18 (7%)
Paternal grandparents	1 (1%)	0	0	1 (<1%)
Sibling	9 (10%)	10 (11%)	7 (8%)	26 (10%)
Subject	20 (22%)	14 (15%)	18 (20%)	52 (19%)
Biological relatives with pet allergy history				
Father	7 (8%)	9 (10%)	13 (14%)	29 (11%)
Maternal grandparents	2 (2%)	1 (1%)	1 (1%)	4 (1%)
Mother	15 (17%)	16 (17%)	12 (13%)	43 (16%)
Paternal grandparents	1 (1%)	1 (1%)	1 (1%)	3 (1%)
Sibling	14 (16%)	13 (14%)	11 (12%)	38 (14%)
Subject	36 (40%)	46 (50%)	49 (54%)	131 (48%)

Table 6.13
Summary of Disease Characteristics (ITT Population)

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Biological relatives with sinus infection history				
Father	12 (13%)	17 (18%)	10 (11%)	39 (14%)
Maternal grandparents	3 (3%)	8 (9%)	6 (7%)	17 (6%)
Mother	20 (22%)	31 (34%)	17 (19%)	68 (25%)
Paternal grandparents	2 (2%)	7 (8%)	1 (1%)	10 (4%)
Sibling	15 (17%)	21 (23%)	16 (18%)	52 (19%)
Subject	32 (36%)	35 (38%)	37 (41%)	104 (38%)
Biological relatives with seasonal allergy history				
Father	9 (10%)	16 (17%)	10 (11%)	35 (13%)
Maternal grandparents	5 (6%)	5 (5%)	4 (4%)	14 (5%)
Mother	18 (20%)	21 (23%)	18 (20%)	57 (21%)
Paternal grandparents	4 (4%)	7 (8%)	1 (1%)	12 (4%)
Sibling	19 (21%)	25 (27%)	13 (14%)	57 (21%)
Subject	42 (47%)	49 (53%)	45 (49%)	136 (50%)
Biological relatives with year-round hay fever history				
Father	10 (11%)	24 (26%)	19 (21%)	53 (19%)
Maternal grandparents	4 (4%)	9 (10%)	9 (10%)	22 (8%)
Mother	25 (28%)	35 (38%)	21 (23%)	81 (30%)
Paternal grandparents	1 (1%)	10 (11%)	7 (8%)	18 (7%)
Sibling	28 (31%)	42 (46%)	25 (27%)	95 (35%)
Subject	64 (72%)	63 (68%)	62 (68%)	189 (69%)

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Table 6.13
Summary of Disease Characteristics (ITT Population)

Treatment: Salmeterol

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Subjects in treatment group	90	90	92	272
Asthma duration (years)				
n	90	90	92	272
Mean	13.8	16.1	17.1	15.7
SD	10.21	12.52	12.01	11.67
Median	10.8	12.7	14.0	13.0
Min.	1	1	1	1
Max.	41	60	68	68
Duration in categories				
n	90	90	92	272
<6 months	0	0	0	0
>=6 months to <1 year	1 (1%)	1 (1%)	1 (1%)	3 (1%)
>=1 year to <5 years	17 (19%)	14 (16%)	8 (9%)	39 (14%)
>=5 years to <10 years	20 (22%)	15 (17%)	15 (16%)	50 (18%)
>=10 years to <15 years	16 (18%)	20 (22%)	23 (25%)	59 (22%)
>=15 years	36 (40%)	40 (44%)	45 (49%)	121 (44%)
Is the subject exposed to passive smoke?				
n	90	90	92	272
Yes	28 (31%)	17 (19%)	13 (14%)	58 (21%)
No	62 (69%)	73 (81%)	79 (86%)	214 (79%)
Is the subject exposed to pets?				
n	90	90	92	272
Yes	41 (46%)	51 (57%)	47 (51%)	139 (51%)
No	49 (54%)	39 (43%)	45 (49%)	133 (49%)

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Table 6.13
Summary of Disease Characteristics (ITT Population)

Treatment: Salmeterol

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Does the subject attend school?				
n	90	90	92	272
Yes	26 (29%)	36 (40%)	27 (29%)	89 (33%)
No	64 (71%)	54 (60%)	65 (71%)	183 (67%)
Biological relatives with asthma history				
Father	13 (14%)	13 (14%)	13 (14%)	39 (14%)
Maternal grandparents	13 (14%)	12 (13%)	8 (9%)	33 (12%)
Mother	20 (22%)	23 (26%)	13 (14%)	56 (21%)
Paternal grandparents	6 (7%)	6 (7%)	5 (5%)	17 (6%)
Sibling	32 (36%)	23 (26%)	28 (30%)	83 (31%)
Subject	88 (98%)	87 (97%)	91 (99%)	266 (98%)
Biological relatives with croup history				
Father	1 (1%)	1 (1%)	0	2 (<1%)
Maternal grandparents	0	0	0	0
Mother	0	1 (1%)	0	1 (<1%)
Paternal grandparents	0	1 (1%)	0	1 (<1%)
Sibling	3 (3%)	2 (2%)	1 (1%)	6 (2%)
Subject	5 (6%)	5 (6%)	5 (5%)	15 (6%)
Biological relatives with eczema history				
Father	2 (2%)	1 (1%)	3 (3%)	6 (2%)
Maternal grandparents	1 (1%)	2 (2%)	2 (2%)	5 (2%)
Mother	4 (4%)	4 (4%)	5 (5%)	13 (5%)
Paternal grandparents	2 (2%)	0	0	2 (<1%)
Sibling	8 (9%)	7 (8%)	8 (9%)	23 (8%)
Subject	12 (13%)	16 (18%)	14 (15%)	42 (15%)

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Table 6.13
Summary of Disease Characteristics (ITT Population)

Treatment: Salmeterol

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Biological relatives with food allergy history				
Father	3 (3%)	4 (4%)	5 (5%)	12 (4%)
Maternal grandparents	5 (6%)	4 (4%)	1 (1%)	10 (4%)
Mother	5 (6%)	8 (9%)	9 (10%)	22 (8%)
Paternal grandparents	0	3 (3%)	1 (1%)	4 (1%)
Sibling	2 (2%)	5 (6%)	6 (7%)	13 (5%)
Subject	11 (12%)	18 (20%)	13 (14%)	42 (15%)
Biological relatives with hives history				
Father	1 (1%)	1 (1%)	2 (2%)	4 (1%)
Maternal grandparents	2 (2%)	2 (2%)	3 (3%)	7 (3%)
Mother	2 (2%)	6 (7%)	9 (10%)	17 (6%)
Paternal grandparents	0	0	0	0
Sibling	2 (2%)	3 (3%)	4 (4%)	9 (3%)
Subject	12 (13%)	13 (14%)	15 (16%)	40 (15%)
Biological relatives with pet allergy history				
Father	7 (8%)	9 (10%)	9 (10%)	25 (9%)
Maternal grandparents	4 (4%)	4 (4%)	0	8 (3%)
Mother	8 (9%)	14 (16%)	16 (17%)	38 (14%)
Paternal grandparents	1 (1%)	1 (1%)	0	2 (<1%)
Sibling	18 (20%)	10 (11%)	16 (17%)	44 (16%)
Subject	27 (30%)	47 (52%)	54 (59%)	128 (47%)

Table 6.13
Summary of Disease Characteristics (ITT Population)

Treatment: Salmeterol

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)

Biological relatives with sinus infection history				
Father	11 (12%)	12 (13%)	11 (12%)	34 (13%)
Maternal grandparents	4 (4%)	6 (7%)	4 (4%)	14 (5%)
Mother	16 (18%)	14 (16%)	16 (17%)	46 (17%)
Paternal grandparents	0	4 (4%)	1 (1%)	5 (2%)
Sibling	16 (18%)	13 (14%)	16 (17%)	45 (17%)
Subject	26 (29%)	29 (32%)	33 (36%)	88 (32%)
Biological relatives with seasonal allergy history				
Father	10 (11%)	8 (9%)	10 (11%)	28 (10%)
Maternal grandparents	3 (3%)	5 (6%)	3 (3%)	11 (4%)
Mother	14 (16%)	15 (17%)	13 (14%)	42 (15%)
Paternal grandparents	2 (2%)	5 (6%)	1 (1%)	8 (3%)
Sibling	17 (19%)	14 (16%)	20 (22%)	51 (19%)
Subject	41 (46%)	42 (47%)	44 (48%)	127 (47%)
Biological relatives with year-round hay fever history				
Father	19 (21%)	20 (22%)	20 (22%)	59 (22%)
Maternal grandparents	8 (9%)	8 (9%)	8 (9%)	24 (9%)
Mother	26 (29%)	26 (29%)	23 (25%)	75 (28%)
Paternal grandparents	3 (3%)	8 (9%)	3 (3%)	14 (5%)
Sibling	30 (33%)	26 (29%)	35 (38%)	91 (33%)
Subject	62 (69%)	61 (68%)	70 (76%)	193 (71%)

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Table 6.14
Listing of Demographic Characteristics

Trt	Arg16Gly genotype	Inv.	Subj.	Visit Date/ Birth Date	Age (y)	Sex	Ethnicity	Race	Sub-race

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.

Table 6.15
Summary of Screening Pulmonary Function Tests (ITT Population)

Treatment: FSC100/50

		Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Subjects in treatment group		89	92	91	272
FEV1 (L)	n	89	92	91	272
	Mean	2.64	2.75	2.73	2.71
	SD	0.628	0.630	0.624	0.627
	Median	2.47	2.72	2.78	2.70
	Min.	1.38	1.39	1.46	1.38
	Max.	4.31	4.49	4.46	4.49
FEV1 % predicted	n	89	92	91	272
	Mean	82.0	82.5	82.6	82.4
	SD	7.74	7.78	7.70	7.71
	Median	82.8	80.9	82.5	81.8
	Min.	69	70	70	69
	Max.	100	100	100	100
FEV1 % reversibility	n	83	91	90	264
	Mean	19.9	17.9	18.4	18.7
	SD	11.47	6.19	9.11	9.10
	Median	16.6	15.8	15.8	16.0
	Min.	4	12	3	3
	Max.	94	48	62	94
Historical FEV1 % reversibility	n	2	0	0	2
	Mean	13.6			13.6
	SD	0.35			0.35
	Median	13.6			13.6
	Min.	13			13
	Max.	14			14

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Table 6.15
Summary of Screening Pulmonary Function Tests (ITT Population)

Treatment: Salmeterol

		Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Subjects in treatment group		90	90	92	272
FEV1 (L)	n	90	90	92	272
	Mean	2.78	2.72	2.73	2.74
	SD	0.682	0.699	0.656	0.677
	Median	2.66	2.61	2.74	2.67
	Min.	1.39	1.20	1.56	1.20
	Max.	4.42	4.50	4.97	4.97
FEV1 % predicted	n	90	90	92	272
	Mean	83.3	82.1	81.5	82.3
	SD	8.23	8.15	8.44	8.27
	Median	83.4	81.7	80.2	81.5
	Min.	59	70	68	59
	Max.	99	102	100	102
FEV1 % reversibility	n	86	85	88	259
	Mean	19.5	20.9	20.2	20.2
	SD	9.88	12.35	7.79	10.13
	Median	16.2	17.2	17.5	17.1
	Min.	3	10	12	3
	Max.	71	106	54	106
Historical FEV1 % reversibility	n	4	0	0	4
	Mean	18.7			18.7
	SD	6.77			6.77
	Median	18.8			18.8
	Min.	12			12
	Max.	25			25

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Table 6.16
Summary of Percent of Subjects Meeting Continuation Criteria

Treatment: FSC100/50

			Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)

Subjects in treatment group			89	92	91
FEV1 >=70%	Visit 2 (Week -16)	Yes	86 (97%)	89 (97%)	88 (97%)
		No	3 (3%)	3 (3%)	3 (3%)
FEV1 >=70% & <56 puffs/wk rescue	Visit 3 (Week -12)	Yes	89 (100%)	91 (100%)	91 (100%)
		No	0	0	0
	Visit 4 (Week -8)	Yes	88 (99%)	91 (99%)	90 (100%)
		No	1 (1%)	1 (1%)	0
	Visit 5 (Week -4)	Yes	89 (100%)	91 (99%)	91 (100%)
		No	0	1 (1%)	0
	Visit 6 (Day 1)	Yes	88 (99%)	92 (100%)	91 (100%)
		No	1 (1%)	0	0

Table 6.16
Summary of Percent of Subjects Meeting Continuation Criteria

Treatment: Salmeterol

			Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)

Subjects in treatment group			90	90	92
FEV1 >=70%	Visit 2 (Week -16)	Yes	88 (98%)	87 (97%)	88 (96%)
		No	2 (2%)	3 (3%)	4 (4%)
FEV1 >=70% & <56 puffs/wk rescue	Visit 3 (Week -12)	Yes	89 (99%)	90 (100%)	91 (99%)
		No	1 (1%)	0	1 (1%)
	Visit 4 (Week -8)	Yes	90 (100%)	90 (100%)	92 (100%)
		No	0	0	0
	Visit 5 (Week -4)	Yes	89 (99%)	90 (100%)	92 (100%)
		No	1 (1%)	0	0
	Visit 6 (Day 1)	Yes	90 (100%)	87 (97%)	90 (98%)
		No	0	3 (3%)	2 (2%)

Table 6.17
Summary of Predose FEV1 Percent Predicted

Treatment: FSC100/50

			Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)

Subjects in treatment group			89	92	91
FEV1 % predicted	Visit 2 (Week -16)	n	89	92	91
		Mean	86.3	85.9	85.9
		SD	12.76	10.34	10.51
		Median	86.3	86.7	85.1
		Min.	66	59	51
		Max.	144	125	112
	Visit 3 (Week -12)	n	89	92	91
		Mean	86.9	86.0	86.7
		SD	11.16	9.66	10.98
		Median	85.2	86.4	85.0
		Min.	68	70	70
		Max.	124	111	123
	Visit 4 (Week -8)	n	89	92	91
		Mean	86.0	86.8	87.5
		SD	10.64	9.93	11.05
		Median	84.1	88.0	85.6
		Min.	70	70	70
		Max.	126	110	121
	Visit 5 (Week -4)	n	89	92	91
		Mean	87.1	87.2	86.7
		SD	10.72	9.53	11.00
		Median	85.7	86.9	84.9
		Min.	69	70	62
		Max.	118	105	115

Table 6.17
Summary of Predose FEV1 Percent Predicted

Treatment: FSC100/50

			Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)
FEV1 % predicted	Visit 6 (Day 1)	n	89	92	91
		Mean	85.0	86.3	86.7
		SD	10.04	10.46	10.93
		Median	84.3	87.4	85.7
		Min.	68	70	62
		Max.	113	110	113

Table 6.17
Summary of Predose FEV1 Percent Predicted

Treatment: Salmeterol

			Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)
Subjects in treatment group			90	90	92
FEV1 % predicted	Visit 2 (Week -16)	n	90	90	92
		Mean	88.4	85.3	84.5
		SD	11.35	10.05	10.73
		Median	87.8	85.0	83.6
		Min.	61	55	52
		Max.	118	109	116
	Visit 3 (Week -12)	n	90	90	92
		Mean	87.4	87.5	85.1
		SD	11.40	10.86	10.24
		Median	85.8	86.1	83.1
		Min.	69	70	67
		Max.	127	119	108
	Visit 4 (Week -8)	n	90	90	92
		Mean	89.3	86.3	85.7
		SD	12.72	10.23	10.51
		Median	86.8	85.8	83.5
		Min.	70	68	69
		Max.	129	110	117
	Visit 5 (Week -4)	n	90	90	92
		Mean	89.3	87.1	85.4
		SD	11.37	10.76	10.80
		Median	88.7	86.9	83.7
		Min.	68	70	69
		Max.	121	117	117

Table 6.17
Summary of Predose FEV1 Percent Predicted

Treatment: Salmeterol

		Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)
FEV1 % predicted	Visit 6 (Day 1)			
	n	90	90	92
	Mean	87.2	85.6	86.0
	SD	11.31	11.44	11.06
	Median	85.5	84.9	84.7
	Min.	70	65	66
	Max.	135	128	118

Table 6.18
Summary of Current Medical Conditions (ITT Population)

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Subjects in treatment group	89	92	91	272
Any medical condition	66 (74%)	67 (73%)	72 (79%)	205 (75%)
Blood and lymphatic system disorders	6 (7%)	6 (7%)	2 (2%)	14 (5%)
Cardiac disorders	10 (11%)	10 (11%)	9 (10%)	29 (11%)
Congenital, familial and genetic disorders	1 (1%)	0	0	1 (<1%)
Ear and labyrinth disorders	7 (8%)	5 (5%)	12 (13%)	24 (9%)
Endocrine disorders	5 (6%)	3 (3%)	4 (4%)	12 (4%)
Eye disorders	11 (12%)	15 (16%)	16 (18%)	42 (15%)
Gastrointestinal disorders	20 (22%)	15 (16%)	16 (18%)	51 (19%)
General disorders and administration site conditions	6 (7%)	7 (8%)	12 (13%)	25 (9%)
Hepatobiliary disorders	1 (1%)	1 (1%)	0	2 (<1%)
Immune system disorders	23 (26%)	25 (27%)	26 (29%)	74 (27%)
Infections and infestations	1 (1%)	8 (9%)	6 (7%)	15 (6%)
Metabolism and nutrition disorders	2 (2%)	0	2 (2%)	4 (1%)
Musculoskeletal and connective tissue disorders	22 (25%)	16 (17%)	18 (20%)	56 (21%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (3%)	2 (2%)	1 (1%)	6 (2%)
Nervous system disorders	31 (35%)	30 (33%)	25 (27%)	86 (32%)
Psychiatric disorders	10 (11%)	6 (7%)	11 (12%)	27 (10%)
Renal and urinary disorders	2 (2%)	1 (1%)	3 (3%)	6 (2%)
Reproductive system and breast disorders	21 (24%)	16 (17%)	13 (14%)	50 (18%)
Skin and subcutaneous tissue disorders	17 (19%)	22 (24%)	23 (25%)	62 (23%)
Vascular disorders	3 (3%)	6 (7%)	5 (5%)	14 (5%)

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Table 6.18
Summary of Current Medical Conditions (ITT Population)

Treatment: Salmeterol

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Subjects in treatment group	90	90	92	272
Any medical condition	66 (73%)	67 (74%)	65 (71%)	198 (73%)
Blood and lymphatic system disorders	5 (6%)	4 (4%)	4 (4%)	13 (5%)
Cardiac disorders	5 (6%)	11 (12%)	16 (17%)	32 (12%)
Congenital, familial and genetic disorders	0	1 (1%)	2 (2%)	3 (1%)
Ear and labyrinth disorders	6 (7%)	7 (8%)	8 (9%)	21 (8%)
Endocrine disorders	5 (6%)	7 (8%)	3 (3%)	15 (6%)
Eye disorders	21 (23%)	9 (10%)	17 (18%)	47 (17%)
Gastrointestinal disorders	11 (12%)	19 (21%)	17 (18%)	47 (17%)
General disorders and administration site conditions	12 (13%)	6 (7%)	11 (12%)	29 (11%)
Hepatobiliary disorders	1 (1%)	1 (1%)	0	2 (<1%)
Immune system disorders	16 (18%)	18 (20%)	24 (26%)	58 (21%)
Infections and infestations	5 (6%)	4 (4%)	7 (8%)	16 (6%)
Metabolism and nutrition disorders	2 (2%)	8 (9%)	4 (4%)	14 (5%)
Musculoskeletal and connective tissue disorders	18 (20%)	18 (20%)	22 (24%)	58 (21%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1%)	0	3 (3%)	4 (1%)
Nervous system disorders	21 (23%)	26 (29%)	24 (26%)	71 (26%)
Psychiatric disorders	7 (8%)	2 (2%)	9 (10%)	18 (7%)
Renal and urinary disorders	0	2 (2%)	2 (2%)	4 (1%)
Reproductive system and breast disorders	12 (13%)	16 (18%)	6 (7%)	34 (13%)
Skin and subcutaneous tissue disorders	12 (13%)	19 (21%)	21 (23%)	52 (19%)
Vascular disorders	3 (3%)	5 (6%)	3 (3%)	11 (4%)

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Table 6.19
Summary of Prior Asthma Medication Use (ITT Population)

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Subjects in treatment group	89	92	91	272
Subjects with any medication	60 (67%)	68 (74%)	71 (78%)	199 (73%)
RESPIRATORY SYSTEM				
Any medication	60 (67%)	68 (74%)	71 (78%)	199 (73%)
SALBUTAMOL	56 (63%)	60 (65%)	63 (69%)	179 (66%)
MONTELUKAST SODIUM	3 (3%)	3 (3%)	3 (3%)	9 (3%)
SALMETEROL XINAFOATE+FLUTICASONE PROPIONATE	1 (1%)	3 (3%)	3 (3%)	7 (3%)
PIRBUTEROL ACETATE	0	3 (3%)	3 (3%)	6 (2%)
FLUTICASONE PROPIONATE	0	2 (2%)	1 (1%)	3 (1%)
SALBUTAMOL SULFATE+IPRATROPIUM BROMIDE	2 (2%)	0	1 (1%)	3 (1%)
SALMETEROL XINAFOATE	0	2 (2%)	0	2 (<1%)
BUDESONIDE	0	0	1 (1%)	1 (<1%)
EPINEPHRINE	1 (1%)	0	0	1 (<1%)
FENOTEROL	0	1 (1%)	0	1 (<1%)
FORMOTEROL FUMARATE	1 (1%)	0	0	1 (<1%)
FRANOL (NOS)	1 (1%)	0	0	1 (<1%)
LEVOSALBUTAMOL HYDROCHLORIDE	0	1 (1%)	0	1 (<1%)
TRIAMCINOLONE ACETONIDE	0	0	1 (1%)	1 (<1%)
DERMATOLOGICALS				
Any medication	0	2 (2%)	3 (3%)	5 (2%)
FLUTICASONE PROPIONATE	0	2 (2%)	1 (1%)	3 (1%)
BUDESONIDE	0	0	1 (1%)	1 (<1%)
TRIAMCINOLONE ACETONIDE	0	0	1 (1%)	1 (<1%)

Note: A medication may be reported in more than one ATC Level.

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Table 6.19
Summary of Prior Asthma Medication Use (ITT Population)

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
ALIMENTARY TRACT AND METABOLISM				
Any medication	1 (1%)	0	2 (2%)	3 (1%)
BUDESONIDE	0	0	1 (1%)	1 (<1%)
EPINEPHRINE	1 (1%)	0	0	1 (<1%)
TRIAMCINOLONE ACETONIDE	0	0	1 (1%)	1 (<1%)
SENSORY ORGANS				
Any medication	1 (1%)	0	1 (1%)	2 (<1%)
EPINEPHRINE	1 (1%)	0	0	1 (<1%)
TRIAMCINOLONE ACETONIDE	0	0	1 (1%)	1 (<1%)
CARDIOVASCULAR SYSTEM				
Any medication	1 (1%)	0	0	1 (<1%)
EPINEPHRINE	1 (1%)	0	0	1 (<1%)
SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES				
Any medication	0	0	2 (2%)	2 (<1%)
BUDESONIDE	0	0	1 (1%)	1 (<1%)
TRIAMCINOLONE ACETONIDE	0	0	1 (1%)	1 (<1%)
BLOOD AND BLOOD FORMING ORGANS				
Any medication	1 (1%)	0	0	1 (<1%)
EPINEPHRINE	1 (1%)	0	0	1 (<1%)
GENITO URINARY SYSTEM AND SEX HORMONES				
Any medication	0	1 (1%)	0	1 (<1%)
FENOTEROL	0	1 (1%)	0	1 (<1%)

Note: A medication may be reported in more than one ATC Level.

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Table 6.19
Summary of Prior Asthma Medication Use (ITT Population)

Treatment: Salmeterol

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Subjects in treatment group	90	90	92	272
Subjects with any medication	63 (70%)	61 (68%)	65 (71%)	189 (69%)
RESPIRATORY SYSTEM				
Any medication	62 (69%)	61 (68%)	65 (71%)	188 (69%)
SALBUTAMOL	58 (64%)	57 (63%)	60 (65%)	175 (64%)
SALMETEROL XINAFOATE+FLUTICASONE PROPIONATE	0	2 (2%)	4 (4%)	6 (2%)
MONTELUKAST SODIUM	1 (1%)	1 (1%)	1 (1%)	3 (1%)
PIRBUTEROL ACETATE	1 (1%)	1 (1%)	1 (1%)	3 (1%)
FRANOL (NOS)	2 (2%)	0	0	2 (<1%)
SALBUTAMOL SULFATE	1 (1%)	0	1 (1%)	2 (<1%)
SALMETEROL XINAFOATE	0	1 (1%)	1 (1%)	2 (<1%)
EPINEPHRINE	1 (1%)	0	0	1 (<1%)
MONTELUKAST	0	0	1 (1%)	1 (<1%)
THEOPHYLLINE	1 (1%)	0	0	1 (<1%)
THEOPHYLLINE+EPHEDRINE HYDROCHLORIDE	1 (1%)	0	0	1 (<1%)
TRIAMCINOLONE ACETONIDE	0	0	1 (1%)	1 (<1%)
DERMATOLOGICALS				
Any medication	0	0	1 (1%)	1 (<1%)
TRIAMCINOLONE ACETONIDE	0	0	1 (1%)	1 (<1%)
ALIMENTARY TRACT AND METABOLISM				
Any medication	1 (1%)	0	1 (1%)	2 (<1%)
EPINEPHRINE	1 (1%)	0	0	1 (<1%)
TRIAMCINOLONE ACETONIDE	0	0	1 (1%)	1 (<1%)

Note: A medication may be reported in more than one ATC Level.

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Table 6.19
Summary of Prior Asthma Medication Use (ITT Population)

Treatment: Salmeterol

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)

SENSORY ORGANS				
Any medication	1 (1%)	0	1 (1%)	2 (<1%)
EPINEPHRINE	1 (1%)	0	0	1 (<1%)
TRIAMCINOLONE ACETONIDE	0	0	1 (1%)	1 (<1%)
CARDIOVASCULAR SYSTEM				
Any medication	2 (2%)	0	0	2 (<1%)
ATENOLOL	1 (1%)	0	0	1 (<1%)
EPINEPHRINE	1 (1%)	0	0	1 (<1%)
SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES				
Any medication	0	0	1 (1%)	1 (<1%)
TRIAMCINOLONE ACETONIDE	0	0	1 (1%)	1 (<1%)
BLOOD AND BLOOD FORMING ORGANS				
Any medication	1 (1%)	0	0	1 (<1%)
EPINEPHRINE	1 (1%)	0	0	1 (<1%)

Note: A medication may be reported in more than one ATC Level.

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Table 6.20
Relationship of Medication Class, Dictionary Term and Verbatim Text

ATC Level 1	Ingredient(s)	Verbatim Text
ALIMENTARY TRACT AND METABOLISM	ACETYLSALICYLIC ACID	ASA ASAPRIN ASPIRIN ASPIRIN PRN ASPIRINA ASPRIN BABY ASPRIN BAYER ASPIRIN BUFFERIN EQUATE CHILDREN'S ASPIRIN ST. JOSEPH LOW DOSE 81MG ASPIRIN ST. JOSEPH'S ASPIRIN ALKA SELTZER
	ACETYLSALICYLIC ACID+SODIUM BICARBONATE+CITRIC ACID	ALKA-SELTZER ALLERGY ALKASELTZER ACTAL ACTIVATED CHARCOAL TABLETS
	ACTAL (NOS)	MAALOX
	ACTIVATED CHARCOAL	MYLANTA
	ALUMINIUM HYDROXIDE GEL+MAGNESIUM HYDROXIDE	
	ALUMINIUM HYDROXIDE GEL, DRIED+MAGNESIUM HYDROXIDE+SIMETICONE	AIRBORNE SUPPLEMENT
	AMINO ACIDS NOS+MINERALS NOS+VITAMINS NOS+HERBALS NOS ASCORBIC ACID	VITAMIN C VITAMINS C ECHINACHEA & VIT C EHINEACHIA & VIT C ATROPINE
	ASCORBIC ACID+ECHINACEA	BECLATE AQUNASE BECLATE NASAL SPRAY BECONASE PRN DECOMIT
	ATROPINE	
	BECLOMETASONE DIPROPIONATE	MEROCAINE LOZENGE
	BENZOCAINE+CETYLPYRIDINIUM CHLORIDE	

Table 6.20
Relationship of Medication Class, Dictionary Term and Verbatim Text

ATC Level 1	Ingredient(s)	Verbatim Text
ALIMENTARY TRACT AND METABOLISM	BETAMETHASONE	BETAMETHASONE
	BETAMETHASONE DIPROPIONATE	DIPROLENE
	BISACODYL	BISACODYL
	BISMUTH SUBSALICYLATE	PEPTO BISMAL
		PEPTO BISMOL
		PEPTO BISMOL PRN
		PEPTO-BISMOL
		NASOCORT
	BUDESONIDE	PULMICORT
		RHINOCORT AQ
		RHINOCORT AQUA
		CALCIUM
	CALCIUM CARBONATE	TUMS
		TUMS PRN
	CIMETIDINE	CIMETIDINE
	CLOTRIMAZOLE	CANDID V6 PESSANES
		CLORTRIMAZOLE
	CROMOGLICIC ACID	PROVENTOL 90MCG
	DEXAMETHASONE	DECADRON
	DICYCLOVERINE HYDROCHLORIDE	BENTYL
		BENTYL 20
		ROLAIDS
	DIHYDROXYALUMINUM SODIUM CARBONATE	DRAMAMINE
		GRAVOL
	DIMENHYDRINATE	PRAMAMINE
		ULGEL
	DIMETICONE+MAGNESIUM+ALUMINIUM	GAS-X
	DIMETICONE, ACTIVATED	COLACE
	DOCUSATE SODIUM	MOTILIMUM
	DOMPERIDONE	DOXYCYCLINE HYCLATE
	DOXYCYCLINE HYCLATE	DULCOLAX
	DULCOLAX (NOS)	PRIMATENE MIST
	EPINEPHRINE	ESOMEPRAZOL
	ESOMEPRAZOLE	NEXIUM
	ESOMEPRAZOLE MAGNESIUM	

Table 6.20
Relationship of Medication Class, Dictionary Term and Verbatim Text

ATC Level 1	Ingredient(s)	Verbatim Text
ALIMENTARY TRACT AND METABOLISM	FAMOTIDINE	FAMOCID OTC PEPCID PEPCID PEPCID AC GAVISCON GLIDIABET AMARYL GLIPIZIDE HYDROCORTISONE CREAM HYOSCYAMINE HYOSCYAMINE S04 HYOSCYAMINE SULFATE HUMULIN
	INSULIN HUMAN+INSULIN ISOPHANE, HUMAN BIOSYNTHETIC INSULIN NOS INVERT SUGAR+PHOSPHORIC ACID IRON+CALCIUM KAOPECTATE NOS LACTOBACILLUS ACIDOPHILUS LANSOPRAZOLE	INSULIN EMETROL IRON WITH CALCIUM KAOPECTATE ACIDOPHILUS LANZOPRAZOL PREVACID FLAXSEED IMMODIUM IMMODIUM PRN IMODIUM IMODIUM A-D LOPERAMIDA MIRALAX RIOPAN (MAGALDRATE + DIMETICONE) MECLAZINE PENTASA METFORMIN GLUCOPHAGE
	LINUM USITATISSIMUM LOPERAMIDE HYDROCHLORIDE	
	MACROGOL MAGALDRATE+DIMETICONE, ACTIVATED	
	MECLOZINE MESALAZINE METFORMIN METFORMIN HYDROCHLORIDE	

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ATC Level 1	Ingredient(s)	Verbatim Text
ALIMENTARY TRACT AND METABOLISM	METFORMIN HYDROCHLORIDE	METFORMIN ER METFORMIN HYDROCHLORIDE
	METOCLOPRAMIDE	METOCLOPRAMIDE
	METOCLOPRAMIDE HYDROCHLORIDE+DEHYDROCHOLIC ACID+DIMETICONE, ACTIVATED+DIGESTIVE	ENZIMATIK
	POLYENZYME	
	METRONIDAZOLE	AMOBIN METROGEL METRONIDAZOLE
	MICONAZOLE NITRATE	MONISTAT
	MINERALS NOS+VITAMINS NOS	CENTRUM MULTI-PHYTO ONCE A DAY WOMANS VITAMIN PROVIDA
	MINERALS NOS+VITAMINS NOS+ENZYME, NOS+HERBALS NOS	
	MINERALS NOS+VITAMINS NOS+HERBALS NOS	AIRBORNE AIRBOURNE
	NATEGLINIDE	STARLIX
	OMEPRAZOLE	OMEPRAZOLE OMEPRAZOLE 20MG OD PRILOSEC
	OTHER ANTIDIARRHOEALS	ANTIDIARRHEALS "EXACT NAME UNKNOWN"
	PANTOPRAZOLE	PROPONRX PROTONIX
	PAPAVERINE	PAPAVERINE
	PARGEVERINE HYDROCHLORIDE	PLIDAN PLIDAN (PARGEVERINE)
	PHENDIMETRAZINE TARTRATE	BONTRIL PDM
	PHTERMININE	PHTERMININE
	PHTERMININE RESIN	ADIPEX
	PIOGLITAZONE HYDROCHLORIDE	ACTOS ACTOSE
	POLYCARBOPHIL CALCIUM	FIBER CON

Table 6.20
Relationship of Medication Class, Dictionary Term and Verbatim Text

ATC Level 1	Ingredient(s)	Verbatim Text
ALIMENTARY TRACT AND METABOLISM	POLYCARBOPHIL CALCIUM	FIBERCON
	POTASSIUM CHLORIDE	K-DAR
		K-DUR
		POTASSIUM CHLORIDE
	POTASSIUM NOS	POTASSIUM
	PREDNISON	PREDISON
		PREDNISONA
		PREDNISON
		PREDNISON DOSE PACK
	PROMETHAZINE	PHENEGRON
		PHENERGAN
		PHENERGAN 25
		PROMETHASINE
		PROMETHAZINE
		PROMETHAZINE SUPPOSITORIES
		TRICOHIST
	PROTEASE+AMYLASE+LIPASE+ASPERGILLUS NIGER	DIGESTASE
	RABEPRAZOLE SODIUM	ACIPHEX
		RABEPRAZOLE SODIUM
	RANITIDINE	RANITIDINE
	RANITIDINE HYDROCHLORIDE	RANTIDINE
		ZANTAC
		ZANTAC 75
	RETINOL PALMITATE	AVITA (RETINOL PALMITATE)
	RHINOCORT (NOS)	RHINOCORT
		RHINOCORT PRN
	ROSIGLITAZONE MALEATE	AVANDIA
	SENN	SENTACOT
	SODIUM BICARBONATE	ENO
	SODIUM CHLORIDE	AFRIN SALINE
		NASAL SALINE
		NASAL SALINE SPRAY
		OCEAN SPRAY
		SALINE NASAL SPRAY

Table 6.20
Relationship of Medication Class, Dictionary Term and Verbatim Text

ATC Level 1	Ingredient(s)	Verbatim Text
ALIMENTARY TRACT AND METABOLISM	SODIUM CHLORIDE SUCRALFATE TEGASEROD TETRACYCLINE THIAMINE HYDROCHLORIDE+CYANOCOBALAMIN+PYRIDOXINE HYDROCHLORIDE TOCOPHEROL TRIAMCINOLONE ACETONIDE	SODIUM CHLORIDE 0.9% SUCRALFATE ZELNORM TETRACYCLINE NEURORUBINE TORTE VITAMIN E AZMACORT KENALOG NASACORT NASACORT AQ NASACORT PRN TRIAMCINOLONE CREAM TRIAMCINOLONE OINT. TRIAMCINOLONE OINTMENT VITAMIN B B COMPLEX VITAMIN D FLINSTONE KIDS VITAMINS MULT-VITAMIN MULTI VITAMIN MULTI-VITAMIN MULTI-VITAMINS MULTIVITAMIN MULTIVITAMIN (WHOLE FOODS) MULTIVITAMINS VITAMIN SUPPLEMENT ZICAM (ZINC) ZINC ZINC LOZENGE COLDEEZE ZICAM (ZINC GLUCONICUM)
	VITAMIN B NOS VITAMIN B SUBSTANCES NOS VITAMIN D NOS VITAMINS NOS	
	ZINC	
	ZINC GLUCONATE	

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Table 6.20
Relationship of Medication Class, Dictionary Term and Verbatim Text

ATC Level 1	Ingredient(s)	Verbatim Text
ANTIINFECTIVES FOR SYSTEMIC USE	ACYCLOVIR	ACYCLOVIR (TOPICAL) ZOVIRAX
	AMOXICILLIN	AMOXICILLIN AMOXICILLIN CAPS AMOXIL AMOXIL-500MG AMOXYL AUGMENTIN
	AMOXICILLIN TRIHYDRATE+CLAVULANATE	
	POTASSIUM	
	AMPICILLIN	AMPICILLIN
	AZITHROMYCIN	AZITHROMYCIN AZITROMICIN Z PAK Z-PAK ZITHROMAX ZITHROMAX X2 ZITHROMAX Z PAK ZITHROMYCIN ZMAX ZPAK
	BENZYL PENICILLIN	PENICILLIN PENICILLIN (ORAL) PENICILLIN IM X-PEN
	CEFACLOX	CECLOX
	CEFADROXIL	DURICEF
	CEFALEXIN	CEFALEXIN CEPHALEXIN KEFLEX
	CEFDINIR	OMNICEF
	CEFOTAXIME SODIUM	CLAFORAN
	CEFPROZIL	CEFZIL
	CIPROFLOXACIN HYDROCHLORIDE	CIPRO
	CLARITHROMYCIN	BIAXIN

Table 6.20
Relationship of Medication Class, Dictionary Term and Verbatim Text

ATC Level 1	Ingredient(s)	Verbatim Text
ANTIINFECTIVES FOR SYSTEMIC USE	CLARITHROMYCIN	BIAXIN XL
	CLINDAMYCIN	CLINDAMYCIN
	DICLOXACILLIN	DICLOXACILIN
	DOXYCYCLINE	DIOXYCYCLIN
		DOXYCYCLINE
		DOXYCYLINE
	DOXYCYCLINE HYCLATE	DOXYCYCLINE HYCLATE
	DOXYCYCLINE HYDROCHLORIDE	DOXYCYCLINE HCL
	ERYTHROMYCIN	ERYTHROMYCIN
		PANTOMICINA
	FAMCICLOVIR	FAMVIR
	FLUCONAZOLE	DIFLUCAN
		FLUCONAZOLE
	FURADONINE	MACROBID
		NITROFURANTOIN
	GATIFLOXACIN	TEQUIN
		ZYMAR
	INFLUENZA VACCINE	FLU VACCINE
		INFLUENZA VACCINE
	INFLUENZA VIRUS VACCINE INACTIVATED	FLUZONE
	KETOCONAZOLE	KETACONAZONE
	LEVOFLOXACIN	LEVAQUIN
		LEVOQUIN
	METRONIDAZOLE	AMOBIN
		METROGEL
		METRONIDAZOLE
	MICONAZOLE NITRATE	MONISTAT
	MINOCYCLINE	MINOCYCLIN
		MINOCYCLINE
	MINOCYCLINE HYDROCHLORIDE	DYNACIN
	MOXIFLOXACIN	AVELOX
	MOXIFLOXACIN HYDROCHLORIDE	VIGAMOX
	OSELTAMIVIR PHOSPHATE	TAMIFLU
	PHENOXYMETHYLPENICILLIN POTASSIUM	PCN VK

Table 6.20
Relationship of Medication Class, Dictionary Term and Verbatim Text

ATC Level 1	Ingredient(s)	Verbatim Text
ANTIINFECTIVES FOR SYSTEMIC USE	SULFAMETHOXAZOLE+TRIMETHOPRIM	BACTRIN COTRIM SEPTRIN TRIMETHOPRIM-SULFAMETHOXAZOLE
	TELITHROMYCIN	KETEC KETEK
	TETANUS TOXOID+DIPHTHERIA TOXOID	DIPHTHERIA TETANUS SHOT
	TETRACYCLINE	TETRACYCLINE
	VALACICLOVIR	VALACYCLOVIR
	VALACICLOVIR HYDROCHLORIDE	VALTREX
ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	ESTRADIOL	CLIMARA
	ESTROGENS CONJUGATED	PREMARIN
	IMMUNOTHERAPY{NOS}	IMMUNOTHERAPY
	INFLIXIMAB	REMICADE
	LEUPRORELIN ACETATE	LUPRON
	MEDROXYPROGESTERONE	MEDROXY PROGESTERONE
	MEDROXYPROGESTERONE ACETATE	DEPO PROVERA DEPOPROVERA MEDROXYPROGESTERONE ACETATE PROVERA
ANTIPARASITIC PRODUCTS, INSECTICIDES AND REPELLENT	ALBENDAZOLE	ABZ (ALBENDAZOLE)
	AMODIAQUINE	MALARATAB
	LUMEFANTRINE+ARTEMETHER	COARTEM
	METRONIDAZOLE	AMOBIN METROGEL METRONIDAZOLE
	PYRIMETHAMINE+SULFADOXINE	FALCIDIN FANSIDAR FANSIMAX

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Table 6.20
Relationship of Medication Class, Dictionary Term and Verbatim Text

ATC Level 1	Ingredient(s)	Verbatim Text
BLOOD AND BLOOD FORMING ORGANS	ACETYLSALICYLIC ACID	ASA
		ASAPRIN
		ASPIRIN
		ASPIRIN PRN
		ASPIRINA
		ASPRIN
		BABY ASPRIN
		BAYER ASPIRIN
		BUFFERIN
		EQUATE CHILDREN'S ASPIRIN
		ST. JOSEPH LOW DOSE 81MG
	ASCORBIC ACID+FERROUS FUMARATE+FOLIC ACID+CYANOCOBALAMIN+CALCIUM ASCORBATE+SUCCINIC ACID+IRON BISGLY ASCORBIC ACID+IRON BROMELAINS CETYLPYRIDINIUM CHLORIDE	ASPIRIN
		ST. JOSEPH'S ASPIRIN
		REPLIVA
		IRON WITH VITAMIN C
		BROMELAIN
	CYANOCOBALAMIN EPINEPHRINE FERROUS SULPHATE IRON	MEROCET LOZENGES
		MEROCET THROAT LOZENGES
		B-12
		VITAMIN B12
		PRIMATENE MIST
IRON+CALCIUM POTASSIUM CHLORIDE	POTASSIUM NOS SODIUM BICARBONATE SODIUM CHLORIDE	FERROUS SULFATE
		IRON
		IRON SUPPLEMENT
		IRON WITH CALCIUM
		K-DAR
		K-DUR
		POTASSIUM CHLORIDE
		POTASSIUM
		ENO
		AFRIN SALINE
		NASAL SALINE

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Table 6.20
Relationship of Medication Class, Dictionary Term and Verbatim Text

ATC Level 1	Ingredient(s)	Verbatim Text
BLOOD AND BLOOD FORMING ORGANS	SODIUM CHLORIDE	NASAL SALINE SPRAY OCEAN SPRAY SALINE NASAL SPRAY SODIUM CHLORIDE 0.9% TYROSINE
	TYROSINE	
CARDIOVASCULAR SYSTEM	ACETAZOLAMIDE	DIAMOX (500 MG-PRN) DIAMOX (500MG QD)
	AMLODIPINE BESILATE	NORVASC
	ATENOLOL	ATENOLOL PREVENTIL 90 MCG
	ATORVASTATIN CALCIUM	LIPITOR
	BENAZEPRIL HYDROCHLORIDE	LOTENSIN
	BENAZEPRIL HYDROCHLORIDE+AMLODIPINE BESILATE	(GEN.) LOTREL
		LOTREL
	BENZOCAINE	BENZOCAINE EAR DROPS
	BETAMETHASONE	BETAMETHASONE
	BETAMETHASONE DIPROPIONATE	DIPROLENE
	CANDESARTAN CILEXETIL	ATACAND
	CAPTOPRIL	CAPOTEN
	CLONIDINE	CLONODINE
	DEXAMETHASONE	DECADRON
	DIGOXIN	LANOXIN
	DILTIAZEM	DILTIAZEM
	DILTIAZEM HYDROCHLORIDE	CARDIZEM TIAZAC
	DOXAZOSIN MESILATE	DOXAZOSIN MESYLATE
	ENALAPRIL	ENALAPRIL
	EPINEPHRINE	PRIMATENE MIST
	EZETIMIBE	ZEITA ZETIA
	FISH OIL	FISH OIL
	FUROSEMIDE	FUROSEMIDE

Table 6.20
Relationship of Medication Class, Dictionary Term and Verbatim Text

ATC Level 1	Ingredient(s)	Verbatim Text
CARDIOVASCULAR SYSTEM	FUROSEMIDE	LASIX
	GINKGO BILOBA	GINKOBA
	HYDROCHLOROTHIAZIDE	HCTZ
		HYDROCHLORATHIAZIDE
		HYDROCHLOROTHIAZIDE
		HYDROCHLORTHIAZIDE
		HYDROCLOROTHIAZIDE
	HYDROCHLOROTHIAZIDE+CANDESARTAN CILEXETIL	ATACAND HCT
	HYDROCHLOROTHIAZIDE+LOSARTAN POTASSIUM	HYZAAR
	HYDROCHLOROTHIAZIDE+VALSARTAN	DIOVAN HCT
	HYDROCORTISONE	HYDROCORTISONE CREAM
	INDAPAMIDE	LOZOL
	INDOMETACIN	INDOCID
	ISRADIPINE	DYNA CIRC CR
	LIDOCAINE	LIDOCAINE
		XYLOCAINE
	LISINOPRIL	LISINOPRIL
		ZESTRIL
	LOSARTAN POTASSIUM	COZAAR
	LOVASTATIN	LOVASTATIN
	NICOTINIC ACID	NIACIN
	OLMESARTAN	BENICAR
	PHENOL	CHLORASEPTIC SPRAY WITH PHENOL
		CHLORACEPTIC SPRAY
		CHLORASEPTIC SPRAY
	PHENYLEPHRINE HYDROCHLORIDE	NEOSYNEPHRINE
		SUDAFED PE MAXIMUM STRENGTH
	PROCAINE HYDROCHLORIDE	NOVACAINE
	QUINAPRIL	ACCUPRIL
	RAMIPRIL	ALTACE
	SIMVASTATIN	ZOCOR
	SIMVASTATIN+EZETIMIBE	VYTORIN
	SPIRONOLACTONE	SPIRONOLACTENE

Table 6.20
Relationship of Medication Class, Dictionary Term and Verbatim Text

ATC Level 1	Ingredient(s)	Verbatim Text
CARDIOVASCULAR SYSTEM	SPIRONOLACTONE	SPIRONOLACTONE
	TRIAMTERENE	TRIAMTERENE
	TRIAMTERENE+HYDROCHLOROTHIAZIDE	DYAZIDE
		TRIAMTERENE HCTZ
	VALSARTAN	DIOVAN
	VERAPAMIL	VERAPAMIL
	VERAPAMIL HYDROCHLORIDE	COVERA
DERMATOLOGICALS	ACYCLOVIR	ACYCLOVIR (TOPICAL)
		ZOVIRAX
	ADAPALENE	DIFFERIN
	AZELAIC ACID	FINACEA
	BECLOMETASONE DIPROPIONATE	BECLATE AQUNASE
		BECLATE NASAL SPRAY
		BECONASE PRN
		DECOMIT
	BENADRYL (NOS)	BENADRYL
		BENADRYL CREAM
		BENADRYL PRN
		BENEDRYL
	BENZOCAINE	BENZOCAINE EAR DROPS
	BETAMETHASONE	BETAMETHASONE
	BETAMETHASONE DIPROPIONATE	DIPROLENE
	BUDESONIDE	NASOCORT
		PULMICORT
		RHINOCORT AQ
		RHINOCORT AQUA
	CALAMINE+PRAMOCAINE HYDROCHLORIDE	CALADRYL LOTION
	CETYLPIRIDINIUM CHLORIDE	MEROCET LOZENGES
		MEROCET THROAT LOZENGES
	CLEMASTINE FUMARATE	TAVIST
		TAVIST PRN
	CLINDAMYCIN	CLINDAMYCIN
	CLOBETASOL	CLOBETASOL

Table 6.20
Relationship of Medication Class, Dictionary Term and Verbatim Text

ATC Level 1	Ingredient(s)	Verbatim Text
DERMATOLOGICALS	CLOBETASOL	CLOBETASOL
	CLOTRIMAZOLE	CANDID V6 PESSANES CLORTRIMAZOLE
	DESONIDE	DESONIDE
	DESOXIMETASONE	TOPICORT
	DEXAMETHASONE	DECADRON
	DIPHENHYDRAMINE	DIPHENHYDRAMINE
	DIPHENHYDRAMINE HYDROCHLORIDE	TRICOHIST BENADRYL ALLERGY DIPHEDRYL SIMPLY SLEEP WAL-DRYL ALLERGY
	EMOLLIENTS AND PROTECTIVES	ALOE VESTA
	ERYTHROMYCIN	CETAPHIL SOAP ERYTHROMYCIN
	EUCERIN (NOS)	PANTOMICINA
	FINASTERIDE	EUCERIN CREAM
	FLUCONAZOLE	PROPECIA
	FLUTICASONE PROPIONATE	DIFLUCAN FLUCONAZOLE FLONASE FLONASE NASAL FLOVENT FLOVENT 110 MCG
	HYDROCORTISONE	HYDROCORTISONE CREAM
	IODINE	IODINE
	KETOCONAZOLE	KETACONAZONE
	LIDOCAINE	LIDOCAINE XYLOCAINE
	METHYLPREDNISOLONE	MEDROL MEDROL DOSE PACK MEJORAL (ACETYLSALICYLIC ACID) MEJOROL (ACETYLSALICYLIC ACID) METHYLPREDNISOLONE

Table 6.20
Relationship of Medication Class, Dictionary Term and Verbatim Text

ATC Level 1	Ingredient(s)	Verbatim Text
DERMATOLOGICALS	METHYLPREDNISOLONE	METHYLPREDNISOLONE DOSE PAK METHYLPREDNISONE
	METHYLPREDNISOLONE ACETATE	DEPOMEDROL INJ.
	METRONIDAZOLE	AMOBIN METROGEL METRONIDAZOLE
	MICONAZOLE NITRATE	MONISTAT
	MOMETASONE FUROATE	ELOCON ELOCON CREAM NASONEX NASONEX PRN
	NEOMYCIN SULFATE+POLYMYXIN B SULFATE+BACITRACIN ZINC	NEOSPORIN OINTMENT
	OXICONAZOLE NITRATE	OXISTAT 1% CREAM
	PARAFFIN SOFT	VASELINE
	PHENOL	CHLORASEPTIC SPRAY WITH PHENOL
	PROMETHAZINE	CHLORACEPTIC SPRAY CHLORASEPTIC SPRAY PHENEGRON PHENERGAN PHENERGAN 25 PROMETHASINE PROMETHAZINE PROMETHAZINE SUPPOSITORIES TRICOHIST
	RETINOL PALMITATE	AVITA (RETINOL PALMITATE)
	RHINOCORT (NOS)	RHINOCORT RHINOCORT PRN
	SALICYLIC ACID	SALEX
	SULFACETAMIDE SODIUM+SULFUR	PLEXION CLEANSER
	TERBINAFINE HYDROCHLORIDE	LAMISIL
	TETRACYCLINE	TETRACYCLINE
	TOCOPHEROL	VITAMIN E

Table 6.20
Relationship of Medication Class, Dictionary Term and Verbatim Text

ATC Level 1	Ingredient(s)	Verbatim Text
DERMATOLOGICALS	TRIAMCINOLONE ACETONIDE	AZMACORT KENALOG NASACORT NASACORT AQ NASACORT PRN TRIAMCINOLONE CREAM TRIAMCINOLONE OINT. TRIAMCINOLONE OINTMENT
GENITO URINARY SYSTEM AND SEX HORMONES	ACETIC ACID	APPLE CIDER VINEGAR SUPPLEMENT
	ACETYLSALICYLIC ACID+CAFFEINE+CINNAMEDRINE HYDROCHLORIDE	MIDOL
	CABERGOLINE	DOSTINEX
	CLINDAMYCIN	CLINDAMYCIN
	CLOTRIMAZOLE	CANDID V6 PESSANES CLORTRIMAZOLE
	DIMETHYL SULFONE	MSM
	ESTRADIOL	CLIMARA
	ESTROGENS CONJUGATED	PREMARIN
	ESTROGENS CONJUGATED+MEDROXYPROGESTERONE ACETATE	PREM PRO
	ETHINYLOESTRADIOL+DESOGESTREL	PREMPHASE PREMPRO APRI TAB KARIVA MIRCETTE ORTHO-CEPT GENERIC ORTHOCEPT
	ETHINYLOESTRADIOL+DROSPIRENONE	YASMIN YASMIN 28 YASMINE
	ETHINYLOESTRADIOL+ETONOGESTREL	NEUVO-RING
	ETHINYLOESTRADIOL+ETYNODIOL DIACETATE	DEMULEN

Table 6.20
Relationship of Medication Class, Dictionary Term and Verbatim Text

ATC Level 1	Ingredient(s)	Verbatim Text
GENITO URINARY SYSTEM AND SEX HORMONES	ETHINYLOESTRADIOL+ETYNODIOL DIACETATE	ZOVIA
	ETHINYLOESTRADIOL+FERROUS FUMARATE+NORETHISTERONE ACETATE	LOESTRIN FE
	ETHINYLOESTRADIOL+LEVONORGESTREL	ALESSE AVIANE LEVLEN LEVORA SEASONALE
	ETHINYLOESTRADIOL+NORELGESTROMIN	ORTHO EVRA ORTHO EVRA PATCH ORTHO EVRA PATCHES ORTHO EVRA-PATCH ORTHOEVRA PATCH
	ETHINYLOESTRADIOL+NORETHISTERONE	ORTHO NOVUM 777 OVCON 35 OVCON-50
	ETHINYLOESTRADIOL+NORETHISTERONE ACETATE	LOESTRIN MICROGESTIN
	ETHINYLOESTRADIOL+NORGESTIMATE	ORTHO TRI CYCLEN ORTHO TRI CYCLENE ORTHO TRI-CYCLEN LO ORTHO-TRICYCLEN ORTHO-TRICYCLINE ORTHOCYCLIN ORTHOTRICYCLEN ORTHOTRICYCLEN LO ORTHOTRICYCLINE TRICYCLEN
	ETHINYLOESTRADIOL+NORGESTREL	LO OVRAL LO-OVRAL 28 LO/OVRAL LOOVRAL
	FENOTEROL	FENOTEROL

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Table 6.20
Relationship of Medication Class, Dictionary Term and Verbatim Text

ATC Level 1	Ingredient(s)	Verbatim Text
GENITO URINARY SYSTEM AND SEX HORMONES	FINASTERIDE	PROPECIA
	FURADONINE	MACROBID
	IBUPROFEN	NITROFURANTOIN
		IBUPROFEN
		ADVIL
		ADVIL GEL CAPSULES
		ADVIL MIGRAINE
		ADVIL PRN
		BRUFEN
		IBUPROFEN
		IBUPROFEN (MOTRIN)
		IBUPROFEN PRN
		IBUPROFENO
		IBUPROFIN
		IBUPROPHEN
		MOTRIN
		MOTRIN IB
		MOTRIN IB PRN
		MOTRIN PRN
		KETACONAZONE
	KETOCONAZOLE	MEDROXY PROGESTERONE
	MEDROXYPROGESTERONE	DEPO PROVERA
	MEDROXYPROGESTERONE ACETATE	DEPOPROVERA
		MEDROXYPROGESTERONE ACETATE
	METHYLTESTOSTERONE+ESTROGENS ESTERIFIED	PROVERA
		ESTRA TEST
		ESTRATEST
	METRONIDAZOLE	AMOBIN
		METROGEL
		METRONIDAZOLE
		MONISTAT
		NAPROSYN
	MICONAZOLE NITRATE	NAPROXEN
	NAPROXEN	

Table 6.20
Relationship of Medication Class, Dictionary Term and Verbatim Text

ATC Level 1	Ingredient(s)	Verbatim Text
GENITO URINARY SYSTEM AND SEX HORMONES	NAPROXEN	NAPROXIN
	NAPROXEN SODIUM	ALEVE ALLEVE APRONAX
	NORETHISTERONE+MESTRANOL	ORTHO-NOVUM ORTHONOVUM
	OXICONAZOLE NITRATE	OXISTAT 1% CREAM
	OXYBUTYNIN HYDROCHLORIDE	DITROPAN XL
	PHENAZOPYRIDINE HYDROCHLORIDE	URISTAT
	PROGESTERONE	PROGESTERONE PROMETRIUM
	SOLIFENACIN SUCCINATE	VESICARE
	TOLTERODINE TARTRATE	DETROL LA
MUSCULO-SKELETAL SYSTEM	ALENDRONATE SODIUM	FOSAMAX
	ALLOPURINOL	ALLOPURINOL
	CARISOPRODOL	SOMA
	CELECOXIB	CELEBREX CELECOXIB
	CHONDROITIN+GLUCOSAMINE	CHONDROITIN GLUCOSAMINE
	CYCLOBENZAPRINE	CYCLOBENZAPRINE
	CYCLOBENZAPRINE HYDROCHLORIDE	FLEXARIL FLEXERIL
	DICLOFENAC	DICLOFENAC DICLOFENACO
	DIMETHYL SULFONE	MSM
	ETODOLAC	ETODOLAC
		LODINE
	GLUCOSAMINE	GLUCOSAMINE
	GLUCOSAMINE SULFATE	GLUCOSAMINE SULFATE
	IBUPROFEN	IBUPROFEN ADVIL ADVIL GEL CAPSULES

Table 6.20
Relationship of Medication Class, Dictionary Term and Verbatim Text

ATC Level 1	Ingredient(s)	Verbatim Text
MUSCULO-SKELETAL SYSTEM	IBUPROFEN	ADVIL MIGRAINE ADVIL PRN BRUFEN IBUPROFEN IBUPROFEN (MOTRIN) IBUPROFEN PRN IBUPROFENO IBUPROFIN IBUPROPHEN MOTRIN MOTRIN IB MOTRIN IB PRN MOTRIN PRN INDOCID ORUDIS KT KETOROLAC TORADOL TORADOL (IV) TORADOL (ORAL) TORADOL IV MEFENAMIC ACID TANSTON MELOXICAM MOBIC SKELAXIN NAPROSYN NAPROXEN NAPROXIN ALEVE ALLEVE APRONAX NISE (NIMESULIDE) ORPHENADRINE DAYPRO
	INDOMETACIN	
	KETOPROFEN	
	KETOROLAC	
	KETOROLAC TROMETAMOL	
	MEFENAMIC ACID	
	MELOXICAM	
	METAXALONE	
	NAPROXEN	
	NAPROXEN SODIUM	
	NIMESULIDE	
	ORPHENADRINE	
	OXAPROZIN	

Table 6.20
Relationship of Medication Class, Dictionary Term and Verbatim Text

ATC Level 1	Ingredient(s)	Verbatim Text
MUSCULO-SKELETAL SYSTEM	PIROXICAM	ACTION FELDENE FLASH
	PSEUDOEPHEDRINE+IBUPROFEN	ADVIL COLD & FLU ADVIL SINUS MOTRIN COLD
	PSEUDOEPHEDRINE+NAPROXEN	ALEVE COLD & SINUS ALEVE COLD AND SINUS ALEVE SINUS & HEADACHE ALEVE SINUS HEADACHE
	ROFECOXIB	VIOXX
	SODIUM IBANDRONATE	BONIVA
	TIZANIDINE	TIZANIDINE
	VALDECOXIB	BEXTRA
NERVOUS SYSTEM	ACETYLSALICYLIC ACID	ASA ASAPRIN ASPIRIN ASPIRIN PRN ASPIRINA ASPRIN BABY ASPRIN BAYER ASPIRIN BUFFERIN EQUATE CHILDREN'S ASPIRIN ST. JOSEPH LOW DOSE 81MG ASPIRIN ST. JOSEPH'S ASPIRIN
	ACETYLSALICYLIC ACID+CAFFEINE+CINNAMEDRINE HYDROCHLORIDE	MIDOL
	ACETYLSALICYLIC ACID+CAFFEINE+SALICYLAMIDE	BC POWDER BC POWDER PRN
	ACETYLSALICYLIC ACID+CHLORPHENAMINE MALEATE+PHENYLPROPANOLAMINE BITARTRATE	ALKA SELTZER COLD PLUS
	ACETYLSALICYLIC ACID+OXYCODONE	PERCODAN

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Table 6.20
Relationship of Medication Class, Dictionary Term and Verbatim Text

ATC Level 1	Ingredient(s)	Verbatim Text
NERVOUS SYSTEM	ACETYLSALICYLIC ACID+PARACETAMOL ACETYLSALICYLIC ACID+PARACETAMOL+CAFFEINE	GOODY'S BODY PAIN EXCEDRIN (ACETAMINOPHEN + ASPIRIN + CAFFEINE) EXCEDRIN MIGRAINE EXCEDRINE MIGRAINE EXCEDRIN (ACETAMINOPHEN/ASPIRIN/CAFFEIN E) GOODY POWDER MARA MOJA MIGRAINE EXCEDRINE ALKA SELTZER
	ACETYLSALICYLIC ACID+SODIUM BICARBONATE+CITRIC ACID	ALKA-SELTZER ALLERGY ALKASELTZER ALPRAZOLAM XANAX ADDERALL
	ALPRAZOLAM	
	AMFETAMINE SULFATE+AMFETAMINE ASPARTATE+DEXAMFETAMINE SULFATE+DEXTROAMPHETAMINE SACCHARATE AMITRIPTYLINE	AMITRIPTYLINE TRYPTIZOL GENERAL ANESTHESIA BENZOCAINE EAR DROPS MARCAINE WELLBUTRIN WELLBUTRIN XL BUSPAR BUSPAR 10MG STADOL DOSTINEX GREEN TEA CHLORASEPTIC CELEXA
	ANAESTHETICS, GENERAL BENZOCAINE BUPIVACAINE HYDROCHLORIDE BUPROPION HYDROCHLORIDE	
	BUSPIRONE HYDROCHLORIDE	
	BUTORPHANOL TARTRATE CABERGOLINE CAMELLIA SINENSIS CHLORASEPTIC (NOS) CITALOPRAM HYDROBROMIDE	

Table 6.20
Relationship of Medication Class, Dictionary Term and Verbatim Text

ATC Level 1	Ingredient(s)	Verbatim Text
NERVOUS SYSTEM	CLONAZEPAM	KLONOPIN
	CLONIDINE	CLONODINE
	CODEINE PHOSPHATE+PARACETAMOL	TYLENOL WITH CODEINE
	CYCLOBENZAPRINE	CYCLOBENZAPRINE
	CYCLOBENZAPRINE HYDROCHLORIDE	FLEXARIL
		FLEXERIL
	DEXTROPROPOXYPHENE NAPSILATE+PARACETAMOL	DARVACET
		DARVOCET
		DARVOCET-N
	DIAZEPAM	VALIUM
	DIHYDROERGOTAMINE	TONOPAN
	MESILATE+CAFFEINE+PROPYPHENAZONE	
	DIPHENHYDRAMINE HYDROCHLORIDE+PARACETAMOL	TYLENOL PM
		TYLENOL PM (PRN)
		TYLENOL PM PRN
	DIPHENHYDRAMINE+PARACETAMOL	EXCEDRIN PM
	DROPERIDOL	DROPERIDOL
	DULOXETINE HYDROCHLORIDE	CYMBALTA
	DYCLONINE HYDROCHLORIDE	CEPACOL THROAT SPRAY
	ELETRIPTAN HYDROBROMIDE	RELPAK
	EPINEPHRINE BITARTRATE+PRILOCAINE	CITANEST FORTE 4%
	HYDROCHLORIDE	
	ERGOTAMINE TARTRATE+CAFFEINE	CAFERGOT
	ESCITALOPRAM OXALATE	LEXAPRO
	ESZOPICLONE	LUNESTA
	EXCEDRIN (NOS)	EXCEDRIN
		EXCEDRINE
		EXEDRIN
		EXEDRIN PRN
	FENTANYL	FENTANYL
	FIORINAL NOS	FIORINAL
	FLUOXETINE	FLUOXATINE
		FLUOXETINE
	FLUOXETINE HYDROCHLORIDE	PROZAC

Table 6.20
Relationship of Medication Class, Dictionary Term and Verbatim Text

ATC Level 1	Ingredient(s)	Verbatim Text
NERVOUS SYSTEM	FLUOXETINE HYDROCHLORIDE	SERAFEM
	FLUVOXAMINE MALEATE	LUVOX
	GABAPENTIN	GABAPENTIN
		NEURONTIN
	GINKGO BILOBA	GINKOBA
	HYDROCODONE	HYDROCODONE
		HYDROCODONE 500 MG
	HYDROMORPHONE HYDROCHLORIDE	DILAUDID
	HYDROXYZINE	HYDROXYZINE
	HYDROXYZINE HYDROCHLORIDE	HYDROXYZINE HCL
	IBUPROFEN	IBUPROFEN
		ADVIL
		ADVIL GEL CAPSULES
		ADVIL MIGRAINE
		ADVIL PRN
		BRUFEN
		IBUPROFEN
		IBUPROFEN (MOTRIN)
		IBUPROFEN PRN
		IBUPROFENO
		IBUPROFIN
		IBUPROPHEN
		MOTRIN
		MOTRIN IB
		MOTRIN IB PRN
		MOTRIN PRN
	KETAMINE	KETAMINE
	KETOROLAC TROMETAMOL	TORADOL
		TORADOL (IV)
		TORADOL (ORAL)
		TORADOL IV
	LAMOTRIGINE	LAMICTAL
	LIDOCAINE	LIDOCAINE
		XYLOCAINE

Table 6.20
Relationship of Medication Class, Dictionary Term and Verbatim Text

ATC Level 1	Ingredient(s)	Verbatim Text
NERVOUS SYSTEM	MAGNESIUM SALICYLATE	DOAN'S PILLS
	MEFENAMIC ACID	MEFENAMIC ACID
		TANSTON
	METHYLPHENIDATE HYDROCHLORIDE	CONCERTA
		METHYLPHENIDATE HCL
		RITALIN
	MIDAZOLAM	IV VERSED
		MIDAZOLAM
		VERSED
	MIRTAZAPINE	REMERON
	MORPHINE	MORPHINE
	NALBUPHINE HYDROCHLORIDE	NUBAIN
	NARATRIPTAN HYDROCHLORIDE	AMERGE
	NORTRIPTYLINE	NORTRIPTYLINE
	ORPHENADRINE	ORPHENADRINE
	OXYCODONE	OXYCODONE
	PARACETAMOL	(ACETAMINOPHEN) TYLENOL
		ACETAMINOPHEN
		EXTRA STRENGTH TYLENOL
		HEDEX
		PANACE TAMOL
		PANADOL
		PARACETAMOL
		PARACETAMOL SHOTS
		PARACETANOL
		PARACETOMOL
		TYLENOL
		TYLENOL 500 MG
		TYLENOL EX
		TYLENOL EX PRN
		TYLENOL EXTRA STRENGTH
		TYLENOL PRN
	PARACETAMOL+CAFFEINE	EXCEDRIN TENSION
		EXCEDRIN TENSION HEADACHE

Table 6.20
Relationship of Medication Class, Dictionary Term and Verbatim Text

ATC Level 1	Ingredient(s)	Verbatim Text
NERVOUS SYSTEM	PARACETAMOL+CAFFEINE+BUTALBITAL	ESGIC FIORICET
	PARACETAMOL+CAFFEINE+SALICYLAMIDE+PHENYLTOL OXAMINE	DURABAC
	PARACETAMOL+CHLORPHENAMINE MALEATE+PHENYLEPHRINE HYDROCHLORIDE	ALKA SELTZER PLUS
	PARACETAMOL+CHLORPHENAMINE MALEATE+PSEUDOEPHEDRINE HYDROCHLORIDE	ALKA SELTZER COLD
		ALLERGY SINUS DAY FLU (CHLORPHENAMINE + PARACETAMOL + PSEUDOEPHEDRINE HYDROCHLORIDE) THERA FLU THERA-FLU THERAFLU THERAFLU COLD THERMA FLU TYLENOL ALLERGY & SINUS TYLENOL ALLERGY COMPLETE TYLENOL ALLERGY SINUS TYLENOL ALLERGY/SINUS TYLENOL SINUS AND ALLERGY
	PARACETAMOL+DICHLORALPHENAZONE+ISOMETHEPTEN E MUCATE	MIDRIN
	PARACETAMOL+HYDROCODONE PARACETAMOL+HYDROCODONE BITARTRATE	HYDROCODONE + APAP LORTAB LORTAB PRN VICODEN VICODIN
	PARACETAMOL+MEPYRAMINE MALEATE+PAMABROM PARACETAMOL+OXYCODONE HYDROCHLORIDE PARACETAMOL+PHENYLTOLOXAMINE PARACETAMOL+TRAMADOL HYDROCHLORIDE	PAMPRIN PERCOCET RHINOFLEX ULTRACET ULTRASET

Table 6.20
Relationship of Medication Class, Dictionary Term and Verbatim Text

ATC Level 1	Ingredient(s)	Verbatim Text
NERVOUS SYSTEM	PAROXETINE PAROXETINE HYDROCHLORIDE PETHIDINE PETHIDINE HYDROCHLORIDE PHENOBARBITAL+ERGOTAMINE TARTRATE+ATROPA BELLADONNA PHENOL PRILOCAINE PROCAINE HYDROCHLORIDE PROMETHAZINE QUETIAPINE FUMARATE RIZATRIPTAN BENZOATE SERTRALINE HYDROCHLORIDE SUMATRIPTAN TEMAZEPAM TOPIRAMATE TRAMADOL TRAMADOL HYDROCHLORIDE TRAZODONE TYLENOL #3 (NOS)	PAROXETINE PAXIL MEPERIDINE DEMEROL (IV) IV DEMEROL BELLAMINE-S CHLORASEPTIC SPRAY WITH PHENOL CHLORACEPTIC SPRAY CHLORASEPTIC SPRAY PRILOCAINE NOVACAINE PHENEGRON PHENERGAN PHENERGAN 25 PROMETHASINE PROMETHAZINE PROMETHAZINE SUPPOSITORIES TRICOHIST SEROQUEL MAXALT ZOLOFT IMITREX IMITREX NASAL SPRAY IMITREX TABS RESTORIL TAMAZEPAM TOPAMAX TRAMADOL TRAMADOL PRN ULTRAM TRAZADONE TYLENOL # 3

Table 6.20
Relationship of Medication Class, Dictionary Term and Verbatim Text

ATC Level 1	Ingredient(s)	Verbatim Text
NERVOUS SYSTEM	TYLENOL #3 (NOS)	TYLENOL #3 TYLENOL 3
	UNISOM NOS	UNISOM
	VALPROIC ACID	DEPAKOTE
	VENLAFAXINE HYDROCHLORIDE	EFFEXOR
	ZALEPLON	SONATA
	ZIPRASIDONE HYDROCHLORIDE	GEODON
	ZOLMITRIPTAN	ZOMIG
	ZOLPIDEM TARTRATE	AMBIEN
RESPIRATORY SYSTEM	ACETYLSALICYLIC ACID+CHLORPHENAMINE MALEATE+PHENYLPROPANOLAMINE BITARTRATE	ALKA SELTZER COLD PLUS
	AMBROXOL HYDROCHLORIDE	MUCOSOLVAN
	AMINOPHYLLINE	AMINOPHYLLINE
	AZELASTINE HYDROCHLORIDE	ASTELIN ASTELIN (PRN) ASTELIN NASAL
		OPTIVAR OPTIVAR OPHTHALMIC SOLUTION OPTIVAR SOLUTION 0.05% PRN
	BECLOMETASONE DIPROPIONATE	BECLATE AQUNASE BECLATE NASAL SPRAY BECONASE PRN
		DECOMIT
	BENADRYL (NOS)	BENADRYL BENADRYL CREAM BENADRYL PRN
		BENEDRYL
	BENZOCAINE	BENZOCAINE EAR DROPS
	BENZOCAINE+CETYLPYRIDINIUM CHLORIDE	MEROCAINE LOZENGE
	BENZONATATE	BENZONATATE
		TESSALON PERLES
	BETAMETHASONE	BETAMETHASONE
	BETAMETHASONE DIPROPIONATE	DIPROLENE

Table 6.20
Relationship of Medication Class, Dictionary Term and Verbatim Text

ATC Level 1	Ingredient(s)	Verbatim Text
RESPIRATORY SYSTEM	BETAMETHASONE DIPROPIONATE+SALBUTAMOL BETAMETHASONE+CHLORPHENAMINE MALEATE BROMHEXINE HYDROCHLORIDE+GUAIFENESIN+SALBUTAMOL SULFATE+LEVOMENTHOL BROMPHENIRAMINE BUDESONIDE	AEROCORT CELESTAMINE ASCORIL EXPECTORANT
	CAMPHOR+LEVOMENTHOL+EUCALYPTUS GLOBULUS OIL CARBINOXAMINE MALEATE CERTUSS (NOS) CETIRIZINE CETIRIZINE HYDROCHLORIDE	BROVEX NASOCORT PULMICORT RHINOCORT AQ RHINOCORT AQUA VICKS VAPORUB CREAM PALGIC CERTUSS (NOS) CETIRIZINE CETIRIZINE HYDROCHLORIDE CETRIZET CETRIZET 10MG ZRYTEC ZRYTEC ZRYTEC 10MG PRN MERO CET LOZENGES MERO CET THROAT LOZENGES CHLORPHENIRAMINE CLORFENAMINE PIRITON PIRITON 4MG STORE BRAND ANTIHISTAMINE CHIOR-TRIMETON CHLORTABS CHLORTRIMETON TRIAMINIC COLD
	CETYLPYRIDINIUM CHLORIDE	
	CHLORPHENAMINE	
	CHLORPHENAMINE MALEATE	
	CHLORPHENAMINE MALEATE+PHENYLPROPANOLAMINE HYDROCHLORIDE CHLORPHENAMINE MALEATE+PSEUDOEPHEDRINE HYDROCHLORIDE	DECONAMINE

Table 6.20
Relationship of Medication Class, Dictionary Term and Verbatim Text

ATC Level 1	Ingredient(s)	Verbatim Text
RESPIRATORY SYSTEM	CHLORPHENAMINE MALEATE+PSEUDOEPHEDRINE HYDROCHLORIDE	HISTEX
	CHLORPHENAMINE MALEATE+PSEUDOEPHEDRINE HYDROCHLORIDE+IBUPROFEN	SUDAFED ALLERGY SINUS ADVIL MULTI SYMPTOM COLD CAPLETS
	CHLORPHENAMINE TANNATE	CHLORPHENIRAMINE TANNATE
	CHLORPHENAMINE+PSEUDOEPHEDRINE	CPM/PSE GENAFED PLUS
	CLEMASTINE FUMARATE	TAVIST TAVIST PRN
	CODEINE PHOSPHATE+GUAIFENESIN+PSEUDOEPHEDRINE HYDROCHLORIDE+TRIPROLIDINE HYDROCHLORIDE	LINCTIFED EXPECTORANT
	CONTAC NOS COUGH COLD PREPARATIONS NOS	LINCTIFED-FORTE SYRUP CONTACT COUGH SYRUP STORE BRAND COUGH & COLD CAPLETS TYLENOL COLD & SINUS WALDRYL COUGH GELS
	CROMOGLICATE SODIUM CROMOGLICIC ACID DAY FLU (NOS) DES Loratadine	NASAL CROM PROVENTOL 90MCG DAY FLU CLARINEX DAZIT DES Loratadine
	DEXAMETHASONE Dextromethorphan	DECADRON Dextromethorphan VICKS (Dextromethorphan)
	Dextromethorphan Hydrobromide+Ambroxol Hydrochloride	HISTIACIL
	Dextromethorphan Hydrobromide+Doxylamine Succinate	VICKS 44

Table 6.20
Relationship of Medication Class, Dictionary Term and Verbatim Text

ATC Level 1	Ingredient(s)	Verbatim Text
RESPIRATORY SYSTEM	DEXTROMETHORPHAN HYDROBROMIDE+CHLORPHENAMINE MALEATE+PSEUDOEPHEDRINE HYDROCHLORIDE DEXTROMETHORPHAN HYDROBROMIDE+PSEUDOEPHEDRINE HYDROCHLORIDE DICHLOOROBENZYL ALCOHOL+AMYL METACRESOL DIMENHYDRINATE	ROBITUSSIN PM VICK 44D STREPSIL DRAMAMINE GRAVOL PRAMAMINE DIMETAP DIMETAPP DIPHENHYDRAMINE TRICOHIST BENADRYL ALLERGY DIPHEDRYL SIMPLY SLEEP WAL-DRYL ALLERGY BENYLIN WITH CODEINE
	DIMETAPP NOS	
	DIPHENHYDRAMINE	
	DIPHENHYDRAMINE HYDROCHLORIDE	
	DIPHENHYDRAMINE HYDROCHLORIDE+CODEINE PHOSPHATE+SODIUM CHLORIDE+LEVOMENTHOL DIPHENHYDRAMINE HYDROCHLORIDE+PARACETAMOL	TYLENOL PM TYLENOL PM (PRN) TYLENOL PM PRN DYTAN CS
	DIPHENHYDRAMINE TANNATE+PHENYLEPHRINE TANNATE+PENTOXOYVERINE TANNATE DIPHENHYDRAMINE HYDROCHLORIDE+PARACETAMOL+PSEUDOEPHEDRINE HYDROCHLORIDE EPINASTINE HYDROCHLORIDE	WAL-DRYL ELESTAT ELISTAT EYE DROPS PRIMATENE MIST FENOTEROL ALLEGIX ALLEGIX - FEXOFENADINE ALLEGRA
	EPINEPHRINE FENOTEROL FEXOFENADINE FEXOFENADINE HYDROCHLORIDE	

Table 6.20
Relationship of Medication Class, Dictionary Term and Verbatim Text

ATC Level 1	Ingredient(s)	Verbatim Text
RESPIRATORY SYSTEM	FEXOFENADINE HYDROCHLORIDE	ALLEGRA 180 ALLEGRA 180 MG ALLEGRA 180MG
	FLUNISOLIDE	NASALIDE PRN NASAREL
	FLUTICASONE PROPIONATE	FLONASE FLONASE NASAL FLOVENT FLOVENT 110 MCG
	FORMOTEROL FUMARATE	FORADIL
	FRANOL (NOS)	FRANOL
	GUAIFENESIN	GUAIFENISEN GUAIFENESIN GUAIFENSIN MUCINEX RITE AID TUSSIN TUSSIN COUGH SYRUP
	GUAIFENESIN+DEXTROMETHORPHAN HYDROBROMIDE	CVS BRAND ROBITUSSIN DM MUCINEX D.M. MUCINEX DM MUCO-FEN DM ROBITUSSIN DM ROBITUSSIN DM SYRUP WAL TUSSIN-DM WALTUSSIN DM SINUTUSS DM
	GUAIFENESIN+DEXTROMETHORPHAN HYDROBROMIDE+PHENYLEPHRINE HYDROCHLORIDE	ROBITUSSIN CF
	GUAIFENESIN+DEXTROMETHORPHAN HYDROBROMIDE+PHENYLPROPANOLAMINE HYDROCHLORIDE	
	GUAIFENESIN+DEXTROMETHORPHAN HYDROBROMIDE+PSEUDOEPHEDRINE HYDROCHLORIDE	PROFEN FORTE DM PROTEN FORTE DM ROBITUSSIN COUGH AND COLD

Table 6.20
Relationship of Medication Class, Dictionary Term and Verbatim Text

ATC Level 1	Ingredient(s)	Verbatim Text
RESPIRATORY SYSTEM	GUAIFENESIN+DEXTROMETHORPHAN HYDROBROMIDE+PSEUDOEPHEDRINE HYDROCHLORIDE	WALTUSSIN CF
	GUAIFENESIN+PHENYLEPHRINE GUAIFENESIN+PHENYLEPHRINE HYDROCHLORIDE	DURAPHEN II ENTEX LA
	GUAIFENESIN+PHENYLPROPANOLAMINE HYDROCHLORIDE	PROFEN FORTE
	GUAIFENESIN+PSEUDOEPHEDRINE GUAIFENESIN+PSEUDOEPHEDRINE HYDROCHLORIDE	EQUATE SINUS RELIEF ENTEX PSE GUAIFENEX PSE MAXIFED G NALEX ROBITUSSIN SEVERE CONGESTION SINUVENT PE ACTIFED EXPECTORANT
	GUAIFENESIN+PSEUDOEPHEDRINE HYDROCHLORIDE+TRIPROLIDINE HYDROCHLORIDE HYDROCODONE	HYDROCODONE HYDROCODONE 500 MG TUSSIONEX
	HYDROCODONE+PHENYLTOLOXAMINE HYOSCINE METHONITRATE+CHLORPHENAMINE MALEATE+PHENYLEPHRINE HYDROCHLORIDE	EXTENDRYL JUNIOR (CHLORPHENIRAMINE/PHENYLEPHRINE/METHSCOPALAMINE) RALIX ALLERX
	HYOSCINE METHONITRATE+CHLORPHENAMINE MALEATE+PSEUDOEPHEDRINE HYDROCHLORIDE IPRATROPIUM BROMIDE	ATROVENT ATROVENT INHALATION SOLUTION ZADITOR
	KETOTIFEN FUMARATE LEVOMENTHOL+EUCALYPTUS GLOBULUS	HALLS COUGH DROPS HALLS MAX LOZENGE VICKS KINGO
	LEVOSALBUTAMOL HYDROCHLORIDE LIDOCAINE	XOPENEX LIDOCAINE XYLOCAINE
	LORATADINE	ALAVERT

Table 6.20
Relationship of Medication Class, Dictionary Term and Verbatim Text

ATC Level 1	Ingredient(s)	Verbatim Text
RESPIRATORY SYSTEM	LORATADINE	ALEVERT CLARITIN CLARITIN 24 HOUR CLARITIN PRN CLARITIN-5 MG-PRN CLARITON CLARTIN LORATADINE LORATIDINE MECLAZINE BONINE DRAMAMINE LESS DROWSY RYNA-12 ELOCON ELOCON CREAM NASONEX NASONEX PRN MONTELUKAST SINGULAIR SINGULAIR (10 MG) SINGULAR OXYGEN AFRIN AFRIN NASAL SPRAY COLD CAP
	MECLOZINE MECLOZINE HYDROCHLORIDE	
	MEPYRAMINE TANNATE+PHENYLEPHRINE TANNATE MOMETASONE FUROATE	
	MONTELUKAST MONTELUKAST SODIUM	
	OXYGEN OXYMETAZOLINE HYDROCHLORIDE	
	PARACETAMOL+CAFFEINE+CHLORPHENAMINE MALEATE+PSEUDOEPHEDRINE HYDROCHLORIDE PARACETAMOL+CHLORPHENAMINE+PSEUDOEPHEDRINE	COLD-CAP COMTrex COLD ALKA SELTZER PLUS
	PARACETAMOL+CHLORPHENAMINE MALEATE+PHENYLEPHRINE HYDROCHLORIDE PARACETAMOL+CHLORPHENAMINE MALEATE+PSEUDOEPHEDRINE HYDROCHLORIDE	ALKA SELTZER COLD ALLERGY SINUS

Table 6.20
Relationship of Medication Class, Dictionary Term and Verbatim Text

ATC Level 1	Ingredient(s)	Verbatim Text
RESPIRATORY SYSTEM	PARACETAMOL+CHLORPHENAMINE MALEATE+PSEUDOEPHEDRINE HYDROCHLORIDE	DAY FLU (CHLORPHENAMINE + PARACETAMOL + PSEUDOEPHEDRINE HYDROCHLORIDE) THERA FLU THERA-FLU THERAFLU THERAFLU COLD THERMA FLU TYLENOL ALLERGY & SINUS TYLENOL ALLERGY COMPLETE TYLENOL ALLERGY SINUS TYLENOL ALLERGY/SINUS TYLENOL SINUS AND ALLERGY
	PARACETAMOL+DEXTROMETHORPHAN+CHLORPHENAMINE MALEATE+PSEUDOEPHEDRINE HYDROCHLORIDE	ALKA SELTZER PLUS COLD & COUGH
	PARACETAMOL+DEXTROMETHORPHAN HYDROBROMIDE+CHLORPHENAMINE MALEATE+PHENYLPROPANOLAMINE HYDROCHLORIDE	COMTREX
	PARACETAMOL+DEXTROMETHORPHAN HYDROBROMIDE+CHLORPHENAMINE MALEATE+PSEUDOEPHEDRINE HYDROCHLORIDE	TYLENOL COLD & FLU
	PARACETAMOL+DEXTROMETHORPHAN HYDROBROMIDE+DOXYLAMINE SUCCINATE	NYQUIL WALGREEN GENERIC
	PARACETAMOL+DEXTROMETHORPHAN HYDROBROMIDE+PHENYLEPHRINE HYDROCHLORIDE	VICKS NYQUIL COLD/FLU RELIEF DAYQUIL COLD
	PARACETAMOL+DEXTROMETHORPHAN HYDROBROMIDE+PSEUDOEPHEDRINE HYDROCHLORIDE	DAYQUIL WALMART GENERIC TYLENOL COLD MULTI-SYMPTOMS DAY QUIL
		DAYQUIL TYLENOL FLU TYLENOL FLU DAYTIME

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Table 6.20
Relationship of Medication Class, Dictionary Term and Verbatim Text

ATC Level 1	Ingredient(s)	Verbatim Text
RESPIRATORY SYSTEM	PARACETAMOL+DEXTROMETHORPHAN HYDROBROMIDE+PSEUDOEPHEDRINE HYDROCHLORIDE+DOXYLAMINE SUCCINATE	ALKA SELTZER PLUS NIGHT TIME COLD MEDICINE DOXYLAMINE SUCCINATE, PSEUDOEPHEDRINE HCL, ACETAMINOPHEN, & DEXTROMETHORPHEN HB NYQUIL VICKS DAYQUIL
	PARACETAMOL+GUAIFENESIN+DEXTROMETHORPHAN HYDROBROMIDE+PSEUDOEPHEDRINE HYDROCHLORIDE PARACETAMOL+GUAIFENESIN+PSEUDOEPHEDRINE HYDROCHLORIDE PARACETAMOL+HYDROCODONE PARACETAMOL+PHENYLTOLOXAMINE PARACETAMOL+PSEUDOEPHEDRINE	TYLENOL SEVERE COLD HYDROCODONE + APAP RHINOFLEX PSEUDOEPHEDRINE W/ACETAMINOPHEN DAYQUIL SINUS SUDAFED SINUS WALGREEN'S NIGHTTIME
	PARACETAMOL+PSEUDOEPHEDRINE HYDROCHLORIDE PARACETAMOL+PSEUDOEPHEDRINE HYDROCHLORIDE+DOXYLAMINE SUCCINATE PARACETAMOL+SALICYLIC ACID+CAFFEINE+CHLORPHENAMINE MALEATE PHENOL	COLD CAP CHLORASEPTIC SPRAY WITH PHENOL CHLORASEPTIC SPRAY CHLORASEPTIC SPRAY NEOSYNEPHRINE SUDAFED PE MAXIMUM STRENGTH MAXAIR MAXAIR (200MCG) MAXAIR 200 MCG PHENEGRON PHENERGAN PHENERGAN 25
	PHENYLEPHRINE HYDROCHLORIDE	
	PIRBUTEROL ACETATE	
	PROMETHAZINE	

Table 6.20
Relationship of Medication Class, Dictionary Term and Verbatim Text

ATC Level 1	Ingredient(s)	Verbatim Text
RESPIRATORY SYSTEM	PROMETHAZINE	PROMETHASINE PROMETHAZINE PROMETHAZINE SUPPOSITORIES TRICOHIST
	PSEUDOEPHEDRINE HYDROCHLORIDE	CONTAC 12 HR COLD SUDAFED SUDAFED (PSEUDOEPHEDRINE) SUDAFED PRN SUDAPHED
	PSEUDOEPHEDRINE HYDROCHLORIDE+CETIRIZINE HYDROCHLORIDE	CETRICET-D CETRIZET-D ZYRTEC D ZYRTEC-D
	PSEUDOEPHEDRINE HYDROCHLORIDE+FEXOFENADINE HYDROCHLORIDE	ALEGRA D ALLEGRA D ALLEGRA-D
	PSEUDOEPHEDRINE HYDROCHLORIDE+IBUPROFEN	ADVIL COLD ADVIL COLD & SINUS ADVIL COLD AND SINUS ADVIL COLD AND SINUS TABLETS ADVIL COLD/SINUS
	PSEUDOEPHEDRINE HYDROCHLORIDE+TRIPROLIDINE HYDROCHLORIDE	ACTIFED ACTIFED PRN ACTIFED PRN COLD & ALLERGY ACTIPHED
	PSEUDOEPHEDRINE SULFATE+LORATADINE	SUDAFED SINUS NIGHTTIME CLARITIN D CLARITIN D 12 HOUR CLARITIN-D
	PSEUDOEPHEDRINE+IBUPROFEN	ADVIL COLD & FLU ADVIL SINUS

Table 6.20
Relationship of Medication Class, Dictionary Term and Verbatim Text

ATC Level 1	Ingredient(s)	Verbatim Text
RESPIRATORY SYSTEM	PSEUDOEPHEDRINE+IBUPROFEN PSEUDOEPHEDRINE+LORATADINE PSEUDOEPHEDRINE+NAPROXEN	MOTRIN COLD CLARITYNE D ALEVE COLD & SINUS ALEVE COLD AND SINUS ALEVE SINUS & HEADACHE ALEVE SINUS HEADACHE
	RETINOL PALMITATE RHINOCORT (NOS)	AVITA (RETINOL PALMITATE) RHINOCORT RHINOCORT PRN
	ROBITUSSIN (NOS)	ROBITUSSIN ROBITUSSIN
	SALBUTAMOL	ALBUTEROL ALBUTEROL (180 MCG) ALBUTEROL (90 MCG) ALBUTEROL (90MCG) ALBUTEROL (PRN) MCG ALBUTEROL 1.25 MG ALBUTEROL 180 MCG ALBUTEROL 180MCG ALBUTEROL 90 MCG ALBUTEROL 90MCG ALBUTEROL 90MCG/INH ALBUTEROL 90MG ALBUTEROL INH ALBUTEROL INHALER ALBUTEROL MDI ALBUTEROL NEB ALBUTEROL NEBULES ALBUTEROL NEBULES .02% MG ALBUTEROL NEBULIZER ALBUTEROL PRN ALBUTEROL SOLUTION ALBUTERON PROVENTIL

Table 6.20
Relationship of Medication Class, Dictionary Term and Verbatim Text

ATC Level 1	Ingredient(s)	Verbatim Text
RESPIRATORY SYSTEM	SALBUTAMOL	PROVENTIL (90 MCG) SALBUTAMAL SALBUTAMEL SALBUTAMOL SALBUTAMOL 100MG SALBUTANOL SALBUTAUIROL SALBUTEROL SALBUTOMAL VENTOLIN VENTOLIN (90MCG) VENTOLIN 4MG VENTOLIN 90 MCG VENTOLIN 90MCG VENTOLIN 90MCG/INH VENTOLIN SALBUTAMOL PROVENTIL HFA VENTOLIN EVOHALER COMBIVENT COMBIVENT MDI DUONEB SEREVENT SEREVENT (50 MCG) ADVAIR ADVAIR (100/50) ADVAIR (250/50 MCG) ADVAIR 100/50 ADVAIR 250/50 SINUTAB AFRIN SALINE NASAL SALINE NASAL SALINE SPRAY OCEAN SPRAY SALINE NASAL SPRAY
	SALBUTAMOL SULFATE	PROVENTIL HFA VENTOLIN EVOHALER
	SALBUTAMOL SULFATE+IPRATROPIUM BROMIDE	COMBIVENT COMBIVENT MDI DUONEB
	SALMETEROL XINAFOATE	SEREVENT SEREVENT (50 MCG)
	SALMETEROL XINAFOATE+FLUTICASONE PROPIONATE	ADVAIR ADVAIR (100/50) ADVAIR (250/50 MCG) ADVAIR 100/50 ADVAIR 250/50
	SINUTAB (NOS) SODIUM CHLORIDE	SINUTAB AFRIN SALINE NASAL SALINE NASAL SALINE SPRAY OCEAN SPRAY SALINE NASAL SPRAY

Table 6.20
Relationship of Medication Class, Dictionary Term and Verbatim Text

ATC Level 1	Ingredient(s)	Verbatim Text
RESPIRATORY SYSTEM	SODIUM CHLORIDE	SODIUM CHLORIDE 0.9%
	TERBUTALINE	TERBUTALINE
	TETRYZOLINE HYDROCHLORIDE	VISINE EYE GTTS
	THEOPHYLLINE	THEOPHYLLINE
		UNIPHYLLINE
	THEOPHYLLINE+EPHEDRINE HYDROCHLORIDE	PRIMATENE TABS
	TRIAMCINOLONE ACETONIDE	AZMACORT
		KENALOG
		NASACORT
		NASACORT AQ
		NASACORT PRN
		TRIAMCINOLONE CREAM
		TRIAMCINOLONE OINT.
		TRIAMCINOLONE OINTMENT
SENSORY ORGANS	TYLENOL COLD NOS	TYLENOL COLD
	TYLENOL SINUS (NOS)	TYLENOL SINUS
		TYLENOL SINUS CONGESTION
		TYLENOL SINUS PRN
		TYLNEOL SINUS
	VICKS VAPORUB NOS	VICKS VAPORUB
	XYLOMETAZOLINE HYDROCHLORIDE	NASTIZOL
	ACETAZOLAMIDE	DIAMOX (500 MG-PRN)
		DIAMOX (500MG QD)
	ACETIC ACID	APPLE CIDER VINEGAR SUPPLEMENT
	ACYCLOVIR	ACYCLOVIR (TOPICAL)
		ZOVIRAX
	AMPICILLIN	AMPICILLIN
	ARTIFICIAL TEARS NOS	PRESERVATIVE TEARS
	ATROPINE	ATROPINE
	BENZYL PENICILLIN	PENICILLIN
		PENICILLIN (ORAL)
		PENICILLIN IM
		X-PEN

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Table 6.20
Relationship of Medication Class, Dictionary Term and Verbatim Text

ATC Level 1	Ingredient(s)	Verbatim Text
SENSORY ORGANS	BETAMETHASONE SODIUM PHOSPHATE+NEOMYCIN SULFATE	PROBETA-N
		PROBETA-N EYE DROPS
	CIPROFLOXACIN HYDROCHLORIDE	CIPRO
	CLONIDINE	CLONODINE
	CORTISONE	CORTISONE SHOT
	CROMOGLICATE SODIUM	NASAL CROM
	CROMOGLICIC ACID	PROVENTOL 90MCG
	DESONIDE	DESONIDE
	DEXAMETHASONE	DECADRON
	DEXAMETHASONE+CIPROFLOXACIN	CIPRODEX EAR DROPS
	DEXAMETHASONE+FRAMYCETIN+GRAMICIDIN	ALLERDEX
	DICLOFENAC	DICLOFENAC
		DICLOFENACO
	EPINEPHRINE	PRIMATENE MIST
	ERYTHROMYCIN	ERYTHROMYCIN
		PANTOMICINA
	FAMCICLOVIR	FAMVIR
	HYDROCORTISONE	HYDROCORTISONE CREAM
	HYDROCORTISONE+CIPROFLOXACIN HYDROCHLORIDE	CIPRO HC
	INDOMETACIN	INDOCID
	KETOROLAC	KETOROLAC
	KETOROLAC TROMETAMOL	TORADOL
		TORADOL (IV)
		TORADOL (ORAL)
		TORADOL IV
	KETOTIFEN FUMARATE	ZADITOR
	LIDOCAINE	LIDOCAINE
		XYLOCAINE
	LOTEPREDNOL ETABONATE	LOTAMAX
	METHYLPREDNISOLONE	MEDROL
		MEDROL DOSE PACK
		MEJORAL (ACETYLSALICYLIC ACID)
		MEJOROL (ACETYLSALICYLIC ACID)

Table 6.20
Relationship of Medication Class, Dictionary Term and Verbatim Text

ATC Level 1	Ingredient(s)	Verbatim Text
SENSORY ORGANS	METHYLPREDNISOLONE	METHYLPREDNISOLONE METHYLPREDNISOLONE DOSE PAK METHYLPREDNISONE MONISTAT NEOSPORIN OINTMENT
	MICONAZOLE NITRATE	PATANOL
	NEOMYCIN SULFATE+POLYMYXIN B	BAUSH & LOMB
	SULFATE+BACITRACIN ZINC	AFRIN
	OLOPATADINE HYDROCHLORIDE	AFRIN NASAL SPRAY
	OPHTHALMOLOGICALS	RITE AID EYE DROPS
	OXYMETAZOLINE HYDROCHLORIDE	
	PHENIRAMINE MALEATE+NAPHAZOLINE	VISINE A
	HYDROCHLORIDE	VISINEAR
		NEOSYNEPHRINE
	PHENYLEPHRINE HYDROCHLORIDE	SUDAFED PE MAXIMUM STRENGTH
		ACTION
	PIROXICAM	FELDENE FLASH
		POLYTRIM
	POLYMYXIN B SULFATE+TRIMETHOPRIM	NOVACAINE
	PROCAINE HYDROCHLORIDE	AVITA (RETINOL PALMITATE)
	RETINOL PALMITATE	SALEX
	SALICYLIC ACID	AFRIN SALINE
	SODIUM CHLORIDE	NASAL SALINE
		NASAL SALINE SPRAY
		OCEAN SPRAY
		SALINE NASAL SPRAY
		SODIUM CHLORIDE 0.9%
	TETRACYCLINE	TETRACYCLINE
	TETRYZOLINE HYDROCHLORIDE	VISINE EYE GTTS
	TRIAMCINOLONE ACETONIDE	AZMACORT
		KENALOG
		NASACORT
		NASACORT AQ

Table 6.20
Relationship of Medication Class, Dictionary Term and Verbatim Text

ATC Level 1	Ingredient(s)	Verbatim Text
SENSORY ORGANS	TRIAMCINOLONE ACETONIDE	NASACORT PRN TRIAMCINOLONE CREAM TRIAMCINOLONE OINT. TRIAMCINOLONE OINTMENT
	XYLOMETAZOLINE HYDROCHLORIDE	NASTIZOL
	ZINC SULFATE+TETRYZOLINE HYDROCHLORIDE	VISINE- AC
SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES	BETAMETHASONE	BETAMETHASONE
	BETAMETHASONE DIPROPIONATE	DIPROLENE
	BETAMETHASONE+CHLORPHENAMINE MALEATE	CELESTAMINE
	BUDESONIDE	NASOCORT PULMICORT RHINOCORT AQ RHINOCORT AQUA CORTISONE SHOT
	CORTISONE	DECADRON
	DEXAMETHASONE	HYDROCORTISONE CREAM
	HYDROCORTISONE	IODINE
	IODINE	LEVOTHYROXIN
	LEVOTHYROXINE	LEVOTHROID
	LEVOTHYROXINE SODIUM	LEVOTIROXINE LEVOXYL SYNTHROID
	MELATONIN	MELATONIN
	METHYLPREDNISOLONE	MEDROL MEDROL DOSE PACK MEJORAL (ACETYLSALICYLIC ACID) MEJOROL (ACETYLSALICYLIC ACID) METHYLPREDNISOLONE METHYLPREDNISOLONE DOSE PAK METHYLPREDNISONE DEPOMEDROL INJ. PREDISONE
	METHYLPREDNISOLONE ACETATE	
	PREDNISONE	

Table 6.20
Relationship of Medication Class, Dictionary Term and Verbatim Text

ATC Level 1	Ingredient(s)	Verbatim Text
SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES	PREDNISONE	PREDNISONA
		PREDNISONE
		PREDNISONE DOSE PACK
	THYROID	ARMOUR THYROID
	TRIAMCINOLONE ACETONIDE	AZMACORT
		KENALOG
		NASACORT
		NASACORT AQ
		NASACORT PRN
		TRIAMCINOLONE CREAM
VARIOUS		TRIAMCINOLONE OINT.
		TRIAMCINOLONE OINTMENT
	ALLERGENS (NOS)	ALLERGY SHOT
		ALLERGY SHOTS
	ALLIUM SATIVUM	GARLIC TABLET
	AMBIGUOUS MEDICATION	CEPACOL
		UNKNOWN CEPACOL SPRAY
		ZICAM
	ASCORBIC ACID+ECHINACEA	ECHINACHEA & VIT C
		EHINEACHIA & VIT C
	BARIUM	BARIUM
	CAFFEINE+PRASTERONE+HERBALS NOS	ESTRIN D
	CHONDROITIN+GLUCOSAMINE	CHONDROITIN GLUCOSAMINE
	CREATINE	CREATINE
	DIMETHYL SULFONE	MSM
	ECHINACEA	ECHINACEA
	FLUCAPS (NOS)	FLUCAPS
	GINKGO BILOBA EXTRACT+OXITRIPTAN+MAGNESIUM OXIDE+MALIC ACID+VANADYL SULPHATE+HERBAL EXTRACTS NOS+VIT	SATIETE
	HYDRASTIS CANADENSIS	
	LINUM USITATISSIMUM	GOLDEN SEAL
		FLAXSEED

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Table 6.20
Relationship of Medication Class, Dictionary Term and Verbatim Text

ATC Level 1	Ingredient(s)	Verbatim Text
VARIOUS	MINERALS NOS+VITAMINS NOS+HERBALS NOS	AIRBORNE
		AIRBOURNE
	OXYGEN	OXYGEN
	TYROSINE	TYROSINE
	TYROSINE+ACETYLCARNITINE+PAULLINIA	XENADRINE
	CUPANA+EPHEDRA SINICA+ZINGIBER	
	OFFICINALE+SALIX PURPUREA+CITRUS A	

Table 6.21
Summary of Asthma Medication Use (ITT Population)

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Subjects in treatment group	89	92	91	272
Subjects with any medication	45 (51%)	28 (30%)	26 (29%)	99 (36%)
RESPIRATORY SYSTEM				
Any medication	44 (49%)	28 (30%)	26 (29%)	98 (36%)
SALBUTAMOL	40 (45%)	26 (28%)	24 (26%)	90 (33%)
IPRATROPIUM BROMIDE	2 (2%)	0	2 (2%)	4 (1%)
PIRBUTEROL ACETATE	0	2 (2%)	1 (1%)	3 (1%)
FLUTICASONE PROPIONATE	1 (1%)	1 (1%)	0	2 (<1%)
SALMETEROL XINAFOATE+FLUTICASONE PROPIONATE	1 (1%)	0	1 (1%)	2 (<1%)
AMBROXOL HYDROCHLORIDE	0	0	1 (1%)	1 (<1%)
AMINOPHYLLINE	1 (1%)	0	0	1 (<1%)
BECLOMETASONE DIPROPIONATE	0	0	1 (1%)	1 (<1%)
BETAMETHASONE DIPROPIONATE+SALBUTAMOL	1 (1%)	0	0	1 (<1%)
BROMHEXINE HYDROCHLORIDE+GUAIFENESIN+SALBUTAMOL SULFATE+LEVOMENTHOL	0	0	1 (1%)	1 (<1%)
EPINEPHRINE	0	0	1 (1%)	1 (<1%)
FENOTEROL	1 (1%)	0	0	1 (<1%)
GUAIFENESIN+DEXTROMETHORPHAN HYDROBROMIDE	1 (1%)	0	0	1 (<1%)
LEVOSALBUTAMOL HYDROCHLORIDE	1 (1%)	0	0	1 (<1%)
SALBUTAMOL SULFATE	0	0	1 (1%)	1 (<1%)
SALBUTAMOL SULFATE+IPRATROPIUM BROMIDE	1 (1%)	0	0	1 (<1%)
THEOPHYLLINE	1 (1%)	0	0	1 (<1%)

Note: A medication may be reported in more than one ATC Level.

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Table 6.21
Summary of Asthma Medication Use (ITT Population)

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
ALIMENTARY TRACT AND METABOLISM				
Any medication	4 (4%)	0	4 (4%)	8 (3%)
PREDNISONE	4 (4%)	0	2 (2%)	6 (2%)
BECLOMETASONE DIPROPIONATE	0	0	1 (1%)	1 (<1%)
EPINEPHRINE	0	0	1 (1%)	1 (<1%)
SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES				
Any medication	4 (4%)	0	2 (2%)	6 (2%)
PREDNISONE	4 (4%)	0	2 (2%)	6 (2%)
DERMATOLOGICALS				
Any medication	1 (1%)	1 (1%)	1 (1%)	3 (1%)
FLUTICASONE PROPIONATE	1 (1%)	1 (1%)	0	2 (<1%)
BECLOMETASONE DIPROPIONATE	0	0	1 (1%)	1 (<1%)
SENSORY ORGANS				
Any medication	0	0	1 (1%)	1 (<1%)
EPINEPHRINE	0	0	1 (1%)	1 (<1%)
ANTIINFECTIVES FOR SYSTEMIC USE				
Any medication	3 (3%)	0	0	3 (1%)
AZITHROMYCIN	1 (1%)	0	0	1 (<1%)
GATIFLOXACIN	1 (1%)	0	0	1 (<1%)
MOXIFLOXACIN	1 (1%)	0	0	1 (<1%)
CARDIOVASCULAR SYSTEM				
Any medication	0	0	1 (1%)	1 (<1%)
EPINEPHRINE	0	0	1 (1%)	1 (<1%)

Note: A medication may be reported in more than one ATC Level.

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Table 6.21
Summary of Asthma Medication Use (ITT Population)

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
BLOOD AND BLOOD FORMING ORGANS				
Any medication	0	0	1 (1%)	1 (<1%)
EPINEPHRINE	0	0	1 (1%)	1 (<1%)
GENITO URINARY SYSTEM AND SEX HORMONES				
Any medication	1 (1%)	0	0	1 (<1%)
FENOTEROL	1 (1%)	0	0	1 (<1%)

Note: A medication may be reported in more than one ATC Level.

Table 6.21
Summary of Asthma Medication Use (ITT Population)

Treatment: Salmeterol

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Subjects in treatment group	90	90	92	272
Subjects with any medication	35 (39%)	33 (37%)	34 (37%)	102 (38%)
RESPIRATORY SYSTEM				
Any medication	34 (38%)	33 (37%)	31 (34%)	98 (36%)
SALBUTAMOL	30 (33%)	32 (36%)	30 (33%)	92 (34%)
IPRATROPIUM BROMIDE	2 (2%)	1 (1%)	5 (5%)	8 (3%)
LEVOSALBUTAMOL HYDROCHLORIDE	1 (1%)	1 (1%)	1 (1%)	3 (1%)
PIRBUTEROL ACETATE	1 (1%)	1 (1%)	0	2 (<1%)
CROMOGLICIC ACID	1 (1%)	0	0	1 (<1%)
DEXAMETHASONE	1 (1%)	0	0	1 (<1%)
FLUTICASONE PROPIONATE	0	0	1 (1%)	1 (<1%)
PARACETAMOL+CHLORPHENAMINE	1 (1%)	0	0	1 (<1%)
MALEATE+PSEUDOEPHEDRINE HYDROCHLORIDE				
PSEUDOEPHEDRINE HYDROCHLORIDE+FEXOFENADINE	0	0	1 (1%)	1 (<1%)
HYDROCHLORIDE				
SALBUTAMOL SULFATE+IPRATROPIUM BROMIDE	0	1 (1%)	0	1 (<1%)
SALMETEROL XINAFOATE+FLUTICASONE PROPIONATE	0	0	1 (1%)	1 (<1%)
TERBUTALINE	0	1 (1%)	0	1 (<1%)
ALIMENTARY TRACT AND METABOLISM				
Any medication	6 (7%)	2 (2%)	3 (3%)	11 (4%)
PREDNISONE	4 (4%)	2 (2%)	3 (3%)	9 (3%)
CROMOGLICIC ACID	1 (1%)	0	0	1 (<1%)
DEXAMETHASONE	1 (1%)	0	0	1 (<1%)

Note: A medication may be reported in more than one ATC Level.

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Table 6.21
Summary of Asthma Medication Use (ITT Population)

Treatment: Salmeterol

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES				
Any medication	5 (6%)	2 (2%)	4 (4%)	11 (4%)
PREDNISONE	4 (4%)	2 (2%)	3 (3%)	9 (3%)
DEXAMETHASONE	1 (1%)	0	0	1 (<1%)
METHYLPREDNISOLONE	0	0	1 (1%)	1 (<1%)
DERMATOLOGICALS				
Any medication	1 (1%)	0	2 (2%)	3 (1%)
DEXAMETHASONE	1 (1%)	0	0	1 (<1%)
FLUTICASONE PROPIONATE	0	0	1 (1%)	1 (<1%)
METHYLPREDNISOLONE	0	0	1 (1%)	1 (<1%)
SENSORY ORGANS				
Any medication	2 (2%)	0	1 (1%)	3 (1%)
CROMOGLICIC ACID	1 (1%)	0	0	1 (<1%)
DEXAMETHASONE	1 (1%)	0	0	1 (<1%)
METHYLPREDNISOLONE	0	0	1 (1%)	1 (<1%)
CARDIOVASCULAR SYSTEM				
Any medication	1 (1%)	0	0	1 (<1%)
DEXAMETHASONE	1 (1%)	0	0	1 (<1%)
NERVOUS SYSTEM				
Any medication	1 (1%)	0	0	1 (<1%)
PARACETAMOL+CHLORPHENAMINE	1 (1%)	0	0	1 (<1%)
MALEATE+PSEUDOEPHEDRINE HYDROCHLORIDE				

Note: A medication may be reported in more than one ATC Level.

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Table 6.22
Summary of Non-Asthma Medication Use (ITT Population)

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Subjects in treatment group	89	92	91	272
Subjects with any medication	79 (89%)	84 (91%)	78 (86%)	241 (89%)
NERVOUS SYSTEM				
Any medication	64 (72%)	69 (75%)	68 (75%)	201 (74%)
PARACETAMOL	42 (47%)	35 (38%)	43 (47%)	120 (44%)
IBUPROFEN	27 (30%)	45 (49%)	36 (40%)	108 (40%)
ACETYLSALICYLIC ACID	3 (3%)	11 (12%)	16 (18%)	30 (11%)
PARACETAMOL+CHLORPHENAMINE	3 (3%)	4 (4%)	10 (11%)	17 (6%)
MALEATE+PSEUDOEPHEDRINE HYDROCHLORIDE				
EXCEDRIN (NOS)	4 (4%)	5 (5%)	3 (3%)	12 (4%)
PARACETAMOL+HYDROCODONE BITARTRATE	5 (6%)	2 (2%)	4 (4%)	11 (4%)
PROMETHAZINE	2 (2%)	2 (2%)	5 (5%)	9 (3%)
DIPHENHYDRAMINE HYDROCHLORIDE+PARACETAMOL	3 (3%)	2 (2%)	3 (3%)	8 (3%)
ACETYLSALICYLIC ACID+PARACETAMOL+CAFFEINE	2 (2%)	4 (4%)	1 (1%)	7 (3%)
CYCLOBENZAPRINE HYDROCHLORIDE	0	4 (4%)	2 (2%)	6 (2%)
HYDROCODONE	2 (2%)	3 (3%)	1 (1%)	6 (2%)
ACETYLSALICYLIC ACID+CAFFEINE+CINNAMEDRINE	3 (3%)	0	1 (1%)	4 (1%)
HYDROCHLORIDE				
FLUOXETINE HYDROCHLORIDE	1 (1%)	1 (1%)	2 (2%)	4 (1%)
TYLENOL #3 (NOS)	3 (3%)	1 (1%)	0	4 (1%)
ALPRAZOLAM	0	0	3 (3%)	3 (1%)
DEXTROPROPOXYPHENE NAPSILATE+PARACETAMOL	2 (2%)	1 (1%)	0	3 (1%)
GABAPENTIN	2 (2%)	0	1 (1%)	3 (1%)
PARACETAMOL+OXYCODONE HYDROCHLORIDE	1 (1%)	0	2 (2%)	3 (1%)
SUMATRIPTAN	2 (2%)	1 (1%)	0	3 (1%)
ACETYLSALICYLIC ACID+SODIUM BICARBONATE+CITRIC	1 (1%)	1 (1%)	0	2 (<1%)
ACID				

Note: A medication may be reported in more than one ATC Level.

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Table 6.22
Summary of Non-Asthma Medication Use (ITT Population)

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
AMFETAMINE SULFATE+AMFETAMINE	2 (2%)	0	0	2 (<1%)
ASPARTATE+DEXAMFETAMINE				
SULFATE+DEXTROAMPHETAMINE SACCHARATE				
AMITRIPTYLINE	0	0	2 (2%)	2 (<1%)
BUPROPION HYDROCHLORIDE	1 (1%)	0	1 (1%)	2 (<1%)
CITALOPRAM HYDROBROMIDE	0	0	2 (2%)	2 (<1%)
ESZOPICLONE	1 (1%)	0	1 (1%)	2 (<1%)
HYDROMORPHONE HYDROCHLORIDE	1 (1%)	0	1 (1%)	2 (<1%)
HYDROXYZINE	0	2 (2%)	0	2 (<1%)
MIDAZOLAM	0	1 (1%)	1 (1%)	2 (<1%)
ORPHENADRINE	0	0	2 (2%)	2 (<1%)
OXYCODONE	0	2 (2%)	0	2 (<1%)
PARACETAMOL+CAFFEINE	1 (1%)	0	1 (1%)	2 (<1%)
PARACETAMOL+CAFFEINE+BUTALBITAL	2 (2%)	0	0	2 (<1%)
PARACETAMOL+MEPYRAMINE MALEATE+PAMABROM	0	2 (2%)	0	2 (<1%)
PAROXETINE HYDROCHLORIDE	0	2 (2%)	0	2 (<1%)
TOPIRAMATE	1 (1%)	0	1 (1%)	2 (<1%)
TRAMADOL	2 (2%)	0	0	2 (<1%)
TRAMADOL HYDROCHLORIDE	0	1 (1%)	1 (1%)	2 (<1%)
ZOLPIDEM TARTRATE	1 (1%)	0	1 (1%)	2 (<1%)
ACETYLSALICYLIC ACID+CAFFEINE+SALICYLAMIDE	0	1 (1%)	0	1 (<1%)
ANAESTHETICS, GENERAL	1 (1%)	0	0	1 (<1%)
BUPIVACAINE HYDROCHLORIDE	0	1 (1%)	0	1 (<1%)
BUSPIRONE HYDROCHLORIDE	0	1 (1%)	0	1 (<1%)
CABERGOLINE	0	0	1 (1%)	1 (<1%)
CLONAZEPAM	0	0	1 (1%)	1 (<1%)
DIAZEPAM	0	0	1 (1%)	1 (<1%)
DIPHENHYDRAMINE+PARACETAMOL	1 (1%)	0	0	1 (<1%)
DROPERIDOL	0	0	1 (1%)	1 (<1%)
DULOXETINE HYDROCHLORIDE	1 (1%)	0	0	1 (<1%)
ERGOTAMINE TARTRATE+CAFFEINE	1 (1%)	0	0	1 (<1%)

Note: A medication may be reported in more than one ATC Level.

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Table 6.22
Summary of Non-Asthma Medication Use (ITT Population)

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
ESCITALOPRAM OXALATE	0	0	1 (1%)	1 (<1%)
FENTANYL	0	0	1 (1%)	1 (<1%)
FLUOXETINE	0	0	1 (1%)	1 (<1%)
FLUVOXAMINE MALEATE	0	1 (1%)	0	1 (<1%)
HYDROXYZINE HYDROCHLORIDE	0	1 (1%)	0	1 (<1%)
KETAMINE	0	1 (1%)	0	1 (<1%)
KETOROLAC TROMETAMOL	0	1 (1%)	0	1 (<1%)
LIDOCAINE	0	1 (1%)	0	1 (<1%)
MEFENAMIC ACID	0	0	1 (1%)	1 (<1%)
METHYLPHENIDATE HYDROCHLORIDE	0	0	1 (1%)	1 (<1%)
MORPHINE	0	1 (1%)	0	1 (<1%)
NALBUPHINE HYDROCHLORIDE	0	1 (1%)	0	1 (<1%)
NORTRIPTYLINE	1 (1%)	0	0	1 (<1%)
PARACETAMOL+CHLORPHENAMINE MALEATE+PHENYLEPHRINE HYDROCHLORIDE	0	0	1 (1%)	1 (<1%)
PARACETAMOL+DICHLORALPHENAZONE+ISOMETHEPTENE MUCATE	0	0	1 (1%)	1 (<1%)
PARACETAMOL+HYDROCODONE	0	1 (1%)	0	1 (<1%)
PARACETAMOL+PHENYLTOLOXAMINE	0	0	1 (1%)	1 (<1%)
PARACETAMOL+TRAMADOL HYDROCHLORIDE	0	1 (1%)	0	1 (<1%)
PAROXETINE	1 (1%)	0	0	1 (<1%)
PETHIDINE HYDROCHLORIDE	0	1 (1%)	0	1 (<1%)
PHENOBARBITAL+ERGOTAMINE TARTRATE+ATROPA BELLADONNA	1 (1%)	0	0	1 (<1%)
PHENOL	1 (1%)	0	0	1 (<1%)
PROCAINE HYDROCHLORIDE	0	1 (1%)	0	1 (<1%)
RIZATRIPTAN BENZOATE	1 (1%)	0	0	1 (<1%)
SERTRALINE HYDROCHLORIDE	0	1 (1%)	0	1 (<1%)
UNISOM NOS	1 (1%)	0	0	1 (<1%)
VALPROIC ACID	1 (1%)	0	0	1 (<1%)
VENLAFAXINE HYDROCHLORIDE	1 (1%)	0	0	1 (<1%)

Note: A medication may be reported in more than one ATC Level.

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Table 6.22
Summary of Non-Asthma Medication Use (ITT Population)

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)

ZALEPLON	0	1 (1%)	0	1 (<1%)
ZOLMITRIPTAN	0	0	1 (1%)	1 (<1%)
RESPIRATORY SYSTEM				
Any medication	58 (65%)	58 (63%)	67 (74%)	183 (67%)
FEXOFENADINE HYDROCHLORIDE	11 (12%)	15 (16%)	9 (10%)	35 (13%)
LORATADINE	10 (11%)	11 (12%)	12 (13%)	33 (12%)
BENADRYL (NOS)	7 (8%)	6 (7%)	16 (18%)	29 (11%)
PSEUDOEPHEDRINE HYDROCHLORIDE	13 (15%)	7 (8%)	8 (9%)	28 (10%)
FLUTICASONE PROPIONATE	8 (9%)	7 (8%)	8 (9%)	23 (8%)
PARACETAMOL+DEXTROMETHORPHAN	6 (7%)	7 (8%)	10 (11%)	23 (8%)
HYDROBROMIDE+PSEUDOEPHEDRINE				
HYDROCHLORIDE+DOXYLAMINE SUCCINATE				
CETIRIZINE HYDROCHLORIDE	8 (9%)	5 (5%)	4 (4%)	17 (6%)
PARACETAMOL+CHLORPHENAMINE	3 (3%)	4 (4%)	10 (11%)	17 (6%)
MALEATE+PSEUDOEPHEDRINE HYDROCHLORIDE				
PARACETAMOL+DEXTROMETHORPHAN	4 (4%)	2 (2%)	9 (10%)	15 (6%)
HYDROBROMIDE+PSEUDOEPHEDRINE HYDROCHLORIDE				
DESLORATADINE	7 (8%)	2 (2%)	5 (5%)	14 (5%)
MOMETASONE FUROATE	8 (9%)	3 (3%)	3 (3%)	14 (5%)
PSEUDOEPHEDRINE HYDROCHLORIDE+FEXOFENADINE	3 (3%)	6 (7%)	4 (4%)	13 (5%)
HYDROCHLORIDE				
PSEUDOEPHEDRINE HYDROCHLORIDE+CETIRIZINE	3 (3%)	4 (4%)	5 (5%)	12 (4%)
HYDROCHLORIDE				
ROBITUSSIN (NOS)	4 (4%)	2 (2%)	6 (7%)	12 (4%)
TRIAMCINOLONE ACETONIDE	2 (2%)	4 (4%)	6 (7%)	12 (4%)
GUAIFENESIN	3 (3%)	5 (5%)	3 (3%)	11 (4%)
CHLORPHENAMINE	5 (6%)	0	4 (4%)	9 (3%)
PROMETHAZINE	2 (2%)	2 (2%)	5 (5%)	9 (3%)
DIPHENHYDRAMINE HYDROCHLORIDE+PARACETAMOL	3 (3%)	2 (2%)	3 (3%)	8 (3%)
TYLENOL SINUS (NOS)	4 (4%)	2 (2%)	2 (2%)	8 (3%)

Note: A medication may be reported in more than one ATC Level.

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Table 6.22
Summary of Non-Asthma Medication Use (ITT Population)

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
OXYMETAZOLINE HYDROCHLORIDE	3 (3%)	2 (2%)	2 (2%)	7 (3%)
TYLENOL COLD NOS	2 (2%)	1 (1%)	4 (4%)	7 (3%)
GUAIFENESIN+DEXTROMETHORPHAN HYDROBROMIDE	0	4 (4%)	2 (2%)	6 (2%)
GUAIFENESIN+PSEUDOEPHEDRINE HYDROCHLORIDE	3 (3%)	0	3 (3%)	6 (2%)
HYDROCODONE	2 (2%)	3 (3%)	1 (1%)	6 (2%)
AZELASTINE HYDROCHLORIDE	0	2 (2%)	3 (3%)	5 (2%)
PSEUDOEPHEDRINE SULFATE+LORATADINE	1 (1%)	2 (2%)	2 (2%)	5 (2%)
RHINOCORT (NOS)	0	2 (2%)	3 (3%)	5 (2%)
CETIRIZINE	1 (1%)	1 (1%)	2 (2%)	4 (1%)
DIPHENHYDRAMINE HYDROCHLORIDE	0	2 (2%)	2 (2%)	4 (1%)
PSEUDOEPHEDRINE HYDROCHLORIDE+IBUPROFEN	1 (1%)	2 (2%)	1 (1%)	4 (1%)
BUDESONIDE	0	0	3 (3%)	3 (1%)
CHLORPHENAMINE MALEATE+PSEUDOEPHEDRINE HYDROCHLORIDE	2 (2%)	1 (1%)	0	3 (1%)
DIPHENHYDRAMINE	0	0	3 (3%)	3 (1%)
PSEUDOEPHEDRINE+IBUPROFEN	0	1 (1%)	2 (2%)	3 (1%)
PSEUDOEPHEDRINE+NAPROXEN	0	1 (1%)	2 (2%)	3 (1%)
SODIUM CHLORIDE	2 (2%)	1 (1%)	0	3 (1%)
BECLOMETASONE DIPROPIONATE	1 (1%)	0	1 (1%)	2 (<1%)
BENZONATATE	1 (1%)	0	1 (1%)	2 (<1%)
CHLORPHENAMINE+PSEUDOEPHEDRINE	0	0	2 (2%)	2 (<1%)
COUGH COLD PREPARATIONS NOS	0	1 (1%)	1 (1%)	2 (<1%)
DEXAMETHASONE	1 (1%)	1 (1%)	0	2 (<1%)
DIMENHYDRINATE	0	0	2 (2%)	2 (<1%)
FLUNISOLIDE	1 (1%)	1 (1%)	0	2 (<1%)
GUAIFENESIN+DEXTROMETHORPHAN HYDROBROMIDE+PSEUDOEPHEDRINE HYDROCHLORIDE	0	0	2 (2%)	2 (<1%)
MECLOZINE HYDROCHLORIDE	1 (1%)	1 (1%)	0	2 (<1%)
MONTELUKAST SODIUM	2 (2%)	0	0	2 (<1%)
PARACETAMOL+CHLORPHENAMINE+PSEUDOEPHEDRINE	2 (2%)	0	0	2 (<1%)
PHENYLEPHRINE HYDROCHLORIDE	0	1 (1%)	1 (1%)	2 (<1%)

Note: A medication may be reported in more than one ATC Level.

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Table 6.22
Summary of Non-Asthma Medication Use (ITT Population)

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
PSEUDOEPHEDRINE HYDROCHLORIDE+TRIPROLIDINE HYDROCHLORIDE	0	1 (1%)	1 (1%)	2 (<1%)
BENZOCAINE+CETYLPIRIDINIUM CHLORIDE	1 (1%)	0	0	1 (<1%)
BETAMETHASONE	0	1 (1%)	0	1 (<1%)
BETAMETHASONE DIPROPIONATE	1 (1%)	0	0	1 (<1%)
BETAMETHASONE+CHLORPHENAMINE MALEATE	1 (1%)	0	0	1 (<1%)
CAMPHOR+LEVOMENTHOL+EUCALYPTUS GLOBULUS OIL	0	0	1 (1%)	1 (<1%)
CERTUSS (NOS)	0	0	1 (1%)	1 (<1%)
CHLORPHENAMINE MALEATE	0	1 (1%)	0	1 (<1%)
CHLORPHENAMINE MALEATE+PHENYLPROPANOLAMINE HYDROCHLORIDE	0	1 (1%)	0	1 (<1%)
CHLORPHENAMINE TANNATE	0	1 (1%)	0	1 (<1%)
CLEMASTINE FUMARATE	1 (1%)	0	0	1 (<1%)
DEXTROMETHORPHAN	0	1 (1%)	0	1 (<1%)
DEXTROMETHORPHAN HYDROBROMIDE+AMBROXOL HYDROCHLORIDE	0	1 (1%)	0	1 (<1%)
DEXTROMETHORPHAN HYDROBROMIDE+CHLORPHENAMINE MALEATE+PSEUDOEPHEDRINE HYDROCHLORIDE	0	0	1 (1%)	1 (<1%)
DEXTROMETHORPHAN HYDROBROMIDE+DOXYLAMINE SUCCINATE	1 (1%)	0	0	1 (<1%)
DEXTROMETHORPHAN HYDROBROMIDE+PSEUDOEPHEDRINE HYDROCHLORIDE	0	0	1 (1%)	1 (<1%)
DIMETAPP NOS	1 (1%)	0	0	1 (<1%)
DIPHENHYDRAMINE	0	0	1 (1%)	1 (<1%)
HYDROCHLORIDE+PARACETAMOL+PSEUDOEPHEDRINE HYDROCHLORIDE	0	0	1 (1%)	1 (<1%)
EPINASTINE HYDROCHLORIDE	0	0	1 (1%)	1 (<1%)
FEXOFENADINE	0	0	1 (1%)	1 (<1%)
GUAIFENESIN+DEXTROMETHORPHAN	1 (1%)	0	0	1 (<1%)
HYDROBROMIDE+PHENYLPROPANOLAMINE HYDROCHLORIDE	0	0	1 (1%)	1 (<1%)
GUAIFENESIN+PHENYLEPHRINE	0	0	1 (1%)	1 (<1%)

Note: A medication may be reported in more than one ATC Level.

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Table 6.22
Summary of Non-Asthma Medication Use (ITT Population)

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
GUAIFENESIN+PSEUDOEPHEDRINE HYDROCHLORIDE+TRIPROLIDINE HYDROCHLORIDE	0	0	1 (1%)	1 (<1%)
HYDROCODONE+PHENYLTOLOXAMINE	0	0	1 (1%)	1 (<1%)
HYOSCINE METHONITRATE+CHLORPHENAMINE MALEATE+PHENYLEPHRINE HYDROCHLORIDE	0	1 (1%)	0	1 (<1%)
LIDOCAINE	0	1 (1%)	0	1 (<1%)
MECLOZINE	0	0	1 (1%)	1 (<1%)
OXYGEN	0	0	1 (1%)	1 (<1%)
PARACETAMOL+CHLORPHENAMINE MALEATE+PHENYLEPHRINE HYDROCHLORIDE	0	0	1 (1%)	1 (<1%)
PARACETAMOL+DEXTROMETHORPHAN	0	0	1 (1%)	1 (<1%)
HYDROBROMIDE+DOXYLAMINE SUCCINATE				
PARACETAMOL+DEXTROMETHORPHAN	1 (1%)	0	0	1 (<1%)
HYDROBROMIDE+CHLORPHENAMINE MALEATE+PSEUDOEPHEDRINE HYDROCHLORIDE				
PARACETAMOL+GUAIFENESIN+DEXTROMETHORPHAN	0	0	1 (1%)	1 (<1%)
HYDROBROMIDE+PSEUDOEPHEDRINE HYDROCHLORIDE				
PARACETAMOL+GUAIFENESIN+PSEUDOEPHEDRINE HYDROCHLORIDE	1 (1%)	0	0	1 (<1%)
PARACETAMOL+HYDROCODONE	0	1 (1%)	0	1 (<1%)
PARACETAMOL+PHENYLTOLOXAMINE	0	0	1 (1%)	1 (<1%)
PARACETAMOL+PSEUDOEPHEDRINE	1 (1%)	0	0	1 (<1%)
PARACETAMOL+PSEUDOEPHEDRINE HYDROCHLORIDE	0	1 (1%)	0	1 (<1%)
PARACETAMOL+PSEUDOEPHEDRINE	1 (1%)	0	0	1 (<1%)
HYDROCHLORIDE+DOXYLAMINE SUCCINATE				
PARACETAMOL+SALICYLIC ACID+CAFFEINE+CHLORPHENAMINE MALEATE				
PHENOL	1 (1%)	0	0	1 (<1%)
PSEUDOEPHEDRINE+LORATADINE	0	1 (1%)	0	1 (<1%)
SINUTAB (NOS)	0	1 (1%)	0	1 (<1%)
TETRYZOLINE HYDROCHLORIDE	1 (1%)	0	0	1 (<1%)

Note: A medication may be reported in more than one ATC Level.

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Table 6.22
Summary of Non-Asthma Medication Use (ITT Population)

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
VICKS VAPORUB NOS	1 (1%)	0	0	1 (<1%)
XYLOMETAZOLINE HYDROCHLORIDE	1 (1%)	0	0	1 (<1%)
GENITO URINARY SYSTEM AND SEX HORMONES				
Any medication	40 (45%)	54 (59%)	49 (54%)	143 (53%)
IBUPROFEN	27 (30%)	45 (49%)	36 (40%)	108 (40%)
NAPROXEN SODIUM	11 (12%)	9 (10%)	10 (11%)	30 (11%)
ETHINYLOESTRADIOL+NORGESTIMATE	3 (3%)	1 (1%)	4 (4%)	8 (3%)
ETHINYLOESTRADIOL+NORELGESTROMIN	3 (3%)	3 (3%)	1 (1%)	7 (3%)
NAPROXEN	3 (3%)	3 (3%)	0	6 (2%)
ETHINYLOESTRADIOL+DESOGESTREL	0	2 (2%)	3 (3%)	5 (2%)
ACETYSALICYLIC ACID+CAFFEINE+CINNAMEDRINE HYDROCHLORIDE	3 (3%)	0	1 (1%)	4 (1%)
CLINDAMYCIN	2 (2%)	1 (1%)	1 (1%)	4 (1%)
ETHINYLOESTRADIOL+DROSPIRENONE	0	2 (2%)	2 (2%)	4 (1%)
ETHINYLOESTRADIOL+LEVONORGESTREL	1 (1%)	2 (2%)	1 (1%)	4 (1%)
ETHINYLOESTRADIOL+NORGESTREL	1 (1%)	2 (2%)	1 (1%)	4 (1%)
ETHINYLOESTRADIOL+ETYNODIOL DIACETATE	1 (1%)	1 (1%)	1 (1%)	3 (1%)
MEDROXYPROGESTERONE ACETATE	0	2 (2%)	1 (1%)	3 (1%)
METRONIDAZOLE	1 (1%)	1 (1%)	1 (1%)	3 (1%)
ESTROGENS CONJUGATED	0	2 (2%)	0	2 (<1%)
ESTROGENS CONJUGATED+MEDROXYPROGESTERONE ACETATE	1 (1%)	0	1 (1%)	2 (<1%)
ETHINYLOESTRADIOL+NORETHISTERONE ACETATE	1 (1%)	0	1 (1%)	2 (<1%)
NORETHISTERONE+MESTRANOL	1 (1%)	0	1 (1%)	2 (<1%)
PROGESTERONE	1 (1%)	0	1 (1%)	2 (<1%)
ACETIC ACID	0	0	1 (1%)	1 (<1%)
CABERGOLINE	0	0	1 (1%)	1 (<1%)
CLOTRIMAZOLE	1 (1%)	0	0	1 (<1%)
ESTRADIOL	1 (1%)	0	0	1 (<1%)
FINASTERIDE	0	1 (1%)	0	1 (<1%)
MEDROXYPROGESTERONE	0	0	1 (1%)	1 (<1%)

Note: A medication may be reported in more than one ATC Level.

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Table 6.22
Summary of Non-Asthma Medication Use (ITT Population)

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
METHYLTESTOSTERONE+ESTROGENS ESTERIFIED	0	0	1 (1%)	1 (<1%)
MICONAZOLE NITRATE	1 (1%)	0	0	1 (<1%)
OXYBUTYNIN HYDROCHLORIDE	1 (1%)	0	0	1 (<1%)
PHENAZOPYRIDINE HYDROCHLORIDE	1 (1%)	0	0	1 (<1%)
MUSCULO-SKELETAL SYSTEM				
Any medication	41 (46%)	49 (53%)	46 (51%)	136 (50%)
IBUPROFEN	27 (30%)	45 (49%)	36 (40%)	108 (40%)
NAPROXEN SODIUM	11 (12%)	9 (10%)	10 (11%)	30 (11%)
CYCLOBENZAPRINE HYDROCHLORIDE	0	4 (4%)	2 (2%)	6 (2%)
NAPROXEN	3 (3%)	3 (3%)	0	6 (2%)
CELECOXIB	4 (4%)	0	1 (1%)	5 (2%)
CARISOPRODOL	1 (1%)	1 (1%)	1 (1%)	3 (1%)
PSEUDOEPHEDRINE+IBUPROFEN	0	1 (1%)	2 (2%)	3 (1%)
PSEUDOEPHEDRINE+NAPROXEN	0	1 (1%)	2 (2%)	3 (1%)
ALENDRONATE SODIUM	1 (1%)	1 (1%)	0	2 (<1%)
ALLOPURINOL	0	0	2 (2%)	2 (<1%)
DICLOFENAC	1 (1%)	0	1 (1%)	2 (<1%)
MELOXICAM	1 (1%)	0	1 (1%)	2 (<1%)
ORPHENADRINE	0	0	2 (2%)	2 (<1%)
CHONDROITIN+GLUCOSAMINE	0	0	1 (1%)	1 (<1%)
GLUCOSAMINE	0	0	1 (1%)	1 (<1%)
INDOMETACIN	1 (1%)	0	0	1 (<1%)
KETOPROFEN	1 (1%)	0	0	1 (<1%)
KETOROLAC	0	0	1 (1%)	1 (<1%)
KETOROLAC TROMETAMOL	0	1 (1%)	0	1 (<1%)
MEFENAMIC ACID	0	0	1 (1%)	1 (<1%)
METAXALONE	1 (1%)	0	0	1 (<1%)
OXAPROZIN	0	0	1 (1%)	1 (<1%)
ROFECOXIB	0	0	1 (1%)	1 (<1%)
SODIUM IBANDRONATE	1 (1%)	0	0	1 (<1%)

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Table 6.22
Summary of Non-Asthma Medication Use (ITT Population)

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)

ALIMENTARY TRACT AND METABOLISM				
Any medication	37 (42%)	30 (33%)	47 (52%)	114 (42%)
ACETYLSALICYLIC ACID	3 (3%)	11 (12%)	16 (18%)	30 (11%)
VITAMINS NOS	4 (4%)	5 (5%)	9 (10%)	18 (7%)
TRIAMCINOLONE ACETONIDE	2 (2%)	4 (4%)	6 (7%)	12 (4%)
ESOMEPRAZOLE MAGNESIUM	3 (3%)	4 (4%)	2 (2%)	9 (3%)
PROMETHAZINE	2 (2%)	2 (2%)	5 (5%)	9 (3%)
BISMUTH SUBSALICYLATE	4 (4%)	2 (2%)	1 (1%)	7 (3%)
RANITIDINE HYDROCHLORIDE	1 (1%)	5 (5%)	1 (1%)	7 (3%)
ASCORBIC ACID	2 (2%)	3 (3%)	1 (1%)	6 (2%)
CALCIUM CARBONATE	2 (2%)	2 (2%)	2 (2%)	6 (2%)
LANSOPRAZOLE	1 (1%)	0	4 (4%)	5 (2%)
RANITIDINE	2 (2%)	1 (1%)	2 (2%)	5 (2%)
RHINOCORT (NOS)	0	2 (2%)	3 (3%)	5 (2%)
CALCIUM	1 (1%)	2 (2%)	1 (1%)	4 (1%)
FAMOTIDINE	1 (1%)	0	3 (3%)	4 (1%)
BUDESONIDE	0	0	3 (3%)	3 (1%)
METRONIDAZOLE	1 (1%)	1 (1%)	1 (1%)	3 (1%)
MINERALS NOS+VITAMINS NOS	1 (1%)	0	2 (2%)	3 (1%)
PREDNISONE	2 (2%)	0	1 (1%)	3 (1%)
SODIUM CHLORIDE	2 (2%)	1 (1%)	0	3 (1%)
ACETYLSALICYLIC ACID+SODIUM BICARBONATE+CITRIC ACID	1 (1%)	1 (1%)	0	2 (<1%)
ALUMINIUM HYDROXIDE GEL+MAGNESIUM HYDROXIDE	2 (2%)	0	0	2 (<1%)
ALUMINIUM HYDROXIDE GEL, DRIED+MAGNESIUM HYDROXIDE+SIMETICONE	1 (1%)	0	1 (1%)	2 (<1%)
ATROPINE	0	1 (1%)	1 (1%)	2 (<1%)
BECLOMETASONE DIPROPIONATE	1 (1%)	0	1 (1%)	2 (<1%)
DEXAMETHASONE	1 (1%)	1 (1%)	0	2 (<1%)
DIMENHYDRINATE	0	0	2 (2%)	2 (<1%)

Note: A medication may be reported in more than one ATC Level.

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Table 6.22
Summary of Non-Asthma Medication Use (ITT Population)

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
HYOSCYAMINE SULFATE	0	1 (1%)	1 (1%)	2 (<1%)
INVERT SUGAR+PHOSPHORIC ACID	0	0	2 (2%)	2 (<1%)
METFORMIN	0	2 (2%)	0	2 (<1%)
METFORMIN HYDROCHLORIDE	1 (1%)	0	1 (1%)	2 (<1%)
MINERALS NOS+VITAMINS NOS+HERBALS NOS	1 (1%)	0	1 (1%)	2 (<1%)
OMEPRAZOLE	1 (1%)	0	1 (1%)	2 (<1%)
PANTOPRAZOLE	2 (2%)	0	0	2 (<1%)
PARGEVERINE HYDROCHLORIDE	0	0	2 (2%)	2 (<1%)
RABEPRAZOLE SODIUM	1 (1%)	1 (1%)	0	2 (<1%)
TETRACYCLINE	1 (1%)	1 (1%)	0	2 (<1%)
TOCOPHEROL	1 (1%)	1 (1%)	0	2 (<1%)
ZINC GLUCONATE	0	0	2 (2%)	2 (<1%)
ACTAL (NOS)	0	0	1 (1%)	1 (<1%)
ACTIVATED CHARCOAL	1 (1%)	0	0	1 (<1%)
ASCORBIC ACID+ECHINACEA	0	1 (1%)	0	1 (<1%)
BENZOCAINE+CETYLPIRIDINIUM CHLORIDE	1 (1%)	0	0	1 (<1%)
BETAMETHASONE	0	1 (1%)	0	1 (<1%)
BETAMETHASONE DIPROPIONATE	1 (1%)	0	0	1 (<1%)
CLOTRIMAZOLE	1 (1%)	0	0	1 (<1%)
DICYCLOVERINE HYDROCHLORIDE	1 (1%)	0	0	1 (<1%)
DOCUSATE SODIUM	0	1 (1%)	0	1 (<1%)
DOXYCYCLINE HYCLATE	0	1 (1%)	0	1 (<1%)
ESOMEPRAZOLE	0	0	1 (1%)	1 (<1%)
GAVISCON NOS	0	1 (1%)	0	1 (<1%)
GLIPIZIDE	0	1 (1%)	0	1 (<1%)
HYDROCORTISONE	0	0	1 (1%)	1 (<1%)
HYOSCYAMINE	0	1 (1%)	0	1 (<1%)
KAOPECTATE NOS	0	0	1 (1%)	1 (<1%)
LACTOBACILLUS ACIDOPHILUS	1 (1%)	0	0	1 (<1%)
LINUM USITATISSIMUM	0	1 (1%)	0	1 (<1%)
LOPERAMIDE HYDROCHLORIDE	0	1 (1%)	0	1 (<1%)

Note: A medication may be reported in more than one ATC Level.

Table 6.22
Summary of Non-Asthma Medication Use (ITT Population)

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
MECLOZINE	0	0	1 (1%)	1 (<1%)
MESALAZINE	1 (1%)	0	0	1 (<1%)
MICONAZOLE NITRATE	1 (1%)	0	0	1 (<1%)
NATEGLINIDE	0	1 (1%)	0	1 (<1%)
PHENTERMINE	0	1 (1%)	0	1 (<1%)
PHENTERMINE RESIN	0	1 (1%)	0	1 (<1%)
POLYCARBOPHIL CALCIUM	0	1 (1%)	0	1 (<1%)
POTASSIUM CHLORIDE	1 (1%)	0	0	1 (<1%)
SUCRALFATE	1 (1%)	0	0	1 (<1%)
THIAMINE HYDROCHLORIDE+CYANOCOBALAMIN+PYRIDOXINE HYDROCHLORIDE	0	0	1 (1%)	1 (<1%)
VITAMIN B NOS	1 (1%)	0	0	1 (<1%)
VITAMIN B SUBSTANCES NOS	1 (1%)	0	0	1 (<1%)
VITAMIN D NOS	1 (1%)	0	0	1 (<1%)
DERMATOLOGICALS				
Any medication	32 (36%)	28 (30%)	42 (46%)	102 (38%)
BENADRYL (NOS)	7 (8%)	6 (7%)	16 (18%)	29 (11%)
FLUTICASONE PROPIONATE	8 (9%)	7 (8%)	8 (9%)	23 (8%)
MOMETASONE FUROATE	8 (9%)	3 (3%)	3 (3%)	14 (5%)
TRIAMCINOLONE ACETONIDE	2 (2%)	4 (4%)	6 (7%)	12 (4%)
PROMETHAZINE	2 (2%)	2 (2%)	5 (5%)	9 (3%)
RHINOCORT (NOS)	0	2 (2%)	3 (3%)	5 (2%)
CLINDAMYCIN	2 (2%)	1 (1%)	1 (1%)	4 (1%)
DIPHENHYDRAMINE HYDROCHLORIDE	0	2 (2%)	2 (2%)	4 (1%)
ACYCLOVIR	1 (1%)	0	2 (2%)	3 (1%)
BUDESONIDE	0	0	3 (3%)	3 (1%)
DIPHENHYDRAMINE	0	0	3 (3%)	3 (1%)
FLUCONAZOLE	2 (2%)	1 (1%)	0	3 (1%)
METRONIDAZOLE	1 (1%)	1 (1%)	1 (1%)	3 (1%)
BECLOMETASONE DIPROPIONATE	1 (1%)	0	1 (1%)	2 (<1%)

Note: A medication may be reported in more than one ATC Level.

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Table 6.22
Summary of Non-Asthma Medication Use (ITT Population)

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
DEXAMETHASONE	1 (1%)	1 (1%)	0	2 (<1%)
TETRACYCLINE	1 (1%)	1 (1%)	0	2 (<1%)
TOCOPHEROL	1 (1%)	1 (1%)	0	2 (<1%)
ADAPALENE	0	1 (1%)	0	1 (<1%)
AZELAIC ACID	1 (1%)	0	0	1 (<1%)
BETAMETHASONE	0	1 (1%)	0	1 (<1%)
BETAMETHASONE DIPROPIONATE	1 (1%)	0	0	1 (<1%)
CLEMASTINE FUMARATE	1 (1%)	0	0	1 (<1%)
CLOBETASOL	0	1 (1%)	0	1 (<1%)
CLOTRIMAZOLE	1 (1%)	0	0	1 (<1%)
DESONIDE	0	1 (1%)	0	1 (<1%)
EMOLLIENTS AND PROTECTIVES	1 (1%)	0	0	1 (<1%)
ERYTHROMYCIN	1 (1%)	0	0	1 (<1%)
EUCERIN (NOS)	1 (1%)	0	0	1 (<1%)
FINASTERIDE	0	1 (1%)	0	1 (<1%)
HYDROCORTISONE	0	0	1 (1%)	1 (<1%)
IODINE	0	1 (1%)	0	1 (<1%)
LIDOCAINE	0	1 (1%)	0	1 (<1%)
METHYLPREDNISOLONE	0	0	1 (1%)	1 (<1%)
METHYLPREDNISOLONE ACETATE	0	1 (1%)	0	1 (<1%)
MICONAZOLE NITRATE	1 (1%)	0	0	1 (<1%)
PARAFFIN SOFT	1 (1%)	0	0	1 (<1%)
PHENOL	1 (1%)	0	0	1 (<1%)
SALICYLIC ACID	0	1 (1%)	0	1 (<1%)
TERBINAFINE HYDROCHLORIDE	0	1 (1%)	0	1 (<1%)
ANTIINFECTIVES FOR SYSTEMIC USE				
Any medication	25 (28%)	21 (23%)	21 (23%)	67 (25%)
AMOXICILLIN	8 (9%)	2 (2%)	2 (2%)	12 (4%)
AZITHROMYCIN	1 (1%)	5 (5%)	2 (2%)	8 (3%)
BENZYL PENICILLIN	1 (1%)	3 (3%)	2 (2%)	6 (2%)

Note: A medication may be reported in more than one ATC Level.

Table 6.22
Summary of Non-Asthma Medication Use (ITT Population)

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
CLINDAMYCIN	2 (2%)	1 (1%)	1 (1%)	4 (1%)
LEVOFLOXACIN	2 (2%)	0	2 (2%)	4 (1%)
ACYCLOVIR	1 (1%)	0	2 (2%)	3 (1%)
AMOXICILLIN TRIHYDRATE+CLAVULANATE POTASSIUM	2 (2%)	1 (1%)	0	3 (1%)
CLARITHROMYCIN	1 (1%)	1 (1%)	1 (1%)	3 (1%)
FLUCONAZOLE	2 (2%)	1 (1%)	0	3 (1%)
METRONIDAZOLE	1 (1%)	1 (1%)	1 (1%)	3 (1%)
MOXIFLOXACIN	3 (3%)	0	0	3 (1%)
TELITHROMYCIN	1 (1%)	2 (2%)	0	3 (1%)
CEFALEXIN	0	0	2 (2%)	2 (<1%)
CEFDINIR	1 (1%)	1 (1%)	0	2 (<1%)
DOXYCYCLINE	0	1 (1%)	1 (1%)	2 (<1%)
SULFAMETHOXAZOLE+TRIMETHOPRIM	1 (1%)	0	1 (1%)	2 (<1%)
TETRACYCLINE	1 (1%)	1 (1%)	0	2 (<1%)
VALACICLOVIR HYDROCHLORIDE	1 (1%)	0	1 (1%)	2 (<1%)
AMPICILLIN	1 (1%)	0	0	1 (<1%)
CEFACLOX	0	0	1 (1%)	1 (<1%)
CEFPROZIL	0	1 (1%)	0	1 (<1%)
DOXYCYCLINE HYCLATE	0	1 (1%)	0	1 (<1%)
DOXYCYCLINE HYDROCHLORIDE	0	0	1 (1%)	1 (<1%)
ERYTHROMYCIN	1 (1%)	0	0	1 (<1%)
FAMCICLOVIR	0	0	1 (1%)	1 (<1%)
GATIFLOXACIN	0	0	1 (1%)	1 (<1%)
INFLUENZA VACCINE	0	0	1 (1%)	1 (<1%)
MICONAZOLE NITRATE	1 (1%)	0	0	1 (<1%)
MINOCYCLINE	0	1 (1%)	0	1 (<1%)
MOXIFLOXACIN HYDROCHLORIDE	0	0	1 (1%)	1 (<1%)
VALACICLOVIR	0	0	1 (1%)	1 (<1%)
SENSORY ORGANS				
Any medication	19 (21%)	16 (17%)	22 (24%)	57 (21%)

Note: A medication may be reported in more than one ATC Level.

Table 6.22
Summary of Non-Asthma Medication Use (ITT Population)

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
TRIAMCINOLONE ACETONIDE	2 (2%)	4 (4%)	6 (7%)	12 (4%)
OXYMETAZOLINE HYDROCHLORIDE	3 (3%)	2 (2%)	2 (2%)	7 (3%)
BENZYL PENICILLIN	1 (1%)	3 (3%)	2 (2%)	6 (2%)
OLOPATADINE HYDROCHLORIDE	0	2 (2%)	2 (2%)	4 (1%)
ACYCLOVIR	1 (1%)	0	2 (2%)	3 (1%)
SODIUM CHLORIDE	2 (2%)	1 (1%)	0	3 (1%)
ATROPINE	0	1 (1%)	1 (1%)	2 (<1%)
BETAMETHASONE SODIUM PHOSPHATE+NEOMYCIN SULFATE	1 (1%)	0	1 (1%)	2 (<1%)
DEXAMETHASONE	1 (1%)	1 (1%)	0	2 (<1%)
DICLOFENAC	1 (1%)	0	1 (1%)	2 (<1%)
PHENYLEPHRINE HYDROCHLORIDE	0	1 (1%)	1 (1%)	2 (<1%)
TETRACYCLINE	1 (1%)	1 (1%)	0	2 (<1%)
ACETAZOLAMIDE	1 (1%)	0	0	1 (<1%)
ACETIC ACID	0	0	1 (1%)	1 (<1%)
AMPICILLIN	1 (1%)	0	0	1 (<1%)
CORTISONE	0	1 (1%)	0	1 (<1%)
DESONIDE	0	1 (1%)	0	1 (<1%)
DEXAMETHASONE+FRAMYCETIN+GRAMICIDIN	1 (1%)	0	0	1 (<1%)
ERYTHROMYCIN	1 (1%)	0	0	1 (<1%)
FAMCICLOVIR	0	0	1 (1%)	1 (<1%)
HYDROCORTISONE	0	0	1 (1%)	1 (<1%)
INDOMETACIN	1 (1%)	0	0	1 (<1%)
KETOROLAC	0	0	1 (1%)	1 (<1%)
KETOROLAC TROMETAMOL	0	1 (1%)	0	1 (<1%)
LIDOCAINE	0	1 (1%)	0	1 (<1%)
METHYLPREDNISOLONE	0	0	1 (1%)	1 (<1%)
MICONAZOLE NITRATE	1 (1%)	0	0	1 (<1%)
OPHTHALMOLOGICALS	0	0	1 (1%)	1 (<1%)
PHENIRAMINE MALEATE+NAPHAZOLINE HYDROCHLORIDE	1 (1%)	0	0	1 (<1%)
PROCAINE HYDROCHLORIDE	0	1 (1%)	0	1 (<1%)
SALICYLIC ACID	0	1 (1%)	0	1 (<1%)

Note: A medication may be reported in more than one ATC Level.

Table 6.22
Summary of Non-Asthma Medication Use (ITT Population)

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
TETRYZOLINE HYDROCHLORIDE	1 (1%)	0	0	1 (<1%)
XYLOMETAZOLINE HYDROCHLORIDE	1 (1%)	0	0	1 (<1%)
ZINC SULFATE+TETRYZOLINE HYDROCHLORIDE	1 (1%)	0	0	1 (<1%)
BLOOD AND BLOOD FORMING ORGANS				
Any medication	9 (10%)	14 (15%)	17 (19%)	40 (15%)
ACETYLSALICYLIC ACID	3 (3%)	11 (12%)	16 (18%)	30 (11%)
IRON	2 (2%)	1 (1%)	0	3 (1%)
SODIUM CHLORIDE	2 (2%)	1 (1%)	0	3 (1%)
CYANOCOBALAMIN	0	1 (1%)	1 (1%)	2 (<1%)
ASCORBIC ACID+IRON	1 (1%)	0	0	1 (<1%)
BROMELAINS	1 (1%)	0	0	1 (<1%)
FERROUS SULPHATE	0	1 (1%)	0	1 (<1%)
POTASSIUM CHLORIDE	1 (1%)	0	0	1 (<1%)
TYROSINE	0	1 (1%)	0	1 (<1%)
CARDIOVASCULAR SYSTEM				
Any medication	13 (15%)	15 (16%)	11 (12%)	39 (14%)
HYDROCHLOROTHIAZIDE	2 (2%)	2 (2%)	2 (2%)	6 (2%)
ATORVASTATIN CALCIUM	2 (2%)	0	2 (2%)	4 (1%)
ENALAPRIL	0	2 (2%)	1 (1%)	3 (1%)
LISINOPRIL	0	0	3 (3%)	3 (1%)
SPIRONOLACTONE	2 (2%)	1 (1%)	0	3 (1%)
AMLODIPINE BESILATE	2 (2%)	0	0	2 (<1%)
CAPTOPRIL	0	1 (1%)	1 (1%)	2 (<1%)
DEXAMETHASONE	1 (1%)	1 (1%)	0	2 (<1%)
OLMESARTAN	1 (1%)	0	1 (1%)	2 (<1%)
PHENYLEPHRINE HYDROCHLORIDE	0	1 (1%)	1 (1%)	2 (<1%)
VERAPAMIL	1 (1%)	0	1 (1%)	2 (<1%)
ACETAZOLAMIDE	1 (1%)	0	0	1 (<1%)
ATENOLOL	0	0	1 (1%)	1 (<1%)

Note: A medication may be reported in more than one ATC Level.

Table 6.22
Summary of Non-Asthma Medication Use (ITT Population)

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
BENAZEPRIL HYDROCHLORIDE	0	1 (1%)	0	1 (<1%)
BENAZEPRIL HYDROCHLORIDE+AMLODIPINE BESILATE	0	0	1 (1%)	1 (<1%)
BETAMETHASONE	0	1 (1%)	0	1 (<1%)
BETAMETHASONE DIPROPIONATE	1 (1%)	0	0	1 (<1%)
CANDESARTAN CILEXETIL	0	1 (1%)	0	1 (<1%)
DIGOXIN	0	0	1 (1%)	1 (<1%)
DILTIAZEM	1 (1%)	0	0	1 (<1%)
DILTIAZEM HYDROCHLORIDE	0	1 (1%)	0	1 (<1%)
EZETIMIBE	0	1 (1%)	0	1 (<1%)
FISH OIL	0	1 (1%)	0	1 (<1%)
FUROSEMIDE	1 (1%)	0	0	1 (<1%)
HYDROCHLOROTHIAZIDE+CANDESARTAN CILEXETIL	0	1 (1%)	0	1 (<1%)
HYDROCORTISONE	0	0	1 (1%)	1 (<1%)
INDOMETACIN	1 (1%)	0	0	1 (<1%)
ISRADIPINE	0	1 (1%)	0	1 (<1%)
LIDOCAINE	0	1 (1%)	0	1 (<1%)
NICOTINIC ACID	0	1 (1%)	0	1 (<1%)
PHENOL	1 (1%)	0	0	1 (<1%)
PROCAINE HYDROCHLORIDE	0	1 (1%)	0	1 (<1%)
SIMVASTATIN	0	1 (1%)	0	1 (<1%)
TRIAMTERENE	1 (1%)	0	0	1 (<1%)
VALSARTAN	1 (1%)	0	0	1 (<1%)
VERAPAMIL HYDROCHLORIDE	0	0	1 (1%)	1 (<1%)
SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES				
Any medication	9 (10%)	10 (11%)	14 (15%)	33 (12%)
TRIAMCINOLONE ACETONIDE	2 (2%)	4 (4%)	6 (7%)	12 (4%)
LEVOTHYROXINE SODIUM	3 (3%)	1 (1%)	1 (1%)	5 (2%)
BUDESONIDE	0	0	3 (3%)	3 (1%)
PREDNISONE	2 (2%)	0	1 (1%)	3 (1%)
DEXAMETHASONE	1 (1%)	1 (1%)	0	2 (<1%)

Note: A medication may be reported in more than one ATC Level.

Table 6.22
Summary of Non-Asthma Medication Use (ITT Population)

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
THYROID	0	0	2 (2%)	2 (<1%)
BETAMETHASONE	0	1 (1%)	0	1 (<1%)
BETAMETHASONE DIPROPIONATE	1 (1%)	0	0	1 (<1%)
BETAMETHASONE+CHLORPHENAMINE MALEATE	1 (1%)	0	0	1 (<1%)
CORTISONE	0	1 (1%)	0	1 (<1%)
HYDROCORTISONE	0	0	1 (1%)	1 (<1%)
IODINE	0	1 (1%)	0	1 (<1%)
LEVOTHYROXINE	0	0	1 (1%)	1 (<1%)
MELATONIN	1 (1%)	0	0	1 (<1%)
METHYLPREDNISOLONE	0	0	1 (1%)	1 (<1%)
METHYLPREDNISOLONE ACETATE	0	1 (1%)	0	1 (<1%)
ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS				
Any medication	3 (3%)	6 (7%)	5 (5%)	14 (5%)
IMMUNOTHERAPY{NOS}	1 (1%)	4 (4%)	2 (2%)	7 (3%)
MEDROXYPROGESTERONE ACETATE	0	2 (2%)	1 (1%)	3 (1%)
ESTROGENS CONJUGATED	0	2 (2%)	0	2 (<1%)
ESTRADIOL	1 (1%)	0	0	1 (<1%)
INFLIXIMAB	0	0	1 (1%)	1 (<1%)
LEUPRORELIN ACETATE	1 (1%)	0	0	1 (<1%)
MEDROXYPROGESTERONE	0	0	1 (1%)	1 (<1%)
VARIOUS				
Any medication	1 (1%)	5 (5%)	6 (7%)	12 (4%)
AMBIGUOUS MEDICATION	0	3 (3%)	0	3 (1%)
MINERALS NOS+VITAMINS NOS+HERBALS NOS	1 (1%)	0	1 (1%)	2 (<1%)
ASCORBIC ACID+ECHINACEA	0	1 (1%)	0	1 (<1%)
CAFFEINE+PRASTERONE+HERBALS NOS	0	0	1 (1%)	1 (<1%)
CHONDROITIN+GLUCOSAMINE	0	0	1 (1%)	1 (<1%)
FLUCAPS (NOS)	0	0	1 (1%)	1 (<1%)

Note: A medication may be reported in more than one ATC Level.

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Table 6.22
Summary of Non-Asthma Medication Use (ITT Population)

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
GINKGO BILOBA EXTRACT+OXITRIPTAN+MAGNESIUM OXIDE+MALIC ACID+VANADYL SULPHATE+HERBAL EXTRACTS NOS+VIT	0	1 (1%)	0	1 (<1%)
HYDRASTIS CANADENSIS	0	0	1 (1%)	1 (<1%)
LINUM USITATISSIMUM	0	1 (1%)	0	1 (<1%)
OXYGEN	0	0	1 (1%)	1 (<1%)
TYROSINE	0	1 (1%)	0	1 (<1%)
ANTIPARASITIC PRODUCTS, INSECTICIDES AND REPELLENT				
Any medication	2 (2%)	1 (1%)	3 (3%)	6 (2%)
METRONIDAZOLE	1 (1%)	1 (1%)	1 (1%)	3 (1%)
ALBENDAZOLE	0	0	1 (1%)	1 (<1%)
AMODIAQUINE	0	0	1 (1%)	1 (<1%)
LUMEFANTRINE+ARTEMETHER	1 (1%)	0	0	1 (<1%)
PYRIMETHAMINE+SULFADOXINE	0	0	1 (1%)	1 (<1%)

Note: A medication may be reported in more than one ATC Level.

Table 6.22
Summary of Non-Asthma Medication Use (ITT Population)

Treatment: Salmeterol

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Subjects in treatment group	90	90	92	272
Subjects with any medication	81 (90%)	81 (90%)	80 (87%)	242 (89%)
NERVOUS SYSTEM				
Any medication	59 (66%)	62 (69%)	68 (74%)	189 (69%)
IBUPROFEN	33 (37%)	36 (40%)	31 (34%)	100 (37%)
PARACETAMOL	35 (39%)	29 (32%)	33 (36%)	97 (36%)
ACETYLSALICYLIC ACID	4 (4%)	9 (10%)	15 (16%)	28 (10%)
EXCEDRIN (NOS)	5 (6%)	9 (10%)	5 (5%)	19 (7%)
PARACETAMOL+HYDROCODONE BITARTRATE	4 (4%)	2 (2%)	7 (8%)	13 (5%)
PARACETAMOL+CHLORPHENAMINE MALEATE+PSEUDOEPHEDRINE HYDROCHLORIDE	2 (2%)	3 (3%)	3 (3%)	8 (3%)
ACETYLSALICYLIC ACID+PARACETAMOL+CAFFEINE	3 (3%)	1 (1%)	3 (3%)	7 (3%)
ACETYLSALICYLIC ACID+CAFFEINE+CINNAMEDRINE HYDROCHLORIDE	2 (2%)	4 (4%)	0	6 (2%)
CYCLOBENZAPRINE HYDROCHLORIDE	4 (4%)	0	2 (2%)	6 (2%)
ACETYLSALICYLIC ACID+SODIUM BICARBONATE+CITRIC ACID	2 (2%)	1 (1%)	2 (2%)	5 (2%)
BUPROPION HYDROCHLORIDE	0	1 (1%)	4 (4%)	5 (2%)
DIPHENHYDRAMINE HYDROCHLORIDE+PARACETAMOL	0	1 (1%)	3 (3%)	4 (1%)
DEXTROPROPOXYPHENE NAPSILATE+PARACETAMOL	0	0	3 (3%)	3 (1%)
PHENOL	1 (1%)	0	2 (2%)	3 (1%)
PROMETHAZINE	0	1 (1%)	2 (2%)	3 (1%)
SERTRALINE HYDROCHLORIDE	1 (1%)	1 (1%)	1 (1%)	3 (1%)
TOPIRAMATE	2 (2%)	0	1 (1%)	3 (1%)
ACETYLSALICYLIC ACID+CHLORPHENAMINE	1 (1%)	0	1 (1%)	2 (<1%)
MALEATE+PHENYLPROPANOLAMINE BITARTRATE				
CHLORASEPTIC (NOS)	1 (1%)	1 (1%)	0	2 (<1%)
ESCITALOPRAM OXALATE	1 (1%)	1 (1%)	0	2 (<1%)

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Table 6.22
Summary of Non-Asthma Medication Use (ITT Population)

Treatment: Salmeterol

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
FLUOXETINE HYDROCHLORIDE	2 (2%)	0	0	2 (<1%)
HYDROCODONE	0	0	2 (2%)	2 (<1%)
LAMOTRIGINE	1 (1%)	0	1 (1%)	2 (<1%)
METHYLPHENIDATE HYDROCHLORIDE	0	0	2 (2%)	2 (<1%)
MORPHINE	0	1 (1%)	1 (1%)	2 (<1%)
PARACETAMOL+OXYCODONE HYDROCHLORIDE	0	1 (1%)	1 (1%)	2 (<1%)
PAROXETINE HYDROCHLORIDE	1 (1%)	1 (1%)	0	2 (<1%)
TEMAZEPAM	1 (1%)	1 (1%)	0	2 (<1%)
TRAZODONE	1 (1%)	0	1 (1%)	2 (<1%)
TYLENOL #3 (NOS)	0	0	2 (2%)	2 (<1%)
ACETYLSALICYLIC ACID+CAFFEINE+SALICYLAMIDE	0	0	1 (1%)	1 (<1%)
ACETYLSALICYLIC ACID+OXYCODONE	0	0	1 (1%)	1 (<1%)
ACETYLSALICYLIC ACID+PARACETAMOL	0	1 (1%)	0	1 (<1%)
ALPRAZOLAM	0	0	1 (1%)	1 (<1%)
AMFETAMINE SULFATE+AMFETAMINE	1 (1%)	0	0	1 (<1%)
ASPARTATE+DEXAMFETAMINE				
SULFATE+DEXTROAMPHETAMINE SACCHARATE				
BENZOCAINE	1 (1%)	0	0	1 (<1%)
BUSPIRONE HYDROCHLORIDE	0	0	1 (1%)	1 (<1%)
BUTORPHANOL TARTRATE	0	1 (1%)	0	1 (<1%)
CAMELLIA SINENSIS	0	0	1 (1%)	1 (<1%)
CLONIDINE	0	0	1 (1%)	1 (<1%)
CODEINE PHOSPHATE+PARACETAMOL	0	0	1 (1%)	1 (<1%)
CYCLOBENZAPRINE	0	1 (1%)	0	1 (<1%)
DIAZEPAM	0	0	1 (1%)	1 (<1%)
DIHYDROERGOTAMINE	0	1 (1%)	0	1 (<1%)
MESILATE+CAFFEINE+PROPYPHENAZONE				
DIPHENHYDRAMINE+PARACETAMOL	0	0	1 (1%)	1 (<1%)
DULOXETINE HYDROCHLORIDE	1 (1%)	0	0	1 (<1%)
DYCLONINE HYDROCHLORIDE	0	0	1 (1%)	1 (<1%)
ELETRIPTAN HYDROBROMIDE	0	0	1 (1%)	1 (<1%)

Note: A medication may be reported in more than one ATC Level.

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Table 6.22
Summary of Non-Asthma Medication Use (ITT Population)

Treatment: Salmeterol

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
EPINEPHRINE BITARTRATE+PRILOCAINE HYDROCHLORIDE	0	0	1 (1%)	1 (<1%)
FIORINAL NOS	0	0	1 (1%)	1 (<1%)
FLUOXETINE	0	0	1 (1%)	1 (<1%)
GINKGO BILOBA	0	0	1 (1%)	1 (<1%)
HYDROXYZINE	0	1 (1%)	0	1 (<1%)
KETOROLAC TROMETAMOL	0	0	1 (1%)	1 (<1%)
MAGNESIUM SALICYLATE	0	0	1 (1%)	1 (<1%)
MEFENAMIC ACID	0	1 (1%)	0	1 (<1%)
MIDAZOLAM	1 (1%)	0	0	1 (<1%)
MIRTAZAPINE	1 (1%)	0	0	1 (<1%)
NARATRIPTAN HYDROCHLORIDE	0	0	1 (1%)	1 (<1%)
OXYCODONE	0	1 (1%)	0	1 (<1%)
PARACETAMOL+CAFFEINE	0	0	1 (1%)	1 (<1%)
PARACETAMOL+CAFFEINE+BUTALBITAL	1 (1%)	0	0	1 (<1%)
PARACETAMOL+CAFFEINE+SALICYLAMIDE+PHENYLTOLOXAMINE	0	0	1 (1%)	1 (<1%)
PARACETAMOL+DICHLORALPHENAZONE+ISOMETHEPTENE MUCATE	1 (1%)	0	0	1 (<1%)
PARACETAMOL+TRAMADOL HYDROCHLORIDE	1 (1%)	0	0	1 (<1%)
PAROXETINE	0	0	1 (1%)	1 (<1%)
PETHIDINE	1 (1%)	0	0	1 (<1%)
PETHIDINE HYDROCHLORIDE	0	0	1 (1%)	1 (<1%)
PRILOCAINE	0	0	1 (1%)	1 (<1%)
PROCAINE HYDROCHLORIDE	1 (1%)	0	0	1 (<1%)
QUETIAPINE FUMARATE	1 (1%)	0	0	1 (<1%)
RIZATRIPTAN BENZOATE	0	1 (1%)	0	1 (<1%)
VENLAFAXINE HYDROCHLORIDE	0	0	1 (1%)	1 (<1%)
ZIPRASIDONE HYDROCHLORIDE	1 (1%)	0	0	1 (<1%)
ZOLMITRIPTAN	0	0	1 (1%)	1 (<1%)
ZOLPIDEM TARTRATE	0	0	1 (1%)	1 (<1%)

Note: A medication may be reported in more than one ATC Level.

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Table 6.22
Summary of Non-Asthma Medication Use (ITT Population)

Treatment: Salmeterol

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
RESPIRATORY SYSTEM				
Any medication	54 (60%)	61 (68%)	56 (61%)	171 (63%)
LORATADINE	4 (4%)	13 (14%)	13 (14%)	30 (11%)
FEXOFENADINE HYDROCHLORIDE	11 (12%)	9 (10%)	5 (5%)	25 (9%)
BENADRYL (NOS)	8 (9%)	7 (8%)	9 (10%)	24 (9%)
PSEUDOEPHEDRINE HYDROCHLORIDE	6 (7%)	11 (12%)	7 (8%)	24 (9%)
FLUTICASONE PROPIONATE	5 (6%)	7 (8%)	10 (11%)	22 (8%)
PSEUDOEPHEDRINE HYDROCHLORIDE+FEXOFENADINE HYDROCHLORIDE	10 (11%)	3 (3%)	7 (8%)	20 (7%)
CETIRIZINE HYDROCHLORIDE	6 (7%)	6 (7%)	7 (8%)	19 (7%)
MOMETASONE FUROATE	4 (4%)	8 (9%)	3 (3%)	15 (6%)
PARACETAMOL+DEXTROMETHORPHAN	7 (8%)	2 (2%)	5 (5%)	14 (5%)
HYDROBROMIDE+PSEUDOEPHEDRINE HYDROCHLORIDE+DOXYLAMINE SUCCINATE				
AZELASTINE HYDROCHLORIDE	4 (4%)	1 (1%)	7 (8%)	12 (4%)
DESLORATADINE	3 (3%)	5 (6%)	4 (4%)	12 (4%)
TYLENOL SINUS (NOS)	6 (7%)	5 (6%)	1 (1%)	12 (4%)
CHLORPHENAMINE	5 (6%)	4 (4%)	1 (1%)	10 (4%)
GUAIFENESIN	3 (3%)	4 (4%)	3 (3%)	10 (4%)
PSEUDOEPHEDRINE HYDROCHLORIDE+CETIRIZINE HYDROCHLORIDE	4 (4%)	4 (4%)	2 (2%)	10 (4%)
PSEUDOEPHEDRINE SULFATE+LORATADINE	2 (2%)	4 (4%)	4 (4%)	10 (4%)
PARACETAMOL+CHLORPHENAMINE	2 (2%)	3 (3%)	3 (3%)	8 (3%)
MALEATE+PSEUDOEPHEDRINE HYDROCHLORIDE				
TRIAMCINOLONE ACETONIDE	2 (2%)	4 (4%)	2 (2%)	8 (3%)
PARACETAMOL+DEXTROMETHORPHAN	2 (2%)	1 (1%)	2 (2%)	5 (2%)
HYDROBROMIDE+PSEUDOEPHEDRINE HYDROCHLORIDE				
ROBITUSSIN (NOS)	2 (2%)	1 (1%)	2 (2%)	5 (2%)
DIPHENHYDRAMINE HYDROCHLORIDE+PARACETAMOL	0	1 (1%)	3 (3%)	4 (1%)
GUAIFENESIN+DEXTROMETHORPHAN HYDROBROMIDE	1 (1%)	1 (1%)	2 (2%)	4 (1%)
PSEUDOEPHEDRINE HYDROCHLORIDE+IBUPROFEN	1 (1%)	1 (1%)	2 (2%)	4 (1%)

Note: A medication may be reported in more than one ATC Level.

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Table 6.22
Summary of Non-Asthma Medication Use (ITT Population)

Treatment: Salmeterol

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
PSEUDOEPHEDRINE HYDROCHLORIDE+TRIPROLIDINE HYDROCHLORIDE	1 (1%)	2 (2%)	1 (1%)	4 (1%)
TYLENOL COLD NOS	0	3 (3%)	1 (1%)	4 (1%)
CHLORPHENAMINE MALEATE	1 (1%)	1 (1%)	1 (1%)	3 (1%)
COUGH COLD PREPARATIONS NOS	2 (2%)	0	1 (1%)	3 (1%)
LEVOMENTHOL+EUCALYPTUS GLOBULUS	0	0	3 (3%)	3 (1%)
PARACETAMOL+DEXTROMETHORPHAN	2 (2%)	0	1 (1%)	3 (1%)
HYDROBROMIDE+PHENYLEPHRINE HYDROCHLORIDE PHENOL	1 (1%)	0	2 (2%)	3 (1%)
PROMETHAZINE	0	1 (1%)	2 (2%)	3 (1%)
RHINOCORT (NOS)	1 (1%)	2 (2%)	0	3 (1%)
SODIUM CHLORIDE	2 (2%)	0	1 (1%)	3 (1%)
ACETYLSALICYLIC ACID+CHLORPHENAMINE MALEATE+PHENYLPROPANOLAMINE BITARTRATE	1 (1%)	0	1 (1%)	2 (<1%)
BETAMETHASONE+CHLORPHENAMINE MALEATE	2 (2%)	0	0	2 (<1%)
BUDESONIDE	2 (2%)	0	0	2 (<1%)
CODEINE PHOSPHATE+GUAIFENESIN+PSEUDOEPHEDRINE HYDROCHLORIDE+TRIPROLIDINE HYDROCHLORIDE	1 (1%)	1 (1%)	0	2 (<1%)
DIMENHYDRINATE	2 (2%)	0	0	2 (<1%)
DIPHENHYDRAMINE HYDROCHLORIDE	0	2 (2%)	0	2 (<1%)
FLUNISOLIDE	0	1 (1%)	1 (1%)	2 (<1%)
GUAIFENESIN+DEXTROMETHORPHAN	1 (1%)	0	1 (1%)	2 (<1%)
HYDROBROMIDE+PHENYLEPHRINE HYDROCHLORIDE				
GUAIFENESIN+PSEUDOEPHEDRINE HYDROCHLORIDE	1 (1%)	0	1 (1%)	2 (<1%)
HYDROCODONE	0	0	2 (2%)	2 (<1%)
OXYMETAZOLINE HYDROCHLORIDE	1 (1%)	1 (1%)	0	2 (<1%)
PARACETAMOL+DEXTROMETHORPHAN	0	1 (1%)	1 (1%)	2 (<1%)
HYDROBROMIDE+CHLORPHENAMINE MALEATE+PHENYLPROPANOLAMINE HYDROCHLORIDE				

Note: A medication may be reported in more than one ATC Level.

Table 6.22
Summary of Non-Asthma Medication Use (ITT Population)

Treatment: Salmeterol

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
PARACETAMOL+DEXTROMETHORPHAN HYDROBROMIDE+CHLORPHENAMINE MALEATE+PSEUDOEPHEDRINE HYDROCHLORIDE	1 (1%)	0	1 (1%)	2 (<1%)
PSEUDOEPHEDRINE+NAPROXEN	1 (1%)	0	1 (1%)	2 (<1%)
BECLOMETASONE DIPROPIONATE	0	1 (1%)	0	1 (<1%)
BENZOCAINE	1 (1%)	0	0	1 (<1%)
BROMPHENIRAMINE	0	1 (1%)	0	1 (<1%)
CARBINOXAMINE MALEATE	0	0	1 (1%)	1 (<1%)
CETILPYRIDINIUM CHLORIDE	0	1 (1%)	0	1 (<1%)
CHLORPHENAMINE MALEATE+PSEUDOEPHEDRINE HYDROCHLORIDE+IBUPROFEN	1 (1%)	0	0	1 (<1%)
CLEMASTINE FUMARATE	0	1 (1%)	0	1 (<1%)
CONTAC NOS	0	1 (1%)	0	1 (<1%)
CROMOGLICATE SODIUM	0	1 (1%)	0	1 (<1%)
DAY FLU (NOS)	0	1 (1%)	0	1 (<1%)
DEXTROMETHORPHAN	1 (1%)	0	0	1 (<1%)
DICHLOROBENZYL ALCOHOL+AMYL METACRESOL	1 (1%)	0	0	1 (<1%)
DIMETAPP NOS	1 (1%)	0	0	1 (<1%)
DIPHENHYDRAMINE HYDROCHLORIDE+CODEINE PHOSPHATE+SODIUM CHLORIDE+LEVOMENTHOL	1 (1%)	0	0	1 (<1%)
EPINASTINE HYDROCHLORIDE	0	1 (1%)	0	1 (<1%)
GUAIFENESIN+DEXTROMETHORPHAN	1 (1%)	0	0	1 (<1%)
HYDROBROMIDE+PSEUDOEPHEDRINE HYDROCHLORIDE				
GUAIFENESIN+PHENYLEPHRINE HYDROCHLORIDE	1 (1%)	0	0	1 (<1%)
GUAIFENESIN+PHENYLPROPANOLAMINE HYDROCHLORIDE	0	0	1 (1%)	1 (<1%)
GUAIFENESIN+PSEUDOEPHEDRINE	0	0	1 (1%)	1 (<1%)
HYDROCODONE+PHENYLTOLOXAMINE	1 (1%)	0	0	1 (<1%)
HYOSCINE METHONITRATE+CHLORPHENAMINE	0	0	1 (1%)	1 (<1%)
MALEATE+PHENYLEPHRINE HYDROCHLORIDE				
HYOSCINE METHONITRATE+CHLORPHENAMINE MALEATE+PSEUDOEPHEDRINE HYDROCHLORIDE	0	0	1 (1%)	1 (<1%)

Note: A medication may be reported in more than one ATC Level.

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Table 6.22
Summary of Non-Asthma Medication Use (ITT Population)

Treatment: Salmeterol

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
KETOTIFEN FUMARATE	0	0	1 (1%)	1 (<1%)
PARACETAMOL+CAFFEINE+CHLORPHENAMINE MALEATE+PSEUDOEPHEDRINE HYDROCHLORIDE	1 (1%)	0	0	1 (<1%)
PARACETAMOL+DEXTROMETHORPHAN+CHLORPHENAMINE MALEATE+PSEUDOEPHEDRINE HYDROCHLORIDE	0	0	1 (1%)	1 (<1%)
PARACETAMOL+DEXTROMETHORPHAN HYDROBROMIDE+DOXYLAMINE SUCCINATE	0	0	1 (1%)	1 (<1%)
PARACETAMOL+PSEUDOEPHEDRINE HYDROCHLORIDE	1 (1%)	0	0	1 (<1%)
PHENYLEPHRINE HYDROCHLORIDE	0	0	1 (1%)	1 (<1%)
RETINOL PALMITATE	0	0	1 (1%)	1 (<1%)
VICKS VAPORUB NOS	0	0	1 (1%)	1 (<1%)
GENITO URINARY SYSTEM AND SEX HORMONES				
Any medication	42 (47%)	48 (53%)	40 (43%)	130 (48%)
IBUPROFEN	33 (37%)	36 (40%)	31 (34%)	100 (37%)
NAPROXEN SODIUM	9 (10%)	8 (9%)	8 (9%)	25 (9%)
ETHINYLOESTRADIOL+NORGESTIMATE	3 (3%)	3 (3%)	3 (3%)	9 (3%)
ETHINYLOESTRADIOL+NORELGESTROMIN	4 (4%)	2 (2%)	1 (1%)	7 (3%)
ACETYLSALICYLIC ACID+CAFFEINE+CINNAMEDRINE HYDROCHLORIDE	2 (2%)	4 (4%)	0	6 (2%)
NAPROXEN	2 (2%)	3 (3%)	1 (1%)	6 (2%)
ETHINYLOESTRADIOL+DROSPIRENONE	1 (1%)	1 (1%)	1 (1%)	3 (1%)
MEDROXYPROGESTERONE ACETATE	0	1 (1%)	2 (2%)	3 (1%)
CLINDAMYCIN	0	1 (1%)	1 (1%)	2 (<1%)
ESTROGENS CONJUGATED	0	1 (1%)	1 (1%)	2 (<1%)
ESTROGENS CONJUGATED+MEDROXYPROGESTERONE ACETATE	0	1 (1%)	1 (1%)	2 (<1%)
ETHINYLOESTRADIOL+LEVONORGESTREL	1 (1%)	1 (1%)	0	2 (<1%)
ETHINYLOESTRADIOL+NORETHISTERONE	2 (2%)	0	0	2 (<1%)
FURADONINE	0	1 (1%)	1 (1%)	2 (<1%)
DIMETHYL SULFONE	0	0	1 (1%)	1 (<1%)
ETHINYLOESTRADIOL+DESOGESTREL	0	0	1 (1%)	1 (<1%)

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Table 6.22
Summary of Non-Asthma Medication Use (ITT Population)

Treatment: Salmeterol

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
ETHINYLOESTRADIOL+ETONOGESTREL	0	0	1 (1%)	1 (<1%)
ETHINYLOESTRADIOL+ETYNODIOL DIACETATE	0	0	1 (1%)	1 (<1%)
ETHINYLOESTRADIOL+FERROUS FUMARATE+NORETHISTERONE ACETATE	1 (1%)	0	0	1 (<1%)
ETHINYLOESTRADIOL+NORETHISTERONE ACETATE	0	0	1 (1%)	1 (<1%)
FINASTERIDE	0	1 (1%)	0	1 (<1%)
METHYLTESTOSTERONE+ESTROGENS ESTERIFIED	0	1 (1%)	0	1 (<1%)
OXICONAZOLE NITRATE	0	0	1 (1%)	1 (<1%)
PHENAZOPYRIDINE HYDROCHLORIDE	0	1 (1%)	0	1 (<1%)
SOLIFENACIN SUCCINATE	0	0	1 (1%)	1 (<1%)
TOLTERODINE TARTRATE	0	0	1 (1%)	1 (<1%)
MUSCULO-SKELETAL SYSTEM				
Any medication	41 (46%)	45 (50%)	39 (42%)	125 (46%)
IBUPROFEN	33 (37%)	36 (40%)	31 (34%)	100 (37%)
NAPROXEN SODIUM	9 (10%)	8 (9%)	8 (9%)	25 (9%)
CYCLOBENZAPRINE HYDROCHLORIDE	4 (4%)	0	2 (2%)	6 (2%)
NAPROXEN	2 (2%)	3 (3%)	1 (1%)	6 (2%)
CELECOXIB	0	1 (1%)	2 (2%)	3 (1%)
DICLOFENAC	1 (1%)	0	1 (1%)	2 (<1%)
ETODOLAC	0	1 (1%)	1 (1%)	2 (<1%)
GLUCOSAMINE	1 (1%)	0	1 (1%)	2 (<1%)
METAXALONE	0	1 (1%)	1 (1%)	2 (<1%)
PIROXICAM	1 (1%)	1 (1%)	0	2 (<1%)
PSEUDOEPHEDRINE+NAPROXEN	1 (1%)	0	1 (1%)	2 (<1%)
CYCLOBENZAPRINE	0	1 (1%)	0	1 (<1%)
DIMETHYL SULFONE	0	0	1 (1%)	1 (<1%)
GLUCOSAMINE SULFATE	0	0	1 (1%)	1 (<1%)
KETOROLAC	0	0	1 (1%)	1 (<1%)
KETOROLAC TROMETAMOL	0	0	1 (1%)	1 (<1%)
MEFENAMIC ACID	0	1 (1%)	0	1 (<1%)

Note: A medication may be reported in more than one ATC Level.

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Table 6.22
Summary of Non-Asthma Medication Use (ITT Population)

Treatment: Salmeterol

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
MELOXICAM	1 (1%)	0	0	1 (<1%)
NIMESULIDE	0	1 (1%)	0	1 (<1%)
ROFECOXIB	1 (1%)	0	0	1 (<1%)
TIZANIDINE	1 (1%)	0	0	1 (<1%)
VALDECOXIB	0	1 (1%)	0	1 (<1%)
ALIMENTARY TRACT AND METABOLISM				
Any medication	35 (39%)	33 (37%)	42 (46%)	110 (40%)
ACETYLSALICYLIC ACID	4 (4%)	9 (10%)	15 (16%)	28 (10%)
VITAMINS NOS	5 (6%)	3 (3%)	8 (9%)	16 (6%)
BISMUTH SUBSALICYLATE	5 (6%)	5 (6%)	0	10 (4%)
TRIAMCINOLONE ACETONIDE	2 (2%)	4 (4%)	2 (2%)	8 (3%)
CALCIUM CARBONATE	0	2 (2%)	5 (5%)	7 (3%)
LOPERAMIDE HYDROCHLORIDE	1 (1%)	3 (3%)	2 (2%)	6 (2%)
RABEPRAZOLE SODIUM	3 (3%)	1 (1%)	2 (2%)	6 (2%)
ACETYLSALICYLIC ACID+SODIUM BICARBONATE+CITRIC ACID	2 (2%)	1 (1%)	2 (2%)	5 (2%)
PANTOPRAZOLE	1 (1%)	2 (2%)	2 (2%)	5 (2%)
ASCORBIC ACID	0	1 (1%)	3 (3%)	4 (1%)
FAMOTIDINE	1 (1%)	1 (1%)	2 (2%)	4 (1%)
OMEPRazole	0	1 (1%)	3 (3%)	4 (1%)
RANITIDINE HYDROCHLORIDE	0	2 (2%)	2 (2%)	4 (1%)
ALUMINIUM HYDROXIDE GEL+MAGNESIUM HYDROXIDE	1 (1%)	0	2 (2%)	3 (1%)
ALUMINIUM HYDROXIDE GEL, DRIED+MAGNESIUM HYDROXIDE+SIMETICONE	1 (1%)	1 (1%)	1 (1%)	3 (1%)
DIHYDROXYALUMINUM SODIUM CARBONATE	1 (1%)	0	2 (2%)	3 (1%)
DIMETICONE, ACTIVATED	1 (1%)	0	2 (2%)	3 (1%)
ESOMEPRazole MAGNESIUM	1 (1%)	1 (1%)	1 (1%)	3 (1%)
METFORMIN HYDROCHLORIDE	0	1 (1%)	2 (2%)	3 (1%)
PREDNISONE	0	2 (2%)	1 (1%)	3 (1%)
PROMETHAZINE	0	1 (1%)	2 (2%)	3 (1%)

Note: A medication may be reported in more than one ATC Level.

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Table 6.22
Summary of Non-Asthma Medication Use (ITT Population)

Treatment: Salmeterol

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
RHINOCORT (NOS)	1 (1%)	2 (2%)	0	3 (1%)
SODIUM CHLORIDE	2 (2%)	0	1 (1%)	3 (1%)
TOCOPHEROL	0	0	3 (3%)	3 (1%)
ZINC	1 (1%)	1 (1%)	1 (1%)	3 (1%)
BUDESONIDE	2 (2%)	0	0	2 (<1%)
CALCIUM	1 (1%)	0	1 (1%)	2 (<1%)
DIMENHYDRINATE	2 (2%)	0	0	2 (<1%)
LANSOPRAZOLE	0	0	2 (2%)	2 (<1%)
MINERALS NOS+VITAMINS NOS+HERBALS NOS	1 (1%)	0	1 (1%)	2 (<1%)
PIOGLITAZONE HYDROCHLORIDE	1 (1%)	1 (1%)	0	2 (<1%)
POTASSIUM CHLORIDE	0	0	2 (2%)	2 (<1%)
POTASSIUM NOS	0	0	2 (2%)	2 (<1%)
SODIUM BICARBONATE	2 (2%)	0	0	2 (<1%)
ACTAL (NOS)	0	0	1 (1%)	1 (<1%)
AMINO ACIDS NOS+MINERALS NOS+VITAMINS NOS+HERBALS NOS	0	0	1 (1%)	1 (<1%)
BECLOMETASONE DIPROPIONATE	0	1 (1%)	0	1 (<1%)
BISACODYL	0	0	1 (1%)	1 (<1%)
CIMETIDINE	0	0	1 (1%)	1 (<1%)
DICYCLOVERINE HYDROCHLORIDE	0	0	1 (1%)	1 (<1%)
DIMETICONE+MAGNESIUM+ALUMINIUM	1 (1%)	0	0	1 (<1%)
DOMPERIDONE	1 (1%)	0	0	1 (<1%)
DULCOLAX (NOS)	0	0	1 (1%)	1 (<1%)
GLIBENCLAMIDE	0	1 (1%)	0	1 (<1%)
GLIMEPIRIDE	1 (1%)	0	0	1 (<1%)
INSULIN HUMAN+INSULIN ISOPHANE, HUMAN BIOSYNTHETIC	0	1 (1%)	0	1 (<1%)
INSULIN NOS	0	1 (1%)	0	1 (<1%)
IRON+CALCIUM	0	0	1 (1%)	1 (<1%)
LACTOBACILLUS ACIDOPHILUS	0	1 (1%)	0	1 (<1%)
MACROGOL	0	0	1 (1%)	1 (<1%)

Note: A medication may be reported in more than one ATC Level.

Table 6.22
Summary of Non-Asthma Medication Use (ITT Population)

Treatment: Salmeterol

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
MAGALDRATE+DIMETICONE, ACTIVATED	1 (1%)	0	0	1 (<1%)
METOCLOPRAMIDE	1 (1%)	0	0	1 (<1%)
METOCLOPRAMIDE HYDROCHLORIDE+DEHYDROCHOLIC ACID+DIMETICONE, ACTIVATED+DIGESTIVE POLYENZYME	1 (1%)	0	0	1 (<1%)
MINERALS NOS+VITAMINS NOS+ENZYME, NOS+HERBALS NOS	0	0	1 (1%)	1 (<1%)
OTHER ANTIDIARRHOEALS	0	1 (1%)	0	1 (<1%)
PAPAVERINE	0	1 (1%)	0	1 (<1%)
POLYCARBOPHIL CALCIUM	0	0	1 (1%)	1 (<1%)
PROTEASE+AMYLASE+LIPASE+ASPERGILLUS NIGER	0	1 (1%)	0	1 (<1%)
RANITIDINE	0	1 (1%)	0	1 (<1%)
RETINOL PALMITATE	0	0	1 (1%)	1 (<1%)
ROSIGLITAZONE MALEATE	0	1 (1%)	0	1 (<1%)
SENNA	0	1 (1%)	0	1 (<1%)
TEGASEROD	0	0	1 (1%)	1 (<1%)
TETRACYCLINE	1 (1%)	0	0	1 (<1%)
VITAMIN B NOS	0	0	1 (1%)	1 (<1%)
DERMATOLOGICALS				
Any medication	20 (22%)	28 (31%)	32 (35%)	80 (29%)
BENADRYL (NOS)	8 (9%)	7 (8%)	9 (10%)	24 (9%)
FLUTICASONE PROPIONATE	5 (6%)	7 (8%)	10 (11%)	22 (8%)
MOMETASONE FUROATE	4 (4%)	8 (9%)	3 (3%)	15 (6%)
TRIAMCINOLONE ACETONIDE	2 (2%)	4 (4%)	2 (2%)	8 (3%)
METHYLPREDNISOLONE	0	3 (3%)	1 (1%)	4 (1%)
PHENOL	1 (1%)	0	2 (2%)	3 (1%)
PROMETHAZINE	0	1 (1%)	2 (2%)	3 (1%)
RHINOCORT (NOS)	1 (1%)	2 (2%)	0	3 (1%)
TOCOPHEROL	0	0	3 (3%)	3 (1%)
BUDESONIDE	2 (2%)	0	0	2 (<1%)
CLINDAMYCIN	0	1 (1%)	1 (1%)	2 (<1%)

Note: A medication may be reported in more than one ATC Level.

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Table 6.22
Summary of Non-Asthma Medication Use (ITT Population)

Treatment: Salmeterol

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
DIPHENHYDRAMINE HYDROCHLORIDE	0	2 (2%)	0	2 (<1%)
BECLOMETASONE DIPROPIONATE	0	1 (1%)	0	1 (<1%)
BENZOCAINE	1 (1%)	0	0	1 (<1%)
CALAMINE+PRAMOCAINE HYDROCHLORIDE	0	0	1 (1%)	1 (<1%)
CETYLPYRIDINIUM CHLORIDE	0	1 (1%)	0	1 (<1%)
CLEMASTINE FUMARATE	0	1 (1%)	0	1 (<1%)
CLOBETASOL	0	0	1 (1%)	1 (<1%)
DESOXIMETASONE	0	0	1 (1%)	1 (<1%)
ERYTHROMYCIN	0	0	1 (1%)	1 (<1%)
FINASTERIDE	0	1 (1%)	0	1 (<1%)
NEOMYCIN SULFATE+POLYMYXIN B SULFATE+BACITRACIN	0	1 (1%)	0	1 (<1%)
ZINC				
OXICONAZOLE NITRATE	0	0	1 (1%)	1 (<1%)
RETINOL PALMITATE	0	0	1 (1%)	1 (<1%)
SULFACETAMIDE SODIUM+SULFUR	0	1 (1%)	0	1 (<1%)
TERBINAFINE HYDROCHLORIDE	0	1 (1%)	0	1 (<1%)
TETRACYCLINE	1 (1%)	0	0	1 (<1%)
ANTIINFECTIVES FOR SYSTEMIC USE				
Any medication	18 (20%)	17 (19%)	20 (22%)	55 (20%)
AMOXICILLIN	3 (3%)	3 (3%)	4 (4%)	10 (4%)
AZITHROMYCIN	6 (7%)	0	3 (3%)	9 (3%)
TELITHROMYCIN	3 (3%)	1 (1%)	3 (3%)	7 (3%)
CIPROFLOXACIN HYDROCHLORIDE	0	3 (3%)	1 (1%)	4 (1%)
DOXYCYCLINE	0	4 (4%)	0	4 (1%)
LEVOFLOXACIN	0	2 (2%)	1 (1%)	3 (1%)
AMOXICILLIN TRIHYDRATE+CLAVULANATE POTASSIUM	1 (1%)	0	1 (1%)	2 (<1%)
BENZYL PENICILLIN	0	0	2 (2%)	2 (<1%)
CEFALEXIN	1 (1%)	0	1 (1%)	2 (<1%)
CLINDAMYCIN	0	1 (1%)	1 (1%)	2 (<1%)
DICLOXACILLIN	0	1 (1%)	1 (1%)	2 (<1%)

Note: A medication may be reported in more than one ATC Level.

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Table 6.22
Summary of Non-Asthma Medication Use (ITT Population)

Treatment: Salmeterol

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
FURADONINE	0	1 (1%)	1 (1%)	2 (<1%)
INFLUENZA VACCINE	0	1 (1%)	1 (1%)	2 (<1%)
SULFAMETHOXAZOLE+TRIMETHOPRIM	1 (1%)	0	1 (1%)	2 (<1%)
CEFADROXIL	0	1 (1%)	0	1 (<1%)
CEFPROZIL	1 (1%)	0	0	1 (<1%)
CLARITHROMYCIN	0	0	1 (1%)	1 (<1%)
ERYTHROMYCIN	0	0	1 (1%)	1 (<1%)
GATIFLOXACIN	0	0	1 (1%)	1 (<1%)
INFLUENZA VIRUS VACCINE INACTIVATED	1 (1%)	0	0	1 (<1%)
MINOCYCLINE	1 (1%)	0	0	1 (<1%)
OSELTAMIVIR PHOSPHATE	0	0	1 (1%)	1 (<1%)
PHENOXYMETHYLPENICILLIN POTASSIUM	0	1 (1%)	0	1 (<1%)
TETANUS TOXOID+DIPHThERIA TOXOID	0	0	1 (1%)	1 (<1%)
TETRACYCLINE	1 (1%)	0	0	1 (<1%)
VALACICLOVIR HYDROCHLORIDE	0	0	1 (1%)	1 (<1%)
SENSORY ORGANS				
Any medication	12 (13%)	13 (14%)	15 (16%)	40 (15%)
TRIAMCINOLONE ACETONIDE	2 (2%)	4 (4%)	2 (2%)	8 (3%)
CIPROFLOXACIN HYDROCHLORIDE	0	3 (3%)	1 (1%)	4 (1%)
METHYLPREDNISOLONE	0	3 (3%)	1 (1%)	4 (1%)
SODIUM CHLORIDE	2 (2%)	0	1 (1%)	3 (1%)
BENZYL PENICILLIN	0	0	2 (2%)	2 (<1%)
DICLOFENAC	1 (1%)	0	1 (1%)	2 (<1%)
OXYMETAZOLINE HYDROCHLORIDE	1 (1%)	1 (1%)	0	2 (<1%)
PHENIRAMINE MALEATE+NAPHAZOLINE HYDROCHLORIDE	0	0	2 (2%)	2 (<1%)
PIROXICAM	1 (1%)	1 (1%)	0	2 (<1%)
BETAMETHASONE SODIUM PHOSPHATE+NEOMYCIN SULFATE	1 (1%)	0	0	1 (<1%)
CLONIDINE	0	0	1 (1%)	1 (<1%)
CROMOGLICATE SODIUM	0	1 (1%)	0	1 (<1%)
DEXAMETHASONE+CIPROFLOXACIN	1 (1%)	0	0	1 (<1%)

Note: A medication may be reported in more than one ATC Level.

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Table 6.22
Summary of Non-Asthma Medication Use (ITT Population)

Treatment: Salmeterol

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
ERYTHROMYCIN	0	0	1 (1%)	1 (<1%)
HYDROCORTISONE+CIPROFLOXACIN HYDROCHLORIDE	1 (1%)	0	0	1 (<1%)
KETOROLAC	0	0	1 (1%)	1 (<1%)
KETOROLAC TROMETAMOL	0	0	1 (1%)	1 (<1%)
KETOTIFEN FUMARATE	0	0	1 (1%)	1 (<1%)
NEOMYCIN SULFATE+POLYMYXIN B SULFATE+BACITRACIN ZINC	0	1 (1%)	0	1 (<1%)
OLOPATADINE HYDROCHLORIDE	0	1 (1%)	0	1 (<1%)
PHENYLEPHRINE HYDROCHLORIDE	0	0	1 (1%)	1 (<1%)
POLYMYXIN B SULFATE+TRIMETHOPRIM	1 (1%)	0	0	1 (<1%)
PROCAINE HYDROCHLORIDE	1 (1%)	0	0	1 (<1%)
RETINOL PALMITATE	0	0	1 (1%)	1 (<1%)
TETRACYCLINE	1 (1%)	0	0	1 (<1%)
BLOOD AND BLOOD FORMING ORGANS				
Any medication	9 (10%)	11 (12%)	17 (18%)	37 (14%)
ACETYLSALICYLIC ACID	4 (4%)	9 (10%)	15 (16%)	28 (10%)
SODIUM CHLORIDE	2 (2%)	0	1 (1%)	3 (1%)
IRON	1 (1%)	1 (1%)	0	2 (<1%)
POTASSIUM CHLORIDE	0	0	2 (2%)	2 (<1%)
POTASSIUM NOS	0	0	2 (2%)	2 (<1%)
SODIUM BICARBONATE	2 (2%)	0	0	2 (<1%)
ASCORBIC ACID+FERROUS FUMARATE+FOLIC ACID+CYANOCOBALAMIN+CALCIUM ASCORBATE+SUCCINIC ACID+IRON BISGLY	0	0	1 (1%)	1 (<1%)
CETYLPYRIDINIUM CHLORIDE	0	1 (1%)	0	1 (<1%)
IRON+CALCIUM	0	0	1 (1%)	1 (<1%)
CARDIOVASCULAR SYSTEM				
Any medication	5 (6%)	8 (9%)	21 (23%)	34 (13%)
ATORVASTATIN CALCIUM	0	2 (2%)	5 (5%)	7 (3%)

Note: A medication may be reported in more than one ATC Level.

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Table 6.22
Summary of Non-Asthma Medication Use (ITT Population)

Treatment: Salmeterol

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
AMLODIPINE BESILATE	0	2 (2%)	2 (2%)	4 (1%)
DILTIAZEM HYDROCHLORIDE	1 (1%)	1 (1%)	2 (2%)	4 (1%)
FUROSEMIDE	0	1 (1%)	3 (3%)	4 (1%)
HYDROCHLOROTHIAZIDE	1 (1%)	1 (1%)	1 (1%)	3 (1%)
HYDROCHLOROTHIAZIDE+LOSARTAN POTASSIUM	0	0	3 (3%)	3 (1%)
PHENOL	1 (1%)	0	2 (2%)	3 (1%)
VERAPAMIL	0	0	3 (3%)	3 (1%)
BENAZEPRIL HYDROCHLORIDE	0	0	2 (2%)	2 (<1%)
LISINOPRIL	0	1 (1%)	1 (1%)	2 (<1%)
LOSARTAN POTASSIUM	0	2 (2%)	0	2 (<1%)
TRIAMTERENE+HYDROCHLOROTHIAZIDE	0	1 (1%)	1 (1%)	2 (<1%)
BENAZEPRIL HYDROCHLORIDE+AMLODIPINE BESILATE	0	0	1 (1%)	1 (<1%)
BENZOCAINE	1 (1%)	0	0	1 (<1%)
CLONIDINE	0	0	1 (1%)	1 (<1%)
DOXAZOSIN MESILATE	0	1 (1%)	0	1 (<1%)
ENALAPRIL	0	1 (1%)	0	1 (<1%)
EZETIMIBE	0	0	1 (1%)	1 (<1%)
GINKGO BILOBA	0	0	1 (1%)	1 (<1%)
HYDROCHLOROTHIAZIDE+VALSARTAN	0	0	1 (1%)	1 (<1%)
INDAPAMIDE	0	0	1 (1%)	1 (<1%)
LOVASTATIN	0	1 (1%)	0	1 (<1%)
PHENYLEPHRINE HYDROCHLORIDE	0	0	1 (1%)	1 (<1%)
PROCAINE HYDROCHLORIDE	1 (1%)	0	0	1 (<1%)
QUINAPRIL	0	0	1 (1%)	1 (<1%)
RAMIPRIL	0	0	1 (1%)	1 (<1%)
SIMVASTATIN	0	0	1 (1%)	1 (<1%)
SIMVASTATIN+EZETIMIBE	0	0	1 (1%)	1 (<1%)
VALSARTAN	0	1 (1%)	0	1 (<1%)
SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES				
Any medication	9 (10%)	6 (7%)	6 (7%)	21 (8%)

Note: A medication may be reported in more than one ATC Level.

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Table 6.22
Summary of Non-Asthma Medication Use (ITT Population)

Treatment: Salmeterol

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)

TRIAMCINOLONE ACETONIDE	2 (2%)	4 (4%)	2 (2%)	8 (3%)
LEVOTHYROXINE SODIUM	3 (3%)	0	2 (2%)	5 (2%)
METHYLPREDNISOLONE	0	3 (3%)	1 (1%)	4 (1%)
PREDNISONE	0	2 (2%)	1 (1%)	3 (1%)
BETAMETHASONE+CHLORPHENAMINE MALEATE	2 (2%)	0	0	2 (<1%)
BUDESONIDE	2 (2%)	0	0	2 (<1%)
ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS				
Any medication	1 (1%)	4 (4%)	3 (3%)	8 (3%)
IMMUNOTHERAPY{NOS}	1 (1%)	2 (2%)	1 (1%)	4 (1%)
MEDROXYPROGESTERONE ACETATE	0	1 (1%)	2 (2%)	3 (1%)
ESTROGENS CONJUGATED	0	1 (1%)	1 (1%)	2 (<1%)
VARIOUS				
Any medication	1 (1%)	3 (3%)	6 (7%)	10 (4%)
ALLERGENS (NOS)	0	1 (1%)	1 (1%)	2 (<1%)
ECHINACEA	0	1 (1%)	1 (1%)	2 (<1%)
MINERALS NOS+VITAMINS NOS+HERBALS NOS	1 (1%)	0	1 (1%)	2 (<1%)
ALLIUM SATIVUM	0	1 (1%)	0	1 (<1%)
BARIUM	0	0	1 (1%)	1 (<1%)
CREATINE	0	1 (1%)	0	1 (<1%)
DIMETHYL SULFONE	0	0	1 (1%)	1 (<1%)
TYROSINE+ACETYLCARNITINE+PAULLINIA	0	0	1 (1%)	1 (<1%)
CUPANA+EPHEDRA SINICA+ZINGIBER OFFICINALE+SALIX PURPUREA+CITRUS A				
ANTIPARASITIC PRODUCTS, INSECTICIDES AND REPELLENT				
AMODIAQUINE	1 (1%)	0	0	1 (<1%)
Any medication	1 (1%)	0	0	1 (<1%)
PYRIMETHAMINE+SULFADOXINE	1 (1%)	0	0	1 (<1%)

Note: A medication may be reported in more than one ATC Level.

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Table 6.23
Summary of Double-Blind Treatment Compliance

Treatment: FSC100/50

		Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)

Subjects in treatment group		89	92	91	272
Treatment compliance (%)	n	87	92	87	266
	Mean	95.1	96.2	94.6	95.3
	SD	18.15	10.49	12.53	14.00
	Median	98.7	98.7	98.2	98.6
	Min.	24	42	44	24
	Max.	175	114	127	175

Table 6.23
Summary of Double-Blind Treatment Compliance

Treatment: Salmeterol

		Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
-----		-----			
Subjects in treatment group		90	90	92	272
Treatment compliance (%)	n	85	86	89	260
	Mean	95.3	101.1	95.2	97.2
	SD	16.46	24.47	18.32	20.15
	Median	98.2	98.7	97.8	98.3
	Min.	11	31	26	11
	Max.	159	248	204	248

Table 6.24
Summary of Demographic Characteristics (Screen Failure Population)

		Total (N=1429)

Age at screening (y)	n	1428
	Mean	34.1
	SD	15.14
	Median	32.0
	Min.	12
	Max.	84
Sex	n	1429
	Female	894 (63%)
	Male	535 (37%)
Ethnicity	n	1429
	Hispanic or Latino	268 (19%)
	Not Hispanic or Latino	1161 (81%)
Race	n	1429
	Arabic/North African	5 (<1%)
	Black	471 (33%)
	African American	369 (78%)
	African Heritage	102 (22%)
	East & South East Asian	7 (<1%)
	Japanese	3 (<1%)
	South Asian	7 (<1%)
	White/Caucasian	861 (60%)
	Other	75 (5%)
	Native Hawaiian	0
	Other Pacific Islander	2 (3%)
	American Indian	40 (53%)
	Alaska Native	0

Table 6.25
Summary of Disease Characteristics (Screen Failure Population)

	Total (N=1429)

Asthma duration (years)	
n	1374
Mean	16.4
SD	12.90
Median	14.0
Min.	0
Max.	73
Duration in categories	
n	1374
<6 months	15 (1%)
>=6 months to <1 year	13 (<1%)
>=1 year to <5 years	211 (15%)
>=5 years to <10 years	238 (17%)
>=10 years to <15 years	257 (19%)
>=15 years	640 (47%)
Is the subject exposed to passive smoke?	
n	1276
Yes	297 (23%)
No	979 (77%)
Is the subject exposed to pets?	
n	1276
Yes	629 (49%)
No	647 (51%)
Does the subject attend school?	
n	1280
Yes	413 (32%)
No	867 (68%)

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Table 6.25
Summary of Disease Characteristics (Screen Failure Population)

	Total (N=1429)

Biological relatives with asthma history	
Father	147 (10%)
Maternal grandparents	128 (9%)
Mother	285 (20%)
Paternal grandparents	54 (4%)
Sibling	376 (26%)
Subject	1222 (86%)
Biological relatives with croup history	
Father	7 (<1%)
Maternal grandparents	10 (<1%)
Mother	17 (1%)
Paternal grandparents	2 (<1%)
Sibling	41 (3%)
Subject	47 (3%)
Biological relatives with eczema history	
Father	32 (2%)
Maternal grandparents	15 (1%)
Mother	58 (4%)
Paternal grandparents	7 (<1%)
Sibling	84 (6%)
Subject	153 (11%)
Biological relatives with food allergy history	
Father	30 (2%)
Maternal grandparents	9 (<1%)
Mother	83 (6%)
Paternal grandparents	3 (<1%)
Sibling	78 (5%)
Subject	196 (14%)

Table 6.25
Summary of Disease Characteristics (Screen Failure Population)

	Total (N=1429)

Biological relatives with hives history	
Father	28 (2%)
Maternal grandparents	10 (<1%)
Mother	63 (4%)
Paternal grandparents	7 (<1%)
Sibling	61 (4%)
Subject	174 (12%)
Biological relatives with pet allergy history	
Father	67 (5%)
Maternal grandparents	27 (2%)
Mother	132 (9%)
Paternal grandparents	8 (<1%)
Sibling	157 (11%)
Subject	466 (33%)
Biological relatives with sinus infection history	
Father	94 (7%)
Maternal grandparents	41 (3%)
Mother	188 (13%)
Paternal grandparents	12 (<1%)
Sibling	151 (11%)
Subject	373 (26%)

Table 6.25
Summary of Disease Characteristics (Screen Failure Population)

	Total (N=1429)

Biological relatives with seasonal allergy history	
Father	71 (5%)
Maternal grandparents	29 (2%)
Mother	149 (10%)
Paternal grandparents	13 (<1%)
Sibling	162 (11%)
Subject	457 (32%)
Biological relatives with year-round hay fever history	
Father	158 (11%)
Maternal grandparents	76 (5%)
Mother	292 (20%)
Paternal grandparents	40 (3%)
Sibling	323 (23%)
Subject	806 (56%)

Table 6.26
Summary of Screening Pulmonary Function Tests (Screen Failure Population)

		Total (N=1429)
FEV1 (L)	n	1344
	Mean	2.71
	SD	0.783
	Median	2.60
	Min.	0.61
	Max.	5.68
FEV1 % predicted	n	1344
	Mean	82.9
	SD	15.98
	Median	83.4
	Min.	17
	Max.	138
FEV1 % reversibility	n	999
	Mean	14.0
	SD	17.71
	Median	12.5
	Min.	-19
	Max.	388
Historical FEV1 % reversibility	n	88
	Mean	21.3
	SD	10.45
	Median	17.5
	Min.	11
	Max.	58

Table 6.27
Summary of Inclusion/Exclusion Criteria Deviations (Screen Failure Population)

	Total (N=1429)

Any criteria deviations	859 (60%)
Inclusion criteria	
Treatable on outpatient basis	1 (<1%)
Diagnosis of persistent asthma for at least 3 months	6 (<1%)
FEV1 >=70% and <=100% of predicted normal at Visit 1	368 (26%)
Reversibility	463 (32%)
Concurrent anti-asthma therapy	2 (<1%)
Demonstrates correct use of devices	1 (<1%)
Exclusion criteria	
Life-threatening asthma	4 (<1%)
Other concurrent conditions/diseases	11 (<1%)
Drug allergy	10 (<1%)
Tobacco use	18 (1%)
Questionable compliance with medication or visits	3 (<1%)
Asthma instability	1 (<1%)
Other respiratory disease	1 (<1%)
Use of prohibited anti-asthma medications	22 (2%)
Use of prohibited concurrent medications	12 (<1%)
Use of immunosuppressive medications	1 (<1%)
Use of other prohibited medications	1 (<1%)
Respiratory tract infection	12 (<1%)
Antibiotic usage	4 (<1%)

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Table 6.28
Summary of Demographic Characteristics (Open-Label Albuterol Failure Population)

		Arg/Arg (N=37)	Arg/Gly (N=43)	Gly/Gly (N=28)	Total (N=108)
Age at screening (y)	n	37	43	28	108
	Mean	31.7	34.9	34.7	33.7
	SD	14.08	13.64	17.79	14.89
	Median	27.0	32.0	31.5	30.5
	Min.	12	14	12	12
	Max.	74	63	72	74
Sex	n	37	43	28	108
	Female	21 (57%)	27 (63%)	19 (68%)	67 (62%)
	Male	16 (43%)	16 (37%)	9 (32%)	41 (38%)
Ethnicity	n	37	43	28	108
	Hispanic or Latino	8 (22%)	8 (19%)	2 (7%)	18 (17%)
	Not Hispanic or Latino	29 (78%)	35 (81%)	26 (93%)	90 (83%)
Race	n	37	43	28	108
	Arabic/North African	0	0	0	0
	Black	13 (35%)	17 (40%)	10 (36%)	40 (37%)
	African American	12 (92%)	13 (76%)	7 (70%)	32 (80%)
	African Heritage	1 (8%)	4 (24%)	3 (30%)	8 (20%)
	East & South East Asian	0	1 (2%)	0	1 (<1%)
	Japanese	0	0	0	0
	South Asian	1 (3%)	0	0	1 (<1%)
	White/Caucasian	16 (43%)	21 (49%)	17 (61%)	54 (50%)
	Other	7 (19%)	4 (9%)	1 (4%)	12 (11%)
	Native Hawaiian	0	0	0	0
	Other Pacific Islander	0	0	0	0
	American Indian	4 (57%)	3 (75%)	1 (100%)	8 (67%)
	Alaska Native	0	0	0	0

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Table 6.29
Summary of Disease Characteristics (Open-Label Albuterol Failure Population)

	Arg/Arg (N=37)	Arg/Gly (N=43)	Gly/Gly (N=28)	Total (N=108)

Asthma duration (years)				
n	37	43	28	108
Mean	14.6	14.7	15.6	14.9
SD	11.55	12.22	13.99	12.37
Median	13.0	10.0	10.5	11.8
Min.	1	1	1	1
Max.	46	48	49	49
Duration in categories				
n	37	43	28	108
>=6 months to <1 year	1 (3%)	0	1 (4%)	2 (2%)
>=1 year to <5 years	8 (22%)	12 (28%)	4 (14%)	24 (22%)
>=5 years to <10 years	4 (11%)	6 (14%)	7 (25%)	17 (16%)
>=10 years to <15 years	6 (16%)	6 (14%)	6 (21%)	18 (17%)
>=15 years	18 (49%)	19 (44%)	10 (36%)	47 (44%)
Is the subject exposed to passive smoke?				
n	37	43	28	108
Yes	5 (14%)	8 (19%)	5 (18%)	18 (17%)
No	32 (86%)	35 (81%)	23 (82%)	90 (83%)
Is the subject exposed to pets?				
n	37	43	28	108
Yes	15 (41%)	22 (51%)	12 (43%)	49 (45%)
No	22 (59%)	21 (49%)	16 (57%)	59 (55%)
Does the subject attend school?				
n	37	43	28	108
Yes	13 (35%)	12 (28%)	12 (43%)	37 (34%)
No	24 (65%)	31 (72%)	16 (57%)	71 (66%)

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Table 6.29
Summary of Disease Characteristics (Open-Label Albuterol Failure Population)

	Arg/Arg (N=37)	Arg/Gly (N=43)	Gly/Gly (N=28)	Total (N=108)

Biological relatives with asthma history				
Father	3 (8%)	8 (19%)	3 (11%)	14 (13%)
Maternal grandparents	6 (16%)	3 (7%)	2 (7%)	11 (10%)
Mother	8 (22%)	7 (16%)	12 (43%)	27 (25%)
Paternal grandparents	2 (5%)	4 (9%)	5 (18%)	11 (10%)
Sibling	11 (30%)	18 (42%)	12 (43%)	41 (38%)
Subject	35 (95%)	42 (98%)	28 (100%)	105 (97%)
Biological relatives with croup history				
Father	0	0	0	0
Maternal grandparents	0	0	0	0
Mother	0	0	1 (4%)	1 (<1%)
Paternal grandparents	0	0	0	0
Sibling	1 (3%)	0	2 (7%)	3 (3%)
Subject	4 (11%)	1 (2%)	3 (11%)	8 (7%)
Biological relatives with eczema history				
Father	1 (3%)	2 (5%)	3 (11%)	6 (6%)
Maternal grandparents	1 (3%)	0	0	1 (<1%)
Mother	2 (5%)	3 (7%)	2 (7%)	7 (6%)
Paternal grandparents	0	1 (2%)	2 (7%)	3 (3%)
Sibling	6 (16%)	3 (7%)	2 (7%)	11 (10%)
Subject	7 (19%)	7 (16%)	4 (14%)	18 (17%)
Biological relatives with food allergy history				
Father	0	4 (9%)	3 (11%)	7 (6%)
Maternal grandparents	0	1 (2%)	0	1 (<1%)
Mother	2 (5%)	0	2 (7%)	4 (4%)
Paternal grandparents	0	1 (2%)	0	1 (<1%)
Sibling	3 (8%)	0	1 (4%)	4 (4%)
Subject	7 (19%)	5 (12%)	5 (18%)	17 (16%)

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Table 6.29
Summary of Disease Characteristics (Open-Label Albuterol Failure Population)

	Arg/Arg (N=37)	Arg/Gly (N=43)	Gly/Gly (N=28)	Total (N=108)

Biological relatives with hives history				
Father	0	2 (5%)	0	2 (2%)
Maternal grandparents	0	0	0	0
Mother	2 (5%)	1 (2%)	3 (11%)	6 (6%)
Paternal grandparents	1 (3%)	0	0	1 (<1%)
Sibling	4 (11%)	1 (2%)	3 (11%)	8 (7%)
Subject	4 (11%)	4 (9%)	8 (29%)	16 (15%)
Biological relatives with pet allergy history				
Father	3 (8%)	3 (7%)	0	6 (6%)
Maternal grandparents	0	1 (2%)	0	1 (<1%)
Mother	6 (16%)	5 (12%)	4 (14%)	15 (14%)
Paternal grandparents	0	0	0	0
Sibling	5 (14%)	7 (16%)	3 (11%)	15 (14%)
Subject	20 (54%)	18 (42%)	12 (43%)	50 (46%)
Biological relatives with sinus infection history				
Father	3 (8%)	5 (12%)	0	8 (7%)
Maternal grandparents	0	1 (2%)	0	1 (<1%)
Mother	8 (22%)	5 (12%)	6 (21%)	19 (18%)
Paternal grandparents	0	0	0	0
Sibling	6 (16%)	3 (7%)	7 (25%)	16 (15%)
Subject	13 (35%)	15 (35%)	11 (39%)	39 (36%)

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Table 6.29
Summary of Disease Characteristics (Open-Label Albuterol Failure Population)

	Arg/Arg (N=37)	Arg/Gly (N=43)	Gly/Gly (N=28)	Total (N=108)

Biological relatives with seasonal allergy history				
Father	3 (8%)	3 (7%)	1 (4%)	7 (6%)
Maternal grandparents	0	0	4 (14%)	4 (4%)
Mother	7 (19%)	5 (12%)	5 (18%)	17 (16%)
Paternal grandparents	0	0	1 (4%)	1 (<1%)
Sibling	4 (11%)	5 (12%)	3 (11%)	12 (11%)
Subject	15 (41%)	23 (53%)	17 (61%)	55 (51%)
Biological relatives with year-round hay fever history				
Father	5 (14%)	4 (9%)	1 (4%)	10 (9%)
Maternal grandparents	0	0	3 (11%)	3 (3%)
Mother	12 (32%)	12 (28%)	11 (39%)	35 (32%)
Paternal grandparents	0	1 (2%)	1 (4%)	2 (2%)
Sibling	9 (24%)	6 (14%)	9 (32%)	24 (22%)
Subject	28 (76%)	30 (70%)	21 (75%)	79 (73%)

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Table 6.30
Summary of Screening Pulmonary Function Tests (Open-Label Albuterol Failure Population)

		Arg/Arg (N=37)	Arg/Gly (N=43)	Gly/Gly (N=28)	Total (N=108)
FEV1 (L)	n	37	43	28	108
	Mean	2.65	2.63	2.53	2.61
	SD	0.667	0.641	0.607	0.638
	Median	2.55	2.57	2.44	2.56
	Min.	1.33	1.36	1.70	1.33
	Max.	4.36	4.44	4.30	4.44
FEV1 % predicted	n	37	43	28	108
	Mean	78.6	79.8	83.1	80.2
	SD	8.87	9.57	7.88	9.01
	Median	77.6	79.2	84.8	78.7
	Min.	55	57	71	55
	Max.	100	97	99	100
FEV1 % reversibility	n	36	43	28	107
	Mean	20.9	17.0	20.4	19.2
	SD	10.54	8.09	6.59	8.78
	Median	17.4	14.5	17.8	16.4
	Min.	5	0	12	0
	Max.	47	54	35	54
Historical FEV1 % reversibility	n	3	0	1	4
	Mean	25.3		16.0	22.9
	SD	9.00			8.69
	Median	29.0		16.0	22.5
	Min.	15		16	15
	Max.	32		16	32

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Table 6.31
Summary of Demographic Characteristics (Open-Label Ipratropium Failure Population)

		Arg/Arg (N=27)	Arg/Gly (N=62)	Gly/Gly (N=41)	Total (N=130)
Age at screening (y)	n	27	61	41	129
	Mean	32.7	31.0	29.5	30.9
	SD	17.66	12.70	9.90	13.07
	Median	27.0	30.0	30.0	30.0
	Min.	12	12	13	12
	Max.	77	65	63	77
Sex	n	27	61	41	129
	Female	15 (56%)	39 (64%)	27 (66%)	81 (63%)
	Male	12 (44%)	22 (36%)	14 (34%)	48 (37%)
Ethnicity	n	27	61	41	129
	Hispanic or Latino	9 (33%)	26 (43%)	13 (32%)	48 (37%)
	Not Hispanic or Latino	18 (67%)	35 (57%)	28 (68%)	81 (63%)
Race	n	27	61	41	129
	Arabic/North African	0	0	0	0
	Black	7 (26%)	9 (15%)	10 (24%)	26 (20%)
	African American	5 (71%)	9 (100%)	8 (80%)	22 (85%)
	African Heritage	2 (29%)	0	2 (20%)	4 (15%)
	East & South East Asian	1 (4%)	0	0	1 (<1%)
	Japanese	0	0	1 (2%)	1 (<1%)
	South Asian	0	1 (2%)	0	1 (<1%)
	White/Caucasian	16 (59%)	27 (44%)	24 (59%)	67 (52%)
	Other	3 (11%)	24 (39%)	6 (15%)	33 (26%)
	Native Hawaiian	0	0	0	0
	Other Pacific Islander	0	2 (8%)	0	2 (6%)
	American Indian	2 (67%)	19 (79%)	5 (83%)	26 (79%)
	Alaska Native	0	0	0	0

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Table 6.32
Summary of Disease Characteristics (Open-Label Ipratropium Failure Population)

	Arg/Arg (N=27)	Arg/Gly (N=62)	Gly/Gly (N=41)	Total (N=130)
Asthma duration (years)				
n	27	62	41	130
Mean	15.9	14.4	14.4	14.7
SD	13.08	11.00	10.67	11.29
Median	10.0	11.0	12.0	11.0
Min.	1	1	0	0
Max.	55	43	36	55
Duration in categories				
n	27	62	41	130
<6 months	0	0	2 (5%)	2 (2%)
>=6 months to <1 year	0	1 (2%)	0	1 (<1%)
>=1 year to <5 years	2 (7%)	11 (18%)	9 (22%)	22 (17%)
>=5 years to <10 years	6 (22%)	11 (18%)	3 (7%)	20 (15%)
>=10 years to <15 years	10 (37%)	14 (23%)	8 (20%)	32 (25%)
>=15 years	9 (33%)	25 (40%)	19 (46%)	53 (41%)
Is the subject exposed to passive smoke?				
n	27	62	41	130
Yes	6 (22%)	16 (26%)	9 (22%)	31 (24%)
No	21 (78%)	46 (74%)	32 (78%)	99 (76%)
Is the subject exposed to pets?				
n	27	62	41	130
Yes	9 (33%)	38 (61%)	23 (56%)	70 (54%)
No	18 (67%)	24 (39%)	18 (44%)	60 (46%)
Does the subject attend school?				
n	27	62	41	130
Yes	12 (44%)	20 (32%)	14 (34%)	46 (35%)
No	15 (56%)	42 (68%)	27 (66%)	84 (65%)

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Table 6.32
Summary of Disease Characteristics (Open-Label Ipratropium Failure Population)

	Arg/Arg (N=27)	Arg/Gly (N=62)	Gly/Gly (N=41)	Total (N=130)

Biological relatives with asthma history				
Father	5 (19%)	9 (15%)	5 (12%)	19 (15%)
Maternal grandparents	3 (11%)	5 (8%)	4 (10%)	12 (9%)
Mother	6 (22%)	11 (18%)	6 (15%)	23 (18%)
Paternal grandparents	3 (11%)	6 (10%)	0	9 (7%)
Sibling	5 (19%)	21 (34%)	14 (34%)	40 (31%)
Subject	27 (100%)	61 (98%)	41 (100%)	129 (>99%)
Biological relatives with croup history				
Father		0	0	0
Maternal grandparents		1 (2%)	0	1 (<1%)
Mother		0	0	0
Paternal grandparents		0	0	0
Sibling		0	1 (2%)	1 (<1%)
Subject		3 (5%)	0	3 (2%)
Biological relatives with eczema history				
Father	0	2 (3%)	1 (2%)	3 (2%)
Maternal grandparents	0	2 (3%)	2 (5%)	4 (3%)
Mother	2 (7%)	5 (8%)	1 (2%)	8 (6%)
Paternal grandparents	1 (4%)	1 (2%)	1 (2%)	3 (2%)
Sibling	3 (11%)	5 (8%)	3 (7%)	11 (8%)
Subject	2 (7%)	10 (16%)	7 (17%)	19 (15%)
Biological relatives with food allergy history				
Father	1 (4%)	4 (6%)	1 (2%)	6 (5%)
Maternal grandparents	0	1 (2%)	0	1 (<1%)
Mother	4 (15%)	4 (6%)	2 (5%)	10 (8%)
Paternal grandparents	0	1 (2%)	0	1 (<1%)
Sibling	0	8 (13%)	1 (2%)	9 (7%)
Subject	3 (11%)	5 (8%)	4 (10%)	12 (9%)

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Table 6.32
Summary of Disease Characteristics (Open-Label Ipratropium Failure Population)

	Arg/Arg (N=27)	Arg/Gly (N=62)	Gly/Gly (N=41)	Total (N=130)

Biological relatives with hives history				
Father	0	0	1 (2%)	1 (<1%)
Maternal grandparents	0	1 (2%)	2 (5%)	3 (2%)
Mother	3 (11%)	3 (5%)	2 (5%)	8 (6%)
Paternal grandparents	0	2 (3%)	1 (2%)	3 (2%)
Sibling	1 (4%)	3 (5%)	5 (12%)	9 (7%)
Subject	4 (15%)	11 (18%)	6 (15%)	21 (16%)
Biological relatives with pet allergy history				
Father	3 (11%)	3 (5%)	3 (7%)	9 (7%)
Maternal grandparents	0	0	4 (10%)	4 (3%)
Mother	4 (15%)	9 (15%)	8 (20%)	21 (16%)
Paternal grandparents	0	1 (2%)	0	1 (<1%)
Sibling	1 (4%)	13 (21%)	3 (7%)	17 (13%)
Subject	10 (37%)	34 (55%)	24 (59%)	68 (52%)
Biological relatives with sinus infection history				
Father	1 (4%)	6 (10%)	3 (7%)	10 (8%)
Maternal grandparents	2 (7%)	0	2 (5%)	4 (3%)
Mother	3 (11%)	10 (16%)	7 (17%)	20 (15%)
Paternal grandparents	1 (4%)	2 (3%)	1 (2%)	4 (3%)
Sibling	0	5 (8%)	3 (7%)	8 (6%)
Subject	7 (26%)	18 (29%)	12 (29%)	37 (28%)

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Table 6.32
Summary of Disease Characteristics (Open-Label Ipratropium Failure Population)

	Arg/Arg (N=27)	Arg/Gly (N=62)	Gly/Gly (N=41)	Total (N=130)

Biological relatives with seasonal allergy history				
Father	4 (15%)	6 (10%)	5 (12%)	15 (12%)
Maternal grandparents	1 (4%)	1 (2%)	4 (10%)	6 (5%)
Mother	4 (15%)	10 (16%)	6 (15%)	20 (15%)
Paternal grandparents	1 (4%)	1 (2%)	0	2 (2%)
Sibling	5 (19%)	7 (11%)	4 (10%)	16 (12%)
Subject	15 (56%)	25 (40%)	26 (63%)	66 (51%)
Biological relatives with year-round hay fever history				
Father	7 (26%)	9 (15%)	13 (32%)	29 (22%)
Maternal grandparents	2 (7%)	4 (6%)	5 (12%)	11 (8%)
Mother	6 (22%)	14 (23%)	14 (34%)	34 (26%)
Paternal grandparents	3 (11%)	3 (5%)	1 (2%)	7 (5%)
Sibling	9 (33%)	16 (26%)	14 (34%)	39 (30%)
Subject	23 (85%)	46 (74%)	32 (78%)	101 (78%)

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Table 6.33
Summary of Screening Pulmonary Function Tests (Open-Label Ipratropium Failure Population)

		Arg/Arg (N=27)	Arg/Gly (N=62)	Gly/Gly (N=41)	Total (N=130)
FEV1 (L)	n	27	62	41	130
	Mean	2.59	2.70	2.87	2.73
	SD	0.663	0.702	0.483	0.636
	Median	2.52	2.66	2.93	2.73
	Min.	1.38	1.46	1.71	1.38
	Max.	3.90	4.67	3.79	4.67
FEV1 % predicted	n	27	62	41	130
	Mean	82.0	82.5	83.9	82.9
	SD	7.88	8.12	8.05	8.02
	Median	80.4	82.4	84.6	82.4
	Min.	71	70	71	70
	Max.	98	100	99	100
FEV1 % reversibility	n	24	59	38	121
	Mean	18.0	20.8	19.5	19.8
	SD	6.10	9.70	8.10	8.60
	Median	15.6	17.8	16.0	16.1
	Min.	12	4	12	4
	Max.	37	52	49	52
Historical FEV1 % reversibility	n	3	0	4	7
	Mean	16.4		21.7	19.5
	SD	6.38		5.21	5.94
	Median	13.6		22.1	22.0
	Min.	12		15	12
	Max.	24		28	28

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Population: ITT Excluding Investigator [REDACTED]

Figure 7.1
Change from Baseline AM PEF (L/min)

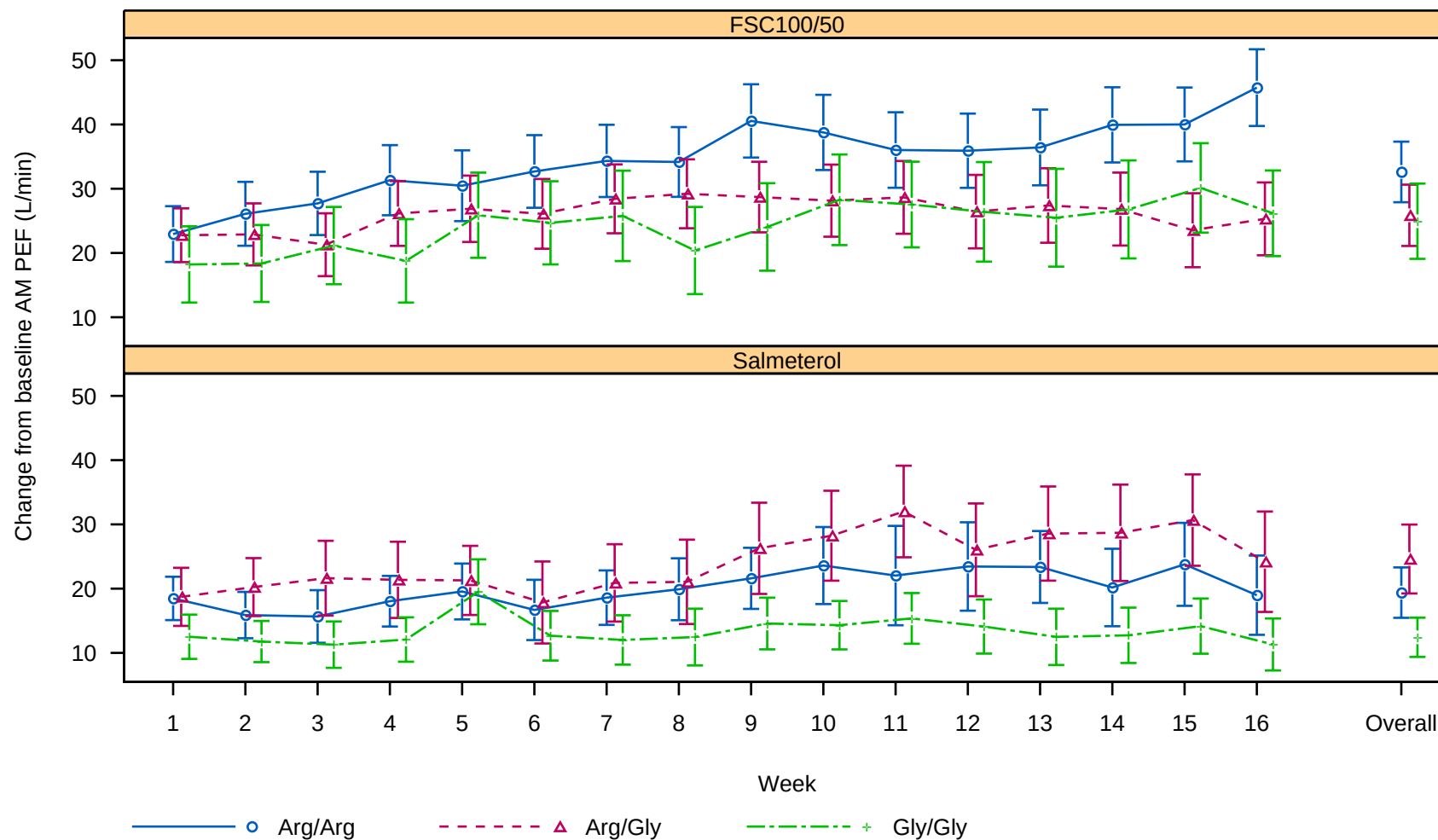


Table 7.1
Summary of AM PEF (L/min)

Treatment: FSC100/50

				Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)

Subjects in treatment group				87	91	90
AM PEF (L/min)	Double-blind	Baseline	n	84	91	89
			Mean	352.1	373.4	371.1
			SE	10.32	9.59	10.01
			Median	346.1	378.7	365.1
			Min.	121	168	213
			Max.	658	637	733
		Weeks 1-4	n	86	91	89
			Mean	376.5	396.9	388.3
			SE	10.27	10.90	9.25
			Median	367.5	388.8	381.9
			Min.	180	149	208
			Max.	703	664	653
		Weeks 5-8	n	83	88	85
			Mean	381.0	401.1	393.0
			SE	10.41	11.40	10.19
			Median	366.3	392.6	377.5
			Min.	222	150	233
			Max.	682	634	678
		Weeks 9-12	n	79	88	79
			Mean	385.3	401.1	398.4
			SE	10.76	11.78	10.98
			Median	370.7	392.7	391.1
			Min.	223	152	232
			Max.	680	676	667
		Weeks 13-16	n	78	86	78

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Table 7.1
Summary of AM PEF (L/min)

Treatment: FSC100/50

				Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)
AM PEF (L/min)	Double-blind	Weeks 13-16	Mean	384.1	401.6	403.4
			SE	10.71	11.81	10.88
			Median	364.6	387.0	388.5
			Min.	218	158	241
			Max.	671	671	675
		Overall	n	86	91	89
			Mean	382.6	399.3	394.3
			SE	10.09	11.07	9.66
			Median	368.8	388.0	383.1
			Min.	221	152	232
			Max.	685	661	659
	Wash-out	Overall	n	77	82	78
			Mean	372.3	393.0	384.8
			SE	10.27	11.26	10.55
			Median	357.1	384.4	378.1
			Min.	216	144	225
			Max.	655	680	645
AM PEF change	Double-blind	Weeks 1-4	n	83	91	88
			Mean	26.9	23.5	19.2
			SE	4.60	4.49	5.95
			Median	18.9	17.0	16.1
			Min.	-80	-103	-304
			Max.	157	172	188
		Weeks 5-8	n	80	88	84
			Mean	32.2	27.7	24.6
			SE	5.16	5.12	6.45
			Median	17.6	17.8	16.6
			Min.	-46	-85	-292

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Table 7.1
Summary of AM PEF (L/min)

Treatment: FSC100/50

				Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)
AM PEF change	Double-blind	Weeks 5-8	Max.	145	172	199
		Weeks 9-12	n	76	88	78
			Mean	37.7	27.7	26.5
			SE	5.48	5.41	6.79
			Median	25.9	14.9	17.6
			Min.	-66	-98	-259
			Max.	166	180	178
		Weeks 13-16	n	75	86	77
			Mean	38.9	26.4	27.0
			SE	5.66	5.57	6.83
			Median	31.3	15.9	16.8
			Min.	-44	-94	-226
			Max.	154	168	210
		Overall	n	83	91	88
			Mean	32.6	25.9	24.9
			SE	4.71	4.77	5.86
			Median	18.7	15.0	17.4
			Min.	-49	-89	-270
			Max.	140	166	194
	Wash-out	Overall	n	74	82	77
			Mean	27.2	17.0	9.1
			SE	5.07	4.58	4.83
			Median	17.9	10.2	6.2
			Min.	-56	-70	-226
			Max.	157	147	103

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Table 7.1
Summary of AM PEF (L/min)

Treatment: Salmeterol

				Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)

Subjects in treatment group				86	89	91
AM PEF (L/min)	Double-blind	Baseline	n	80	86	91
			Mean	386.7	362.1	372.8
			SE	11.47	9.39	10.15
			Median	366.4	345.4	356.0
			Min.	203	180	174
			Max.	658	685	628
		Weeks 1-4	n	81	86	89
			Mean	400.7	384.8	384.4
			SE	11.87	10.50	9.76
			Median	375.7	371.7	371.0
			Min.	210	182	194
			Max.	665	699	667
		Weeks 5-8	n	77	82	83
			Mean	399.6	389.2	386.7
			SE	12.32	11.83	10.61
			Median	378.3	368.2	374.3
			Min.	201	183	174
			Max.	654	827	652
		Weeks 9-12	n	73	77	79
			Mean	400.7	391.8	386.3
			SE	12.71	11.88	10.58
			Median	378.9	380.4	378.7
			Min.	206	231	192
			Max.	651	943	645
		Weeks 13-16	n	68	74	75

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Table 7.1
Summary of AM PEF (L/min)

Treatment: Salmeterol

				Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)
AM PEF (L/min)	Double-blind	Weeks 13-16	Mean	405.4	393.5	385.9
			SE	12.77	12.40	11.21
			Median	375.6	383.2	366.7
			Min.	212	226	180
			Max.	667	975	630
		Overall	n	81	86	89
			Mean	403.1	388.9	385.1
			SE	11.89	11.03	9.84
			Median	378.5	369.9	376.0
			Min.	211	229	185
			Max.	659	859	649
	Wash-out	Overall	n	65	73	75
			Mean	393.5	378.2	374.7
			SE	13.01	12.56	10.83
			Median	375.5	354.3	364.3
			Min.	211	212	183
			Max.	664	980	603
AM PEF change	Double-blind	Weeks 1-4	n	79	85	89
			Mean	17.0	20.6	11.8
			SE	3.43	4.81	2.91
			Median	15.7	7.0	7.7
			Min.	-106	-72	-83
			Max.	119	174	76
		Weeks 5-8	n	75	81	83
			Mean	18.6	20.6	13.5
			SE	4.10	5.77	3.77
			Median	11.5	8.1	8.6
			Min.	-91	-105	-56

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Table 7.1
Summary of AM PEF (L/min)

Treatment: Salmeterol

				Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)
AM PEF change	Double-blind	Weeks 5-8	Max.	133	302	154
		Weeks 9-12	n	72	76	79
			Mean	22.5	27.8	14.8
			SE	5.91	6.79	3.55
			Median	13.9	20.1	11.9
			Min.	-116	-75	-43
			Max.	319	418	124
		Weeks 13-16	n	67	73	75
			Mean	21.7	28.0	12.2
			SE	5.55	7.27	4.04
			Median	22.5	22.6	12.7
			Min.	-110	-92	-68
			Max.	186	451	124
		Overall	n	79	85	89
			Mean	19.4	24.6	12.4
			SE	3.92	5.36	3.05
			Median	14.2	14.5	9.8
			Min.	-106	-73	-83
			Max.	152	334	107
	Wash-out	Overall	n	64	72	75
			Mean	11.6	18.3	1.1
			SE	5.23	7.73	3.75
			Median	13.5	8.4	0.7
			Min.	-139	-102	-86
			Max.	128	456	81

Table 7.2
Analysis of AM PEF (L/min)

			Arg/Arg vs. Arg/Gly	Arg/Arg vs. Gly/Gly	Arg/Gly vs. Gly/Gly
FSC100/50	Double-blind	Weeks 1-4	p-value	0.596	0.263
			LS Means Diff	3.7	7.9
			95% CI for Diff	(-10.1, 17.5)	(-6.0, 21.7)
		Weeks 5-8	p-value	0.579	0.334
			LS Means Diff	4.4	7.6
			95% CI for Diff	(-11.1, 19.8)	(-7.9, 23.2)
		Weeks 9-12	p-value	0.214	0.209
			LS Means Diff	10.3	10.6
			95% CI for Diff	(-6.0, 26.5)	(-6.0, 27.3)
		Weeks 13-16	p-value	0.165	0.227
			LS Means Diff	11.7	10.5
			95% CI for Diff	(-4.8, 28.3)	(-6.5, 27.4)
	Wash-out	Overall	p-value	0.325	0.276
			LS Means Diff	7.1	7.9
			95% CI for Diff	(-7.1, 21.3)	(-6.3, 22.1)
		Overall	p-value	0.218	0.020
			LS Means Diff	8.3	15.9
			95% CI for Diff	(-4.9, 21.5)	(2.5, 29.2)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum and Arg16Gly genotype. Least squares mean differences are calculated as Arg/Arg-Arg/Gly, Arg/Arg-Gly/Gly and Arg/Gly-Gly/Gly.

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Table 7.2
Analysis of AM PEF (L/min)

			Arg/Arg vs. Arg/Gly	Arg/Arg vs. Gly/Gly	Arg/Gly vs. Gly/Gly
Salmeterol	Double-blind	Weeks 1-4	p-value	0.979	0.149
			LS Means Diff	-0.1	7.7
			95% CI for Diff	(-10.8, 10.5)	(-2.8, 18.2)
		Weeks 5-8	p-value	0.725	0.210
			LS Means Diff	2.3	8.2
			95% CI for Diff	(-10.7, 15.4)	(-4.6, 21.0)
		Weeks 9-12	p-value	0.858	0.183
			LS Means Diff	-1.4	10.5
			95% CI for Diff	(-17.2, 14.3)	(-5.0, 25.9)
		Weeks 13-16	p-value	0.761	0.130
			LS Means Diff	-2.5	12.5
			95% CI for Diff	(-19.1, 14.0)	(-3.7, 28.7)
	Wash-out	Overall	p-value	0.836	0.095
			LS Means Diff	-1.2	9.8
			95% CI for Diff	(-13.0, 10.6)	(-1.7, 21.4)
		Overall	p-value	0.596	0.153
			LS Means Diff	-4.6	12.1
			95% CI for Diff	(-21.6, 12.4)	(-4.5, 28.7)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum and Arg16Gly genotype. Least squares mean differences are calculated as Arg/Arg-Arg/Gly, Arg/Arg-Gly/Gly and Arg/Gly-Gly/Gly.

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Table 7.3
Summary of AM PEF (L/min) (Per Protocol Population)

Treatment: FSC100/50

				Arg/Arg (N=153)	Arg/Gly (N=164)	Gly/Gly (N=167)

Subjects in treatment group				76	84	81
AM PEF (L/min)	Double-blind	Baseline	n	73	84	80
			Mean	357.3	379.0	374.1
			SE	11.52	9.93	10.84
			Median	354.0	380.6	365.6
			Min.	121	183	213
			Max.	658	637	733
		Weeks 1-4	n	75	84	80
			Mean	383.2	403.4	389.6
			SE	11.16	11.21	9.99
			Median	373.3	394.7	380.6
			Min.	180	149	208
			Max.	703	664	653
		Weeks 5-8	n	72	82	77
			Mean	387.8	406.8	395.3
			SE	11.55	11.70	10.94
			Median	373.1	397.3	377.5
			Min.	222	150	233
			Max.	682	634	678
		Weeks 9-12	n	70	82	72
			Mean	390.9	406.9	400.6
			SE	11.69	12.16	11.72
			Median	374.2	396.6	391.1
			Min.	223	152	232
			Max.	680	676	667
		Weeks 13-16	n	69	81	73

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Table 7.3
Summary of AM PEF (L/min) (Per Protocol Population)

Treatment: FSC100/50

				Arg/Arg (N=153)	Arg/Gly (N=164)	Gly/Gly (N=167)
AM PEF (L/min)	Double-blind	Weeks 13-16	Mean	389.3	407.1	403.8
			SE	11.67	12.04	11.38
			Median	367.6	390.3	388.2
			Min.	218	158	241
			Max.	671	671	675
		Overall	n	75	84	80
			Mean	389.5	406.0	396.2
			SE	11.06	11.43	10.44
			Median	373.8	398.7	383.0
			Min.	221	152	232
			Max.	685	661	659
	Wash-out	Overall	n	69	78	72
			Mean	375.9	395.3	385.9
			SE	10.93	11.68	11.04
			Median	362.4	386.7	378.1
			Min.	216	144	225
			Max.	655	680	645
AM PEF change	Double-blind	Weeks 1-4	n	72	84	79
			Mean	28.9	24.5	17.7
			SE	4.56	4.79	6.23
			Median	19.9	19.3	15.5
			Min.	-65	-103	-304
			Max.	123	172	188
		Weeks 5-8	n	69	82	76
			Mean	34.3	28.4	24.2
			SE	5.39	5.46	6.83
			Median	24.1	19.1	16.6
			Min.	-46	-85	-292

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Table 7.3
Summary of AM PEF (L/min) (Per Protocol Population)

Treatment: FSC100/50

				Arg/Arg (N=153)	Arg/Gly (N=164)	Gly/Gly (N=167)
AM PEF change	Double-blind	Weeks 5-8	Max.	145	172	199
		Weeks 9-12	n	67	82	71
			Mean	39.7	28.5	25.9
			SE	5.69	5.77	7.14
			Median	27.0	14.9	16.7
			Min.	-66	-98	-259
			Max.	166	180	178
		Weeks 13-16	n	66	81	72
			Mean	40.7	27.6	27.6
			SE	5.70	5.81	6.99
			Median	32.6	17.3	17.5
			Min.	-44	-94	-226
			Max.	154	168	210
		Overall	n	72	84	79
			Mean	34.8	27.1	24.1
			SE	4.81	5.11	6.19
			Median	21.6	17.8	17.4
			Min.	-46	-89	-270
			Max.	140	166	194
	Wash-out	Overall	n	66	78	71
			Mean	26.8	17.4	8.5
			SE	5.02	4.73	4.86
			Median	18.8	10.2	6.2
			Min.	-56	-70	-226
			Max.	157	147	87

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Table 7.3
Summary of AM PEF (L/min) (Per Protocol Population)

Treatment: Salmeterol

				Arg/Arg (N=153)	Arg/Gly (N=164)	Gly/Gly (N=167)

Subjects in treatment group				77	80	86
AM PEF (L/min)	Double-blind	Baseline	n	73	77	86
			Mean	388.1	363.9	367.9
			SE	12.42	9.88	9.96
			Median	368.6	351.2	353.3
			Min.	203	226	174
			Max.	658	685	628
		Weeks 1-4	n	73	77	84
			Mean	403.2	387.1	379.7
			SE	12.93	11.00	9.54
			Median	376.4	377.0	365.7
			Min.	210	232	194
			Max.	665	699	667
		Weeks 5-8	n	69	73	78
			Mean	403.4	394.3	382.6
			SE	13.51	12.66	10.62
			Median	381.5	383.4	370.0
			Min.	201	228	174
			Max.	654	827	652
		Weeks 9-12	n	65	69	75
			Mean	404.0	396.7	382.7
			SE	14.03	12.87	10.45
			Median	378.9	380.6	377.8
			Min.	206	231	192
			Max.	651	943	645
		Weeks 13-16	n	60	67	71

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Table 7.3
Summary of AM PEF (L/min) (Per Protocol Population)

Treatment: Salmeterol

				Arg/Arg (N=153)	Arg/Gly (N=164)	Gly/Gly (N=167)
AM PEF (L/min)	Double-blind	Weeks 13-16	Mean	411.6	397.0	382.1
			SE	14.17	13.32	11.19
			Median	389.5	389.9	365.9
			Min.	212	226	180
			Max.	667	975	630
		Overall	n	73	77	84
			Mean	406.8	392.1	380.7
			SE	12.99	11.82	9.77
			Median	378.9	371.4	371.3
			Min.	211	229	185
			Max.	659	859	649
	Wash-out	Overall	n	57	67	71
			Mean	399.1	381.1	370.7
			SE	14.63	13.42	10.75
			Median	379.2	359.7	357.2
			Min.	211	212	183
			Max.	664	980	603
AM PEF change	Double-blind	Weeks 1-4	n	72	76	84
			Mean	17.0	20.8	12.0
			SE	3.76	5.28	2.99
			Median	14.6	6.2	8.0
			Min.	-106	-72	-83
			Max.	119	174	76
		Weeks 5-8	n	68	72	78
			Mean	20.0	23.0	14.7
			SE	4.48	6.18	3.93
			Median	14.6	9.9	8.6
			Min.	-91	-87	-56

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Table 7.3
Summary of AM PEF (L/min) (Per Protocol Population)

Treatment: Salmeterol

				Arg/Arg (N=153)	Arg/Gly (N=164)	Gly/Gly (N=167)
AM PEF change	Double-blind	Weeks 5-8	Max.	133	302	154
		Weeks 9-12	n	65	68	75
			Mean	23.5	29.7	16.0
			SE	6.53	7.40	3.64
			Median	13.9	20.3	12.9
			Min.	-116	-75	-43
			Max.	319	418	124
		Weeks 13-16	n	60	66	71
			Mean	24.8	29.1	13.4
			SE	5.83	7.89	4.11
			Median	24.7	23.5	13.9
			Min.	-110	-92	-68
			Max.	186	451	124
		Overall	n	72	76	84
			Mean	20.5	25.7	13.0
			SE	4.26	5.87	3.15
			Median	16.2	15.0	9.7
			Min.	-106	-73	-83
			Max.	152	334	107
	Wash-out	Overall	n	57	66	71
			Mean	14.3	18.0	2.0
			SE	5.46	8.34	3.85
			Median	13.9	8.4	4.3
			Min.	-139	-102	-86
			Max.	128	456	81

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Table 7.4
Analysis of AM PEF (L/min) (Per Protocol Population)

				Arg/Arg vs. Arg/Gly	Arg/Arg vs. Gly/Gly	Arg/Gly vs. Gly/Gly
FSC100/50	Double-blind	Weeks 1-4	p-value	0.650	0.151	0.301
			LS Means Diff	3.3	10.6	7.3
			95% CI for Diff	(-11.0, 17.6)	(-3.9, 25.1)	(-6.6, 21.1)
		Weeks 5-8	p-value	0.625	0.274	0.519
			LS Means Diff	4.1	9.2	5.2
			95% CI for Diff	(-12.3, 20.4)	(-7.4, 25.8)	(-10.6, 21.0)
		Weeks 9-12	p-value	0.269	0.175	0.762
			LS Means Diff	9.7	12.2	2.6
			95% CI for Diff	(-7.5, 26.8)	(-5.5, 29.9)	(-14.2, 19.3)
		Weeks 13-16	p-value	0.223	0.226	0.981
			LS Means Diff	10.6	10.8	0.2
			95% CI for Diff	(-6.5, 27.8)	(-6.8, 28.4)	(-16.4, 16.8)
	Wash-out	Overall	p-value	0.382	0.190	0.639
			LS Means Diff	6.6	10.1	3.4
			95% CI for Diff	(-8.3, 21.6)	(-5.0, 25.2)	(-11.0, 17.9)
		Overall	p-value	0.316	0.026	0.186
			LS Means Diff	6.8	15.5	8.7
			95% CI for Diff	(-6.5, 20.1)	(1.9, 29.1)	(-4.2, 21.6)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum and Arg16Gly genotype. Least squares mean differences are calculated as Arg/Arg-Arg/Gly, Arg/Arg-Gly/Gly and Arg/Gly-Gly/Gly.

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Table 7.4
Analysis of AM PEF (L/min) (Per Protocol Population)

				Arg/Arg vs. Arg/Gly	Arg/Arg vs. Gly/Gly	Arg/Gly vs. Gly/Gly
Salmeterol	Double-blind	Weeks 1-4	p-value	0.994	0.180	0.173
			LS Means Diff	0.0	7.6	7.6
			95% CI for Diff	(-11.4,11.5)	(-3.5,18.7)	(-3.3,18.5)
		Weeks 5-8	p-value	0.848	0.256	0.337
			LS Means Diff	1.3	7.8	6.4
			95% CI for Diff	(-12.5,15.2)	(-5.7,21.3)	(-6.7,19.6)
		Weeks 9-12	p-value	0.800	0.227	0.135
			LS Means Diff	-2.2	10.1	12.3
			95% CI for Diff	(-19.2,14.8)	(-6.3,26.5)	(-3.9,28.4)
		Weeks 13-16	p-value	0.923	0.111	0.080
			LS Means Diff	-0.9	13.9	14.7
			95% CI for Diff	(-18.4,16.7)	(-3.2,30.9)	(-1.8,31.2)
		Overall	p-value	0.854	0.108	0.066
	LS Means Diff		-1.2	10.1	11.3	
95% CI for Diff	(-13.9,11.5)		(-2.2,22.4)	(-0.8,23.3)		
Wash-out	Overall	p-value	0.824	0.127	0.066	
		LS Means Diff	-2.0	13.7	15.7	
		95% CI for Diff	(-20.1,16.0)	(-3.9,31.3)	(-1.0,32.4)	

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum and Arg16Gly genotype. Least squares mean differences are calculated as Arg/Arg-Arg/Gly, Arg/Arg-Gly/Gly and Arg/Gly-Gly/Gly.

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Table 7.5
Summary of PM PEF (L/min)

Treatment: FSC100/50

				Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)

Subjects in treatment group				87	91	90
PM PEF (L/min)	Double-blind	Baseline	n	84	91	89
			Mean	369.6	380.8	379.6
			SE	10.57	9.79	9.96
			Median	356.3	387.0	376.6
			Min.	141	166	199
			Max.	667	642	737
		Weeks 1-4	n	86	91	89
			Mean	389.4	403.5	394.8
			SE	10.46	11.17	9.49
			Median	375.2	401.1	392.4
			Min.	205	138	215
			Max.	707	664	677
		Weeks 5-8	n	83	88	86
			Mean	394.8	407.8	398.8
			SE	11.27	11.69	10.17
			Median	369.1	406.0	389.5
			Min.	212	141	241
			Max.	684	662	720
		Weeks 9-12	n	79	88	79
			Mean	396.1	407.5	404.4
			SE	11.12	11.74	10.97
			Median	377.2	401.6	397.4
			Min.	208	151	242
			Max.	684	669	688
		Weeks 13-16	n	78	86	78

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Table 7.5
 Summary of PM PEF (L/min)

Treatment: FSC100/50

				Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)
PM PEF (L/min)	Double-blind	Weeks 13-16	Mean	395.4	408.5	409.9
			SE	11.20	11.75	10.71
			Median	369.1	399.3	395.2
			Min.	205	142	253
			Max.	675	677	691
		Overall	n	86	91	89
			Mean	394.7	405.8	400.2
			SE	10.50	11.20	9.71
			Median	375.4	407.5	395.0
			Min.	207	143	240
			Max.	687	668	679
	Wash-out	Overall	n	77	82	78
			Mean	385.8	398.0	390.9
			SE	10.47	11.21	10.90
			Median	370.6	387.4	382.5
			Min.	204	137	225
			Max.	656	687	679
PM PEF change	Double-blind	Weeks 1-4	n	83	91	88
			Mean	21.7	22.7	17.1
			SE	4.52	4.45	5.70
			Median	15.5	21.4	12.3
			Min.	-78	-118	-298
			Max.	145	137	145
		Weeks 5-8	n	80	88	85
			Mean	27.9	26.8	21.6
			SE	5.46	4.97	6.43
			Median	17.7	19.5	15.6
			Min.	-57	-150	-287

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Table 7.5
Summary of PM PEF (L/min)

Treatment: FSC100/50

				Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)
PM PEF change	Double-blind	Weeks 5-8	Max.	166	155	182
		Weeks 9-12	n	76	88	78
			Mean	29.7	26.5	23.1
			SE	5.46	5.19	6.78
			Median	17.3	21.1	15.3
			Min.	-87	-145	-259
			Max.	151	191	152
		Weeks 13-16	n	75	86	77
			Mean	31.3	25.5	24.7
			SE	5.65	5.14	6.56
			Median	25.0	17.7	14.1
			Min.	-88	-122	-229
			Max.	176	157	159
		Overall	n	83	91	88
			Mean	26.8	25.0	22.4
			SE	4.75	4.57	5.79
			Median	14.8	20.1	13.4
			Min.	-57	-134	-268
			Max.	158	155	147
	Wash-out	Overall	n	74	82	77
			Mean	21.5	15.1	6.4
			SE	5.65	4.55	4.87
			Median	10.3	9.8	5.0
			Min.	-98	-110	-215
			Max.	206	144	105

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Table 7.5
Summary of PM PEF (L/min)

Treatment: Salmeterol

				Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)

Subjects in treatment group				86	89	91
PM PEF (L/min)	Double-blind	Baseline	n	80	87	90
			Mean	398.0	373.4	386.4
			SE	12.59	10.19	10.66
			Median	383.5	362.1	368.6
			Min.	178	165	219
			Max.	744	690	673
		Weeks 1-4	n	81	86	89
			Mean	410.5	393.1	393.9
			SE	13.03	11.17	10.12
			Median	390.1	373.1	387.8
			Min.	214	171	193
			Max.	750	725	662
		Weeks 5-8	n	77	82	83
			Mean	411.6	399.2	398.0
			SE	13.44	12.31	10.87
			Median	387.5	382.6	390.5
			Min.	207	173	166
			Max.	743	842	651
		Weeks 9-12	n	73	77	79
			Mean	411.0	406.9	395.3
			SE	13.62	12.73	10.67
			Median	384.3	391.8	392.5
			Min.	199	221	191
			Max.	649	951	645
		Weeks 13-16	n	70	74	75

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Table 7.5
 Summary of PM PEF (L/min)

Treatment: Salmeterol

				Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)
PM PEF (L/min)	Double-blind	Weeks 13-16	Mean	411.6	406.3	396.1
			SE	13.88	12.97	11.15
			Median	379.9	390.6	384.3
			Min.	195	225	191
			Max.	652	965	638
		Overall	n	81	86	89
			Mean	414.1	399.6	395.7
			SE	13.03	11.59	10.14
			Median	390.0	385.4	391.7
			Min.	211	213	185
			Max.	747	870	649
	Wash-out	Overall	n	65	72	75
			Mean	403.0	392.2	386.5
			SE	13.92	12.96	11.03
			Median	385.4	366.8	372.5
			Min.	213	210	190
			Max.	648	977	646
PM PEF change	Double-blind	Weeks 1-4	n	79	86	88
			Mean	15.8	19.7	8.7
			SE	3.34	5.19	3.18
			Median	9.0	10.3	9.8
			Min.	-103	-69	-117
			Max.	111	222	65
		Weeks 5-8	n	75	82	82
			Mean	20.3	21.8	11.7
			SE	4.50	5.97	3.57
			Median	13.3	10.3	9.5
			Min.	-89	-101	-84

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Table 7.5
Summary of PM PEF (L/min)

Treatment: Salmeterol

				Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)
PM PEF change	Double-blind	Weeks 5-8	Max.	197	313	97
		Weeks 9-12	n	72	77	78
			Mean	22.9	33.0	11.8
			SE	5.40	7.78	3.88
			Median	18.7	17.6	13.3
			Min.	-117	-92	-99
			Max.	262	423	99
		Weeks 13-16	n	69	74	75
			Mean	21.3	30.6	10.7
			SE	5.10	8.12	4.64
			Median	17.3	19.4	10.7
			Min.	-120	-94	-157
			Max.	155	437	108
		Overall	n	79	86	88
			Mean	19.3	26.2	10.5
			SE	3.86	5.89	3.15
			Median	9.0	11.3	11.1
			Min.	-107	-75	-106
			Max.	127	341	79
	Wash-out	Overall	n	64	72	75
			Mean	9.8	22.8	1.1
			SE	5.09	8.63	4.68
			Median	10.9	10.5	3.1
			Min.	-146	-105	-150
			Max.	118	448	113

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Table 7.6
Analysis of PM PEF (L/min)

				Arg/Arg vs. Arg/Gly	Arg/Arg vs. Gly/Gly	Arg/Gly vs. Gly/Gly
FSC100/50	Double-blind	Weeks 1-4	p-value	0.943	0.402	0.429
			LS Means Diff	0.5	5.8	5.3
			95% CI for Diff	(-13.1, 14.1)	(-7.8, 19.4)	(-7.9, 18.5)
		Weeks 5-8	p-value	0.811	0.359	0.483
			LS Means Diff	1.9	7.3	5.4
			95% CI for Diff	(-13.7, 17.5)	(-8.4, 23.0)	(-9.8, 20.6)
		Weeks 9-12	p-value	0.621	0.427	0.745
			LS Means Diff	4.0	6.6	2.6
			95% CI for Diff	(-11.9, 19.9)	(-9.7, 22.9)	(-13.1, 18.3)
		Weeks 13-16	p-value	0.463	0.443	0.958
			LS Means Diff	5.9	6.3	0.4
			95% CI for Diff	(-9.9, 21.6)	(-9.9, 22.5)	(-15.1, 15.9)
	Wash-out	Overall	p-value	0.667	0.433	0.714
			LS Means Diff	3.0	5.6	2.5
			95% CI for Diff	(-10.9, 17.0)	(-8.4, 19.6)	(-11.1, 16.1)
		Overall	p-value	0.406	0.049	0.235
			LS Means Diff	5.8	13.9	8.1
			95% CI for Diff	(-7.9, 19.5)	(0.0, 27.8)	(-5.3, 21.6)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum and Arg16Gly genotype. Least squares mean differences are calculated as Arg/Arg-Arg/Gly, Arg/Arg-Gly/Gly and Arg/Gly-Gly/Gly.

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Table 7.6
Analysis of PM PEF (L/min)

				Arg/Arg vs. Arg/Gly	Arg/Arg vs. Gly/Gly	Arg/Gly vs. Gly/Gly
Salmeterol	Double-blind	Weeks 1-4	p-value	0.957	0.086	0.068
			LS Means Diff	-0.3	9.7	10.0
			95% CI for Diff	(-11.5, 10.9)	(-1.4, 20.8)	(-0.7, 20.7)
		Weeks 5-8	p-value	0.741	0.094	0.165
			LS Means Diff	2.3	11.3	9.1
			95% CI for Diff	(-11.2, 15.7)	(-1.9, 24.6)	(-3.8, 21.9)
		Weeks 9-12	p-value	0.479	0.097	0.015
			LS Means Diff	-6.0	14.0	20.0
			95% CI for Diff	(-22.8, 10.7)	(-2.6, 30.5)	(3.9, 36.2)
		Weeks 13-16	p-value	0.586	0.112	0.028
			LS Means Diff	-4.9	14.0	18.9
			95% CI for Diff	(-22.4, 12.7)	(-3.3, 31.4)	(2.1, 35.7)
	Wash-out	Overall	p-value	0.648	0.062	0.017
			LS Means Diff	-2.9	11.7	14.6
			95% CI for Diff	(-15.4, 9.6)	(-0.6, 24.0)	(2.7, 26.5)
		Overall	p-value	0.301	0.248	0.022
			LS Means Diff	-9.8	10.7	20.5
			95% CI for Diff	(-28.4, 8.8)	(-7.5, 29.0)	(3.0, 38.1)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum and Arg16Gly genotype. Least squares mean differences are calculated as Arg/Arg-Arg/Gly, Arg/Arg-Gly/Gly and Arg/Gly-Gly/Gly.

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Table 7.7
Summary of Pre-dose FEV1 (L)

Treatment: FSC100/50

			Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)
Subjects in treatment group			87	91	90
FEV1 (L)	Visit 2 (Week -16)	n	87	91	90
		Mean	2.77	2.86	2.84
		SE	0.074	0.073	0.071
		Median	2.79	2.77	2.80
		Min.	1.44	1.25	1.31
		Max.	5.03	4.52	4.48
	Visit 3 (Week -12)	n	87	91	90
		Mean	2.81	2.86	2.86
		SE	0.074	0.072	0.068
		Median	2.73	2.76	2.88
		Min.	1.48	1.45	1.56
		Max.	5.02	4.61	4.63
	Visit 4 (Week -8)	n	87	91	90
		Mean	2.78	2.89	2.88
		SE	0.075	0.072	0.062
		Median	2.68	2.83	2.83
		Min.	1.57	1.30	1.62
		Max.	5.08	4.60	4.34
	Visit 5 (Week -4)	n	87	91	90
		Mean	2.81	2.90	2.86
		SE	0.072	0.071	0.067
		Median	2.69	2.85	2.90
		Min.	1.63	1.46	1.59
		Max.	4.74	4.63	4.52

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Table 7.7
Summary of Pre-dose FEV1 (L)

Treatment: FSC100/50

			Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)
FEV1 (L)	Visit 6 (Day 1)	n	87	91	90
		Mean	2.76	2.87	2.86
		SE	0.076	0.073	0.066
		Median	2.68	2.77	2.83
		Min.	1.32	1.33	1.45
		Max.	4.95	4.77	4.34
	Visit 7 (Week 4)	n	81	89	88
		Mean	2.96	3.09	3.04
		SE	0.085	0.081	0.079
		Median	2.84	2.97	3.02
		Min.	1.63	1.36	1.59
		Max.	5.98	4.86	4.79
	Visit 8 (Week 8)	n	79	88	81
		Mean	2.97	3.08	3.05
		SE	0.083	0.085	0.083
		Median	2.95	2.98	3.01
		Min.	1.75	1.20	1.64
		Max.	5.68	4.97	4.89
	Visit 9 (Week 12)	n	78	84	79
		Mean	2.96	3.10	3.05
		SE	0.083	0.088	0.087
		Median	2.90	2.95	2.96
		Min.	1.43	1.22	1.61
		Max.	5.75	5.08	4.90

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Table 7.7
Summary of Pre-dose FEV1 (L)

Treatment: FSC100/50

			Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)
FEV1 (L)	Visit 10 (Week 16)	n	77	83	79
		Mean	2.95	3.09	3.04
		SE	0.084	0.087	0.085
		Median	2.84	2.94	3.06
		Min.	1.62	1.15	1.62
		Max.	5.33	5.02	4.93
	Endpoint	n	81	89	88
		Mean	2.94	3.10	3.05
		SE	0.082	0.083	0.079
		Median	2.83	2.98	3.07
		Min.	1.62	1.15	1.62
		Max.	5.33	5.02	4.93
	Overall	n	81	89	88
		Mean	2.95	3.09	3.05
		SE	0.081	0.083	0.077
		Median	2.87	2.97	3.01
		Min.	1.61	1.23	1.70
		Max.	5.69	4.98	4.86
	Visit 11 (Wash-out)	n	76	82	79
		Mean	2.76	2.89	2.94
		SE	0.086	0.082	0.080
		Median	2.52	2.82	2.89
		Min.	1.27	1.20	1.49
		Max.	4.78	4.62	4.69

Table 7.7
Summary of Pre-dose FEV1 (L)

Treatment: FSC100/50

			Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)
FEV1 change	Visit 7 (Week 4)	n	81	89	88
		Mean	0.22	0.22	0.20
		SE	0.030	0.033	0.037
		Median	0.19	0.16	0.18
		Min.	-0.22	-0.35	-0.80
		Max.	1.03	1.62	1.55
	Visit 8 (Week 8)	n	79	88	81
		Mean	0.22	0.22	0.23
		SE	0.031	0.034	0.032
		Median	0.21	0.12	0.18
		Min.	-0.54	-0.19	-0.51
		Max.	1.18	1.50	1.15
	Visit 9 (Week 12)	n	78	84	79
		Mean	0.22	0.23	0.22
		SE	0.031	0.038	0.035
		Median	0.22	0.15	0.16
		Min.	-0.60	-0.64	-0.38
		Max.	1.04	1.54	1.56
	Visit 10 (Week 16)	n	77	83	79
		Mean	0.21	0.23	0.21
		SE	0.036	0.039	0.042
		Median	0.19	0.16	0.18
		Min.	-0.67	-0.32	-0.74
		Max.	1.29	1.61	1.65

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Table 7.7
 Summary of Pre-dose FEV1 (L)

Treatment: FSC100/50

			Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)
FEV1 change	Endpoint	n	81	89	88
		Mean	0.21	0.23	0.20
		SE	0.034	0.038	0.038
		Median	0.18	0.16	0.19
		Min.	-0.67	-0.32	-0.74
		Max.	1.29	1.61	1.65
	Overall	n	81	89	88
		Mean	0.22	0.22	0.21
		SE	0.027	0.033	0.029
		Median	0.19	0.16	0.17
		Min.	-0.41	-0.29	-0.35
		Max.	1.02	1.52	1.44
	Visit 11 (Wash-out)	n	76	82	79
		Mean	0.03	0.02	0.12
		SE	0.032	0.031	0.035
		Median	0.05	0.03	0.07
		Min.	-1.03	-0.63	-0.58
		Max.	0.60	0.84	1.53

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Table 7.7
Summary of Pre-dose FEV1 (L)

Treatment: Salmeterol

			Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)

Subjects in treatment group			86	89	91
FEV1 (L)	Visit 2 (Week -16)	n	86	89	91
		Mean	2.94	2.81	2.82
		SE	0.079	0.073	0.074
		Median	2.85	2.77	2.75
		Min.	1.60	1.44	1.76
		Max.	4.72	4.76	5.09
	Visit 3 (Week -12)	n	86	89	91
		Mean	2.90	2.90	2.85
		SE	0.078	0.080	0.077
		Median	2.79	2.77	2.77
		Min.	1.64	1.39	1.65
		Max.	4.58	4.66	5.46
	Visit 4 (Week -8)	n	86	89	91
		Mean	2.95	2.85	2.87
		SE	0.079	0.078	0.079
		Median	2.97	2.72	2.74
		Min.	1.58	1.44	1.62
		Max.	4.51	4.69	5.46
	Visit 5 (Week -4)	n	86	89	91
		Mean	2.96	2.87	2.87
		SE	0.080	0.074	0.083
		Median	2.83	2.79	2.75
		Min.	1.62	1.51	1.66
		Max.	4.93	4.61	5.66

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Table 7.7
Summary of Pre-dose FEV1 (L)

Treatment: Salmeterol

			Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)
FEV1 (L)	Visit 6 (Day 1)	n	86	89	91
		Mean	2.89	2.84	2.88
		SE	0.080	0.081	0.077
		Median	2.81	2.76	2.79
		Min.	1.66	1.32	1.54
		Max.	4.53	4.73	4.93
	Visit 7 (Week 4)	n	79	84	84
		Mean	3.11	2.99	3.00
		SE	0.092	0.080	0.088
		Median	3.02	2.90	2.92
		Min.	1.45	1.22	1.64
		Max.	4.87	4.89	5.35
	Visit 8 (Week 8)	n	75	78	79
		Mean	3.00	3.04	2.93
		SE	0.086	0.082	0.084
		Median	2.84	2.96	2.82
		Min.	1.62	1.24	1.32
		Max.	4.47	5.36	5.11
	Visit 9 (Week 12)	n	69	75	76
		Mean	3.10	2.96	2.93
		SE	0.094	0.078	0.084
		Median	3.02	2.92	2.95
		Min.	1.56	1.20	1.52
		Max.	4.82	4.41	4.99

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Table 7.7
Summary of Pre-dose FEV1 (L)

Treatment: Salmeterol

			Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)
FEV1 (L)	Visit 10 (Week 16)	n	66	73	75
		Mean	3.12	2.92	2.91
		SE	0.103	0.077	0.088
		Median	2.94	2.90	2.90
		Min.	1.52	1.22	1.43
		Max.	5.15	4.47	5.09
	Endpoint	n	79	84	84
		Mean	3.08	2.97	2.94
		SE	0.097	0.083	0.088
		Median	2.91	2.90	2.86
		Min.	1.52	1.22	1.43
		Max.	5.15	5.36	5.16
	Overall	n	79	84	84
		Mean	3.07	3.00	2.97
		SE	0.088	0.079	0.085
		Median	3.04	2.95	2.93
		Min.	1.57	1.22	1.65
		Max.	4.71	4.89	5.16
	Visit 11 (Wash-out)	n	65	72	75
		Mean	2.90	2.85	2.81
		SE	0.092	0.080	0.090
		Median	2.83	2.83	2.78
		Min.	1.18	1.10	1.36
		Max.	4.38	4.55	5.32

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Table 7.7
Summary of Pre-dose FEV1 (L)

Treatment: Salmeterol

			Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)
FEV1 change	Visit 7 (Week 4)	n	79	84	84
		Mean	0.25	0.13	0.11
		SE	0.045	0.035	0.032
		Median	0.14	0.12	0.10
		Min.	-0.26	-1.33	-0.78
		Max.	2.38	0.99	1.47
	Visit 8 (Week 8)	n	75	78	79
		Mean	0.16	0.18	0.07
		SE	0.032	0.038	0.037
		Median	0.13	0.13	0.08
		Min.	-0.90	-0.29	-0.84
		Max.	0.82	1.73	1.27
	Visit 9 (Week 12)	n	69	75	76
		Mean	0.20	0.12	0.07
		SE	0.038	0.035	0.031
		Median	0.14	0.10	0.06
		Min.	-0.43	-0.61	-0.60
		Max.	1.27	1.05	1.17
	Visit 10 (Week 16)	n	66	73	75
		Mean	0.22	0.08	0.05
		SE	0.057	0.035	0.033
		Median	0.10	0.08	0.05
		Min.	-0.38	-0.90	-0.96
		Max.	2.54	1.16	0.71

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Table 7.7
 Summary of Pre-dose FEV1 (L)

Treatment: Salmeterol

			Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)
FEV1 change	Endpoint	n	79	84	84
		Mean	0.21	0.11	0.05
		SE	0.049	0.033	0.031
		Median	0.10	0.12	0.06
		Min.	-0.38	-0.90	-0.96
		Max.	2.54	1.16	0.71
	Overall	n	79	84	84
		Mean	0.21	0.13	0.08
		SE	0.032	0.029	0.027
		Median	0.12	0.12	0.07
		Min.	-0.24	-0.47	-0.46
		Max.	1.19	1.05	1.16
	Visit 11 (Wash-out)	n	65	72	75
		Mean	0.01	0.03	-0.06
		SE	0.038	0.036	0.042
		Median	0.02	0.04	-0.05
		Min.	-0.75	-0.75	-1.54
		Max.	0.93	1.03	1.02

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Table 7.8
Analysis of Pre-dose FEV1 (L)

			Arg/Arg vs. Arg/Gly	Arg/Arg vs. Gly/Gly	Arg/Gly vs. Gly/Gly
FSC100/50	Visit 7 (Week 4)	p-value	0.869	0.484	0.581
		LS Means Diff	0.01	0.03	0.03
		95% CI for Diff	(-0.09, 0.10)	(-0.06, 0.13)	(-0.07, 0.12)
	Visit 8 (Week 8)	p-value	0.694	0.988	0.678
		LS Means Diff	0.02	-0.00	-0.02
		95% CI for Diff	(-0.07, 0.11)	(-0.09, 0.09)	(-0.11, 0.07)
	Visit 9 (Week 12)	p-value	0.925	0.820	0.891
		LS Means Diff	0.00	0.01	0.01
		95% CI for Diff	(-0.09, 0.10)	(-0.09, 0.11)	(-0.09, 0.10)
	Visit 10 (Week 16)	p-value	0.775	0.883	0.660
		LS Means Diff	-0.02	0.01	0.02
		95% CI for Diff	(-0.13, 0.09)	(-0.10, 0.12)	(-0.08, 0.13)
	Endpoint	p-value	0.671	0.894	0.565
		LS Means Diff	-0.02	0.01	0.03
		95% CI for Diff	(-0.13, 0.08)	(-0.10, 0.11)	(-0.07, 0.13)
	Overall	p-value	0.953	0.679	0.714
		LS Means Diff	0.00	0.02	0.02
		95% CI for Diff	(-0.08, 0.09)	(-0.07, 0.10)	(-0.07, 0.10)
	Visit 11 (Wash-out)	p-value	0.814	0.094	0.051
		LS Means Diff	0.01	-0.08	-0.09
		95% CI for Diff	(-0.08, 0.10)	(-0.17, 0.01)	(-0.18, 0.00)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum and Arg16Gly genotype. Least squares mean differences are calculated as Arg/Arg-Arg/Gly, Arg/Arg-Gly/Gly and Arg/Gly-Gly/Gly.

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Table 7.8
Analysis of Pre-dose FEV1 (L)

			Arg/Arg vs. Arg/Gly	Arg/Arg vs. Gly/Gly	Arg/Gly vs. Gly/Gly
Salmeterol	Visit 7 (Week 4)	p-value	0.041	0.016	0.712
		LS Means Diff	0.11	0.13	0.02
		95% CI for Diff	(0.00, 0.22)	(0.02, 0.23)	(-0.08, 0.12)
	Visit 8 (Week 8)	p-value	0.736	0.075	0.031
		LS Means Diff	-0.02	0.09	0.11
		95% CI for Diff	(-0.12, 0.08)	(-0.01, 0.19)	(0.01, 0.21)
	Visit 9 (Week 12)	p-value	0.080	0.007	0.331
		LS Means Diff	0.09	0.14	0.05
		95% CI for Diff	(-0.01, 0.19)	(0.04, 0.23)	(-0.05, 0.14)
	Visit 10 (Week 16)	p-value	0.022	0.003	0.517
		LS Means Diff	0.14	0.18	0.04
		95% CI for Diff	(0.02, 0.26)	(0.06, 0.30)	(-0.08, 0.15)
	Endpoint	p-value	0.055	0.004	0.311
		LS Means Diff	0.11	0.16	0.05
		95% CI for Diff	(-0.00, 0.22)	(0.05, 0.27)	(-0.05, 0.16)
	Overall	p-value	0.076	0.003	0.218
		LS Means Diff	0.08	0.13	0.05
		95% CI for Diff	(-0.01, 0.16)	(0.04, 0.21)	(-0.03, 0.13)
	Visit 11 (Wash-out)	p-value	0.539	0.323	0.094
		LS Means Diff	-0.03	0.05	0.09
		95% CI for Diff	(-0.14, 0.08)	(-0.05, 0.16)	(-0.02, 0.19)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum and Arg16Gly genotype. Least squares mean differences are calculated as Arg/Arg-Arg/Gly, Arg/Arg-Gly/Gly and Arg/Gly-Gly/Gly.

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Table 7.9
Summary of Percent of Symptom-Free Days

Treatment: FSC100/50

				Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)

Subjects in treatment				87	91	90
% Symptom-free days	Double-blind	Baseline	n	81	90	89
			Mean	31.5	34.6	32.2
			SE	4.63	4.39	3.70
			Median	0.0	7.1	14.3
			Min.	0	0	0
			Max.	100	100	100
		Weeks 1-4	n	86	91	88
			Mean	42.7	46.6	49.0
			SE	4.49	4.42	4.37
			Median	39.7	53.6	50.0
			Min.	0	0	0
			Max.	100	100	100
		Weeks 5-8	n	83	87	84
			Mean	42.8	48.6	51.3
			SE	4.56	4.43	4.46
			Median	44.4	53.6	60.0
			Min.	0	0	0
			Max.	100	100	100
		Weeks 9-12	n	79	87	79
			Mean	45.4	50.1	49.6
			SE	4.74	4.49	4.59
			Median	42.9	64.3	57.1
			Min.	0	0	0
			Max.	100	100	100
		Weeks 13-16	n	78	84	77
			Mean	46.3	47.8	51.1

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Table 7.9
Summary of Percent of Symptom-Free Days

Treatment: FSC100/50

				Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)
% Symptom-free days	Double-blind	Weeks 13-16	SE	4.96	4.42	4.71
			Median	50.0	48.2	57.1
			Min.	0	0	0
			Max.	100	100	100
		Overall	n	86	91	89
			Mean	43.5	48.6	50.6
			SE	4.41	4.21	4.20
			Median	44.8	51.8	58.2
			Min.	0	0	0
			Max.	100	100	100
	Wash-out	Overall	n	77	82	76
			Mean	41.4	38.7	42.8
			SE	4.92	4.41	4.78
			Median	23.1	24.0	40.7
			Min.	0	0	0
			Max.	100	100	100
% SFD change	Double-blind	Weeks 1-4	n	80	90	87
			Mean	9.5	12.5	16.2
			SE	2.91	3.13	2.99
			Median	0.0	0.0	6.0
			Min.	-39	-29	-43
			Max.	100	96	96
		Weeks 5-8	n	78	87	83
			Mean	9.0	15.1	19.5
			SE	3.11	3.28	3.31
			Median	0.0	0.0	7.1
			Min.	-46	-32	-32
			Max.	100	100	100

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Table 7.9
Summary of Percent of Symptom-Free Days

Treatment: FSC100/50

				Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)
% SFD change	Double-blind	Weeks 9-12	n	74	87	78
			Mean	11.6	16.6	17.4
			SE	3.32	3.72	3.29
			Median	0.0	0.0	7.1
			Min.	-40	-76	-38
			Max.	100	100	100
		Weeks 13-16	n	73	84	76
			Mean	11.0	15.2	18.1
			SE	3.47	4.03	3.28
			Median	0.0	0.0	4.9
			Min.	-50	-78	-35
			Max.	100	100	100
		Overall	n	80	90	88
			Mean	9.9	14.6	18.2
			SE	2.83	3.19	2.88
			Median	0.0	0.0	7.9
			Min.	-35	-44	-23
			Max.	100	99	96
	Wash-out	Overall	n	72	82	75
			Mean	7.5	6.5	9.5
			SE	3.31	2.96	2.91
			Median	0.0	0.0	0.0
			Min.	-64	-55	-43
			Max.	100	100	100

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Table 7.9
Summary of Percent of Symptom-Free Days

Treatment: Salmeterol

				Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)

Subjects in treatment				86	89	91
% Symptom-free days	Double-blind	Baseline	n	80	87	90
			Mean	34.4	35.4	36.1
			SE	4.63	4.31	4.31
			Median	14.3	14.3	14.3
			Min.	0	0	0
			Max.	100	100	100
		Weeks 1-4	n	79	86	88
			Mean	41.3	43.5	41.0
			SE	4.26	4.41	4.26
			Median	39.3	37.5	39.3
			Min.	0	0	0
			Max.	100	100	100
		Weeks 5-8	n	76	82	83
			Mean	45.5	44.2	42.6
			SE	4.48	4.56	4.35
			Median	46.4	42.9	35.7
			Min.	0	0	0
			Max.	100	100	100
		Weeks 9-12	n	72	77	79
			Mean	47.1	45.3	43.3
			SE	4.72	4.85	4.58
			Median	50.9	39.3	36.4
			Min.	0	0	0
			Max.	100	100	100
		Weeks 13-16	n	69	74	75
			Mean	49.8	46.4	40.8

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Table 7.9
Summary of Percent of Symptom-Free Days

Treatment: Salmeterol

				Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)
% Symptom-free days	Double-blind	Weeks 13-16	SE	4.76	4.91	4.62
			Median	60.0	40.0	32.1
			Min.	0	0	0
			Max.	100	100	100
		Overall	n	81	86	89
			Mean	44.9	44.9	43.6
			SE	4.14	4.31	4.18
			Median	47.7	41.6	43.5
			Min.	0	0	0
			Max.	100	100	100
	Wash-out	Overall	n	64	72	75
			Mean	42.4	40.7	37.1
			SE	4.96	5.12	4.80
			Median	33.3	14.6	15.4
			Min.	0	0	0
			Max.	100	100	100
% SFD change	Double-blind	Weeks 1-4	n	78	86	87
			Mean	7.1	7.7	6.7
			SE	3.09	3.08	2.84
			Median	0.0	0.0	0.0
			Min.	-64	-67	-82
			Max.	86	96	93
		Weeks 5-8	n	74	82	82
			Mean	9.8	7.1	7.3
			SE	3.70	3.14	3.04
			Median	0.0	0.0	0.0
			Min.	-86	-100	-86
			Max.	96	100	96

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Table 7.9
 Summary of Percent of Symptom-Free Days

Treatment: Salmeterol

				Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)
% SFD change	Double-blind	Weeks 9-12	n	71	77	78
			Mean	11.5	8.3	9.3
			SE	3.82	2.71	3.03
			Median	0.0	0.0	0.0
			Min.	-61	-57	-82
			Max.	100	100	100
		Weeks 13-16	n	68	74	75
			Mean	12.2	8.3	8.2
			SE	4.30	2.80	3.20
			Median	0.0	0.0	0.0
			Min.	-86	-50	-79
			Max.	100	86	100
		Overall	n	79	86	88
			Mean	9.6	9.1	8.2
			SE	3.21	2.69	2.69
			Median	0.0	0.0	0.0
			Min.	-69	-45	-82
			Max.	94	97	97
	Wash-out	Overall	n	63	72	75
			Mean	4.2	3.2	4.6
			SE	3.97	2.63	3.58
			Median	0.0	0.0	0.0
			Min.	-91	-57	-86
			Max.	100	86	93

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Table 7.10
Analysis of Percent of Symptom-Free Days

				Arg/Arg vs. Arg/Gly	Arg/Arg vs. Gly/Gly	Arg/Gly vs. Gly/Gly
FSC100/50	Double-blind	Weeks 1-4	p-value	0.501	0.144	0.411
			LS Means Diff	-2.8	-6.2	-3.3
			95% CI for Diff	(-11.1, 5.5)	(-14.5, 2.1)	(-11.4, 4.7)
		Weeks 5-8	p-value	0.187	0.028	0.354
			LS Means Diff	-5.9	-9.9	-4.0
	Wash-out	Weeks 9-12	95% CI for Diff	(-14.7, 2.9)	(-18.8, -1.1)	(-12.6, 4.5)
			p-value	0.383	0.316	0.878
		Weeks 13-16	LS Means Diff	-4.1	-4.8	-0.7
			95% CI for Diff	(-13.5, 5.2)	(-14.3, 4.6)	(-9.8, 8.4)
		Overall	p-value	0.503	0.208	0.530
		Overall	LS Means Diff	-3.3	-6.3	-3.0
			95% CI for Diff	(-13.0, 6.4)	(-16.2, 3.6)	(-12.6, 6.5)
			p-value	0.271	0.061	0.419
	Wash-out	Overall	LS Means Diff	-4.5	-7.7	-3.2
			95% CI for Diff	(-12.6, 3.6)	(-15.8, 0.4)	(-11.0, 4.6)
			p-value	0.702	0.697	0.428
	Wash-out	Overall	LS Means Diff	1.6	-1.7	-3.3
			95% CI for Diff	(-6.7, 9.9)	(-10.1, 6.8)	(-11.5, 4.9)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum and Arg16Gly genotype. Least squares mean differences are calculated as Arg/Arg-Arg/Gly, Arg/Arg-Gly/Gly and Arg/Gly-Gly/Gly.

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Table 7.10
Analysis of Percent of Symptom-Free Days

				Arg/Arg vs. Arg/Gly	Arg/Arg vs. Gly/Gly	Arg/Gly vs. Gly/Gly
Salmeterol	Double-blind	Weeks 1-4	p-value	0.981	0.774	0.749
			LS Means Diff	-0.1	1.1	1.2
			95% CI for Diff	(-8.0,7.8)	(-6.7,9.0)	(-6.4,8.9)
		Weeks 5-8	p-value	0.465	0.432	0.960
			LS Means Diff	3.2	3.4	0.2
	95% CI for Diff		(-5.4,11.9)	(-5.2,12.0)	(-8.1,8.5)	
	Weeks 9-12	p-value	0.342	0.394	0.911	
		LS Means Diff	4.2	3.7	-0.5	
		95% CI for Diff	(-4.4,12.7)	(-4.8,12.2)	(-8.7,7.8)	
	Weeks 13-16	p-value	0.357	0.215	0.747	
LS Means Diff		4.3	5.8	1.5		
95% CI for Diff		(-4.9,13.5)	(-3.4,14.9)	(-7.4,10.3)		
	Wash-out	Overall	p-value	0.768	0.583	0.795
			LS Means Diff	1.1	2.1	1.0
			95% CI for Diff	(-6.4,8.6)	(-5.4,9.5)	(-6.3,8.2)
		Overall	p-value	0.687	0.782	0.889
			LS Means Diff	1.9	1.3	-0.6
	95% CI for Diff		(-7.4,11.2)	(-7.9,10.5)	(-9.4,8.2)	

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum and Arg16Gly genotype. Least squares mean differences are calculated as Arg/Arg-Arg/Gly, Arg/Arg-Gly/Gly and Arg/Gly-Gly/Gly.

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Table 7.11
Summary of Supplemental Ipratropium Use (puffs/day)

Treatment: FSC100/50

				Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)

Subjects in treatment group				87	91	90
Ipratropium use	Ipratropium	Weeks 1-4	n	86	90	90
			Mean	1.08	1.18	1.15
			SE	0.108	0.131	0.103
			Median	0.85	0.76	0.84
			Min.	0.0	0.0	0.0
			Max.	4.0	7.3	3.6
		Weeks 5-8	n	85	89	89
			Mean	1.00	1.19	1.08
			SE	0.102	0.139	0.104
			Median	0.71	0.71	0.71
			Min.	0.0	0.0	0.0
			Max.	4.1	7.5	4.6
		Overall	n	86	90	90
			Mean	1.04	1.18	1.13
			SE	0.100	0.132	0.102
			Median	0.79	0.80	0.80
			Min.	0.0	0.0	0.0
			Max.	4.0	7.4	4.3
	Double-blind	Baseline	n	82	87	87
			Mean	0.98	1.15	1.15
			SE	0.115	0.136	0.126
			Median	0.64	0.86	0.86
			Min.	0.0	0.0	0.0
			Max.	4.0	5.0	6.0
		Weeks 1-4	n	86	87	88

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Table 7.11
Summary of Supplemental Ipratropium Use (puffs/day)

Treatment: FSC100/50

				Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)	
Ipratropium use	Double-blind	Weeks 1-4	Mean	0.54	0.61	0.59	
			SE	0.074	0.085	0.078	
			Median	0.21	0.29	0.24	
			Min.	0.0	0.0	0.0	
			Max.	2.8	3.3	2.9	
		Weeks 5-8	n	83	83	84	
			Mean	0.51	0.51	0.54	
			SE	0.076	0.082	0.075	
			Median	0.15	0.14	0.23	
			Min.	0.0	0.0	0.0	
			Max.	2.5	3.6	3.0	
		Weeks 9-12	n	78	86	78	
			Mean	0.54	0.52	0.62	
			SE	0.081	0.074	0.086	
			Median	0.21	0.20	0.36	
			Min.	0.0	0.0	0.0	
			Max.	2.9	2.5	2.8	
		Weeks 13-16	n	78	84	77	
			Mean	0.47	0.57	0.61	
			SE	0.075	0.081	0.096	
			Median	0.13	0.22	0.21	
			Min.	0.0	0.0	0.0	
			Max.	2.2	3.9	3.6	
Overall	n	86	89	89			
	Mean	0.51	0.56	0.57			
	SE	0.068	0.073	0.073			
	Median	0.25	0.22	0.35			
	Min.	0.0	0.0	0.0			

Table 7.11
Summary of Supplemental Ipratropium Use (puffs/day)

Treatment: FSC100/50

				Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)
Ipratropium use	Double-blind	Overall	Max.	2.3	2.8	3.0
			n	77	81	75
	Wash-out	Overall	Mean	0.64	0.75	0.74
			SE	0.097	0.103	0.107
			Median	0.31	0.36	0.29
			Min.	0.0	0.0	0.0
			Max.	4.0	4.4	4.9
Ipratropium change	Double-blind	Weeks 1-4	n	81	87	85
			Mean	-0.47	-0.54	-0.60
			SE	0.112	0.109	0.121
			Median	-0.11	-0.21	-0.29
			Min.	-3.6	-4.9	-5.9
			Max.	1.9	0.8	0.9
		Weeks 5-8	n	78	83	81
			Mean	-0.47	-0.68	-0.67
			SE	0.113	0.119	0.131
			Median	-0.16	-0.29	-0.29
			Min.	-4.0	-5.0	-5.9
			Max.	1.2	0.4	1.5
		Weeks 9-12	n	73	84	75
			Mean	-0.49	-0.69	-0.53
			SE	0.124	0.129	0.115
			Median	-0.21	-0.43	-0.29
			Min.	-4.0	-5.0	-4.7
			Max.	1.8	2.0	1.8
		Weeks 13-16	n	73	82	74
			Mean	-0.55	-0.68	-0.47

Investigator: [REDACTED] Table 7.11
Summary of Supplemental Ipratropium Use (puffs/day)

Treatment: FSC100/50

ment: 15C100/50

				Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)
Ipratropium change	Double-blind	Weeks 13-16	SE	0.115	0.129	0.102
			Median	-0.21	-0.43	-0.29
			Min.	-4.0	-5.0	-3.6
			Max.	1.3	2.0	1.3
		Overall	n	81	87	86
			Mean	-0.49	-0.63	-0.60
			SE	0.110	0.113	0.117
			Median	-0.10	-0.29	-0.29
	Min.	-3.8	-5.0	-5.9		
	Max.	1.4	1.0	1.1		
	Wash-out	Overall	n	72	80	73
			Mean	-0.42	-0.50	-0.39
			SE	0.107	0.130	0.098
			Median	-0.10	-0.24	-0.23
			Min.	-4.0	-5.0	-3.6
Max.			1.2	1.6	2.0	

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Table 7.11
Summary of Supplemental Ipratropium Use (puffs/day)

Treatment: Salmeterol

				Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)

Subjects in treatment group				86	89	91
Ipratropium use	Ipratropium	Weeks 1-4	n	84	85	91
			Mean	1.12	1.17	1.13
			SE	0.111	0.119	0.112
			Median	0.76	0.93	0.82
			Min.	0.0	0.0	0.0
			Max.	4.0	4.7	4.3
		Weeks 5-8	n	82	86	88
			Mean	1.08	1.13	1.09
			SE	0.107	0.131	0.113
			Median	0.91	0.71	0.93
			Min.	0.0	0.0	0.0
			Max.	4.1	6.6	4.1
		Overall	n	84	87	91
			Mean	1.09	1.13	1.10
			SE	0.103	0.120	0.107
			Median	0.81	0.75	0.82
			Min.	0.0	0.0	0.0
			Max.	4.0	5.7	4.1
	Double-blind	Baseline	n	80	86	86
			Mean	1.04	1.15	1.09
			SE	0.121	0.138	0.130
			Median	0.64	0.79	0.57
			Min.	0.0	0.0	0.0
			Max.	4.3	6.7	4.7
		Weeks 1-4	n	80	84	88

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Table 7.11
Summary of Supplemental Ipratropium Use (puffs/day)

Treatment: Salmeterol

				Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)
Ipratropium use	Double-blind	Weeks 1-4	Mean	0.69	0.78	0.73
			SE	0.084	0.089	0.093
			Median	0.33	0.50	0.35
			Min.	0.0	0.0	0.0
			Max.	2.5	3.0	3.1
		Weeks 5-8	n	76	81	83
			Mean	0.72	0.73	0.74
			SE	0.099	0.089	0.105
			Median	0.29	0.43	0.39
			Min.	0.0	0.0	0.0
		Weeks 9-12	n	72	76	79
			Mean	0.62	0.61	0.66
			SE	0.092	0.076	0.092
			Median	0.36	0.39	0.35
			Min.	0.0	0.0	0.0
		Weeks 13-16	n	69	73	75
			Mean	0.54	0.59	0.68
			SE	0.085	0.078	0.094
			Median	0.29	0.21	0.32
			Min.	0.0	0.0	0.0
		Overall	n	81	85	89
			Mean	0.66	0.68	0.71
			SE	0.078	0.077	0.089
			Median	0.36	0.40	0.43
			Min.	0.0	0.0	0.0

Table 7.11
 Summary of Supplemental Ipratropium Use (puffs/day)

Treatment: Salmeterol

				Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)
Ipratropium use	Double-blind	Overall	Max.	2.4	3.0	4.1
			n	65	72	75
	Wash-out	Overall	Mean	0.68	0.86	0.85
			SE	0.097	0.143	0.107
			Median	0.43	0.43	0.43
			Min.	0.0	0.0	0.0
			Max.	3.1	8.0	3.4
Ipratropium change	Double-blind	Weeks 1-4	n	78	84	83
			Mean	-0.34	-0.37	-0.33
			SE	0.105	0.122	0.092
			Median	0.00	-0.09	-0.07
			Min.	-3.8	-6.1	-4.1
			Max.	1.4	1.3	1.9
		Weeks 5-8	n	74	81	78
			Mean	-0.31	-0.38	-0.31
			SE	0.118	0.131	0.095
			Median	-0.02	-0.05	-0.07
			Min.	-3.5	-6.2	-2.9
			Max.	2.4	2.2	1.7
		Weeks 9-12	n	71	76	74
			Mean	-0.42	-0.53	-0.41
			SE	0.119	0.121	0.090
			Median	-0.14	-0.27	-0.14
			Min.	-4.0	-6.0	-2.9
			Max.	1.4	0.9	1.1
		Weeks 13-16	n	68	73	71
			Mean	-0.49	-0.56	-0.42

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Table 7.11
 Summary of Supplemental Ipratropium Use (puffs/day)

Treatment: Salmeterol

				Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)
Ipratropium change	Double-blind	Weeks 13-16	SE	0.118	0.132	0.100
			Median	-0.24	-0.26	-0.18
			Min.	-3.2	-5.4	-4.2
			Max.	1.9	1.0	1.1
		Overall	n	79	85	84
			Mean	-0.36	-0.45	-0.35
			SE	0.102	0.118	0.083
			Median	-0.02	-0.13	-0.08
	Wash-out	Overall	n	64	72	71
			Mean	-0.29	-0.29	-0.23
			SE	0.128	0.111	0.114
			Median	0.00	-0.14	-0.07
			Min.	-3.6	-5.9	-3.4
			Max.	1.4	0.8	1.1

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Table 7.12
Analysis of Supplemental Ipratropium Use (puffs/day)

				Arg/Arg vs. Arg/Gly	Arg/Arg vs. Gly/Gly	Arg/Gly vs. Gly/Gly
FSC100/50	Double-blind	Weeks 1-4	p-value	0.516	0.840	0.646
			LS Means Diff	-0.07	-0.02	0.05
			95% CI for Diff	(-0.27, 0.13)	(-0.22, 0.18)	(-0.15, 0.24)
		Weeks 5-8	p-value	0.702	0.881	0.812
			LS Means Diff	0.04	0.02	-0.02
			95% CI for Diff	(-0.16, 0.24)	(-0.19, 0.22)	(-0.22, 0.17)
		Weeks 9-12	p-value	0.614	0.545	0.254
			LS Means Diff	0.05	-0.06	-0.12
			95% CI for Diff	(-0.15, 0.26)	(-0.27, 0.14)	(-0.32, 0.08)
		Weeks 13-16	p-value	0.750	0.199	0.316
			LS Means Diff	-0.03	-0.14	-0.11
			95% CI for Diff	(-0.25, 0.18)	(-0.36, 0.08)	(-0.32, 0.10)
	Wash-out	Overall	p-value	0.926	0.637	0.697
			LS Means Diff	-0.01	-0.04	-0.03
			95% CI for Diff	(-0.19, 0.17)	(-0.22, 0.14)	(-0.21, 0.14)
		Overall	p-value	0.646	0.296	0.541
			LS Means Diff	-0.05	-0.13	-0.07
			95% CI for Diff	(-0.29, 0.18)	(-0.36, 0.11)	(-0.30, 0.16)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum and Arg16Gly genotype. Least squares mean differences are calculated as Arg/Arg-Arg/Gly, Arg/Arg-Gly/Gly and Arg/Gly-Gly/Gly.

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Table 7.12
Analysis of Supplemental Ipratropium Use (puffs/day)

				Arg/Arg vs. Arg/Gly	Arg/Arg vs. Gly/Gly	Arg/Gly vs. Gly/Gly
Salmeterol	Double-blind	Weeks 1-4	p-value	0.607	0.573	0.959
			LS Means Diff	-0.05	-0.06	-0.01
			95% CI for Diff	(-0.26,0.15)	(-0.26,0.15)	(-0.20,0.19)
		Weeks 5-8	p-value	0.997	0.673	0.660
			LS Means Diff	0.00	-0.05	-0.05
			95% CI for Diff	(-0.23,0.23)	(-0.28,0.18)	(-0.27,0.17)
		Weeks 9-12	p-value	0.799	0.439	0.291
	LS Means Diff		0.03	-0.08	-0.10	
	95% CI for Diff		(-0.17,0.22)	(-0.27,0.12)	(-0.29,0.09)	
	Wash-out	Weeks 13-16	p-value	0.614	0.087	0.210
			LS Means Diff	-0.05	-0.17	-0.12
			95% CI for Diff	(-0.25,0.15)	(-0.38,0.03)	(-0.32,0.07)
		Overall	p-value	0.914	0.347	0.391
			LS Means Diff	-0.01	-0.09	-0.08
95% CI for Diff			(-0.19,0.17)	(-0.26,0.09)	(-0.25,0.10)	
Overall		p-value	0.452	0.292	0.751	
	LS Means Diff	-0.10	-0.15	-0.04		
	95% CI for Diff	(-0.37,0.17)	(-0.42,0.13)	(-0.30,0.22)		

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum and Arg16Gly genotype. Least squares mean differences are calculated as Arg/Arg-Arg/Gly, Arg/Arg-Gly/Gly and Arg/Gly-Gly/Gly.

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Table 7.13
 Summary of Open-Label Treatment Period AM PEF (L/min) by Genotype

Genotype: Arg/Arg

			Open-label Albuterol	Open-label Ipratropium Bromide
-----			-----	
Subjects in genotype			173	173
AM PEF (L/min)	Week 1	n	170	170
		Mean	363.8	369.1
		SE	7.61	7.76
		Median	348.8	355.4
		Min.	67	178
		Max.	693	658
	Week 2	n	170	169
		Mean	361.9	369.0
		SE	7.57	7.93
		Median	350.6	359.1
		Min.	128	163
		Max.	696	669
	Week 3	n	170	170
		Mean	360.5	367.8
		SE	7.40	7.83
		Median	352.4	356.4
		Min.	126	162
		Max.	660	682
	Week 4	n	171	170
		Mean	359.6	369.8
		SE	7.60	7.81
		Median	348.6	358.1
		Min.	132	154
		Max.	647	676

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Table 7.13
Summary of Open-Label Treatment Period AM PEF (L/min) by Genotype

Genotype: Arg/Arg

			Open-label Albuterol	Open-label Ipratropium Bromide

AM PEF (L/min)	Week 5	n	171	169
		Mean	365.1	369.2
		SE	7.80	7.82
		Median	354.7	355.7
		Min.	89	119
		Max.	681	657
	Week 6	n	170	168
		Mean	367.6	368.5
		SE	7.70	7.54
		Median	356.3	354.6
		Min.	108	107
		Max.	676	654
	Week 7	n	171	167
		Mean	370.4	370.8
		SE	7.76	7.75
		Median	361.4	353.1
		Min.	132	116
		Max.	673	681
	Week 8	n	167	163
		Mean	367.1	368.1
		SE	7.64	7.90
		Median	357.1	353.4
		Min.	167	109
		Max.	676	658

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Table 7.13
Summary of Open-Label Treatment Period AM PEF (L/min) by Genotype

Genotype: Arg/Arg

			Open-label Albuterol	Open-label Ipratropium Bromide

AM PEF (L/min)	Weeks 1-4	n	171	170
		Mean	361.6	369.0
		SE	7.41	7.75
		Median	345.9	357.9
		Min.	125	168
		Max.	673	671
	Weeks 5-8	n	171	169
		Mean	367.6	368.2
		SE	7.62	7.64
		Median	357.9	354.3
		Min.	137	113
		Max.	677	654
	Overall	n	171	170
		Mean	364.7	368.3
		SE	7.42	7.64
		Median	350.8	356.4
		Min.	131	147
		Max.	675	647

Table 7.13
Summary of Open-Label Treatment Period AM PEF (L/min) by Genotype

Genotype: Arg/Gly

			Open-label Albuterol	Open-label Ipratropium Bromide
-----			-----	
Subjects in genotype			180	180
AM PEF (L/min)	Week 1	n	176	176
		Mean	365.9	368.3
		SE	6.92	6.81
		Median	356.6	363.6
		Min.	152	169
		Max.	711	684
	Week 2	n	177	176
		Mean	366.8	365.6
		SE	6.80	6.76
		Median	354.3	361.8
		Min.	158	159
		Max.	682	656
	Week 3	n	177	176
		Mean	370.0	364.9
		SE	6.90	6.66
		Median	358.9	362.4
		Min.	145	151
		Max.	672	652
	Week 4	n	177	176
		Mean	367.6	365.4
		SE	7.16	6.61
		Median	359.0	356.7
		Min.	137	164
		Max.	699	669

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Table 7.13
Summary of Open-Label Treatment Period AM PEF (L/min) by Genotype

Genotype: Arg/Gly

			Open-label Albuterol	Open-label Ipratropium Bromide

AM PEF (L/min)	Week 5	n	177	176
		Mean	371.9	371.3
		SE	7.15	6.59
		Median	362.3	362.4
		Min.	120	169
		Max.	687	684
	Week 6	n	177	177
		Mean	368.9	369.6
		SE	6.96	6.70
		Median	364.7	358.4
		Min.	136	164
		Max.	698	676
	Week 7	n	177	177
		Mean	370.0	370.6
		SE	7.19	6.89
		Median	358.0	362.1
		Min.	136	165
		Max.	743	712
	Week 8	n	170	173
		Mean	364.4	369.6
		SE	7.28	6.85
		Median	358.7	361.3
		Min.	97	177
		Max.	684	692

Table 7.13
Summary of Open-Label Treatment Period AM PEF (L/min) by Genotype

Genotype: Arg/Gly

			Open-label Albuterol	Open-label Ipratropium Bromide

AM PEF (L/min)	Weeks 1-4	n	178	176
		Mean	367.6	366.0
		SE	6.77	6.62
		Median	357.0	359.5
		Min.	148	163
		Max.	690	666
	Weeks 5-8	n	178	178
		Mean	368.6	370.1
		SE	6.92	6.61
		Median	361.8	363.2
		Min.	128	166
		Max.	684	691
	Overall	n	178	178
		Mean	368.3	367.9
		SE	6.76	6.53
		Median	357.9	359.8
		Min.	138	164
		Max.	687	679

Table 7.13
Summary of Open-Label Treatment Period AM PEF (L/min) by Genotype

Genotype: Gly/Gly

			Open-label Albuterol	Open-label Ipratropium Bromide
-----			-----	
Subjects in genotype			181	181
AM PEF (L/min)	Week 1	n	180	181
		Mean	370.5	369.0
		SE	6.67	7.06
		Median	358.4	354.6
		Min.	32	182
		Max.	634	711
	Week 2	n	181	181
		Mean	368.0	368.9
		SE	6.84	7.08
		Median	360.4	350.7
		Min.	28	203
		Max.	633	710
	Week 3	n	179	181
		Mean	369.1	370.5
		SE	7.13	7.10
		Median	357.9	354.9
		Min.	27	200
		Max.	630	712
	Week 4	n	180	181
		Mean	367.4	368.8
		SE	7.14	7.36
		Median	355.7	346.4
		Min.	23	190
		Max.	626	715

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Table 7.13
Summary of Open-Label Treatment Period AM PEF (L/min) by Genotype

Genotype: Gly/Gly

			Open-label Albuterol	Open-label Ipratropium Bromide

AM PEF (L/min)	Week 5	n	179	179
		Mean	371.6	371.3
		SE	6.77	7.19
		Median	357.6	358.6
		Min.	150	156
		Max.	637	727
	Week 6	n	178	180
		Mean	373.2	368.6
		SE	6.76	7.00
		Median	357.8	357.4
		Min.	185	180
		Max.	665	731
	Week 7	n	179	178
		Mean	366.6	370.2
		SE	6.81	7.27
		Median	350.7	358.3
		Min.	168	158
		Max.	665	740
	Week 8	n	173	174
		Mean	370.1	370.8
		SE	6.97	7.24
		Median	355.7	358.6
		Min.	185	168
		Max.	699	732

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Table 7.13
 Summary of Open-Label Treatment Period AM PEF (L/min) by Genotype

Genotype: Gly/Gly

			Open-label Albuterol	Open-label Ipratropium Bromide

AM PEF (L/min)	Weeks 1-4	n	181	181
		Mean	368.5	369.3
		SE	6.80	7.06
		Median	358.4	352.4
		Min.	27	201
		Max.	631	712
	Weeks 5-8	n	179	181
		Mean	370.5	369.6
		SE	6.71	6.99
		Median	352.9	358.5
		Min.	187	166
		Max.	661	733
	Overall	n	181	181
		Mean	369.2	369.4
		SE	6.61	6.97
		Median	356.2	354.2
		Min.	138	188
		Max.	633	722

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Table 7.14
Analysis of Open-Label Treatment Period AM PEF (L/min) by Genotype

		Arg/Arg 0-L Alb vs. 0-L Ipr	Arg/Gly 0-L Alb vs. 0-L Ipr	Gly/Gly 0-L Alb vs. 0-L Ipr
Weeks 1-4				
	p-value	0.022	0.803	0.792
	Mean Diff	-7.5	0.7	-0.8
	95% CI for Diff	(-13.9, -1.1)	(-4.7, 6.0)	(-7.1, 5.4)
Weeks 5-8				
	p-value	0.858	0.538	0.848
	Mean Diff	-0.4	-1.5	0.4
	95% CI for Diff	(-4.8, 4.0)	(-6.1, 3.2)	(-4.0, 4.9)
Overall				
	p-value	0.097	0.879	0.923
	Mean Diff	-3.8	0.3	-0.2
	95% CI for Diff	(-8.4, 0.7)	(-3.9, 4.6)	(-4.5, 4.1)

Note: P-values are from paired t-tests.

Mean differences are calculated as open-label albuterol - open-label ipratropium.

Table 7.15
Summary of Open-Label Treatment Period PM PEF (L/min) by Genotype

Genotype: Arg/Arg

			Open-label Albuterol	Open-label Ipratropium Bromide
-----			-----	
Subjects in genotype			173	173
PM PEF (L/min)	Week 1	n	170	170
		Mean	372.4	382.8
		SE	8.08	8.18
		Median	362.4	360.9
		Min.	62	198
		Max.	702	710
	Week 2	n	170	170
		Mean	377.0	382.0
		SE	8.01	8.42
		Median	362.9	366.6
		Min.	147	190
		Max.	710	725
	Week 3	n	171	170
		Mean	375.2	381.1
		SE	7.99	8.40
		Median	358.9	364.4
		Min.	164	193
		Max.	662	733
	Week 4	n	171	169
		Mean	372.1	383.3
		SE	8.26	8.40
		Median	356.7	364.0
		Min.	120	170
		Max.	648	733

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Table 7.15
Summary of Open-Label Treatment Period PM PEF (L/min) by Genotype

Genotype: Arg/Arg

			Open-label Albuterol	Open-label Ipratropium Bromide

PM PEF (L/min)	Week 5	n	171	168
		Mean	373.5	385.3
		SE	8.07	8.24
		Median	360.7	368.4
		Min.	102	164
		Max.	660	715
	Week 6	n	170	168
		Mean	376.4	383.6
		SE	7.82	8.18
		Median	362.9	370.9
		Min.	137	132
		Max.	673	739
	Week 7	n	171	167
		Mean	380.7	383.7
		SE	8.13	8.26
		Median	364.4	370.6
		Min.	148	176
		Max.	677	740
	Week 8	n	167	163
		Mean	380.5	382.9
		SE	7.83	8.34
		Median	372.9	373.3
		Min.	192	141
		Max.	667	742

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Table 7.15
Summary of Open-Label Treatment Period PM PEF (L/min) by Genotype

Genotype: Arg/Arg

			Open-label Albuterol	Open-label Ipratropium Bromide

PM PEF (L/min)	Weeks 1-4	n	171	170
		Mean	374.0	382.3
		SE	7.91	8.27
		Median	361.1	365.6
		Min.	150	194
		Max.	681	725
	Weeks 5-8	n	171	168
		Mean	377.9	383.7
		SE	7.86	8.13
		Median	367.8	371.4
		Min.	166	153
		Max.	669	731
	Overall	n	171	170
		Mean	376.0	382.0
		SE	7.79	8.16
		Median	365.5	365.4
		Min.	165	194
		Max.	673	728

Table 7.15
Summary of Open-Label Treatment Period PM PEF (L/min) by Genotype

Genotype: Arg/Gly

			Open-label Albuterol	Open-label Ipratropium Bromide
-----			-----	
Subjects in genotype			180	180
PM PEF (L/min)	Week 1	n	175	175
		Mean	375.7	380.7
		SE	6.91	7.32
		Median	370.6	370.7
		Min.	174	157
		Max.	692	659
	Week 2	n	177	176
		Mean	374.0	379.4
		SE	7.03	6.98
		Median	369.0	367.1
		Min.	165	142
		Max.	698	662
	Week 3	n	177	176
		Mean	378.3	377.0
		SE	7.04	6.96
		Median	372.9	367.4
		Min.	169	144
		Max.	691	656
	Week 4	n	177	176
		Mean	377.8	378.0
		SE	7.43	7.01
		Median	364.9	369.8
		Min.	170	168
		Max.	693	683

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Table 7.15
Summary of Open-Label Treatment Period PM PEF (L/min) by Genotype

Genotype: Arg/Gly

			Open-label Albuterol	Open-label Ipratropium Bromide

PM PEF (L/min)	Week 5	n	177	177
		Mean	378.9	380.8
		SE	7.10	6.92
		Median	367.4	368.7
		Min.	167	175
		Max.	702	691
	Week 6	n	177	177
		Mean	378.5	380.4
		SE	7.01	7.06
		Median	370.7	368.0
		Min.	166	168
		Max.	715	727
	Week 7	n	177	177
		Mean	379.0	380.3
		SE	7.45	7.20
		Median	364.5	373.4
		Min.	162	166
		Max.	792	745
	Week 8	n	170	173
		Mean	375.6	379.6
		SE	7.32	7.26
		Median	366.0	368.0
		Min.	148	165
		Max.	709	704

Table 7.15
Summary of Open-Label Treatment Period PM PEF (L/min) by Genotype

Genotype: Arg/Gly

			Open-label Albuterol	Open-label Ipratropium Bromide

PM PEF (L/min)	Weeks 1-4	n	178	176
		Mean	376.3	378.7
		SE	6.90	6.98
		Median	361.9	369.0
		Min.	180	156
		Max.	694	665
	Weeks 5-8	n	178	178
		Mean	377.8	380.0
		SE	6.99	6.97
		Median	368.8	366.7
		Min.	166	169
		Max.	702	717
	Overall	n	178	178
		Mean	377.2	379.3
		SE	6.86	6.89
		Median	368.7	366.2
		Min.	176	162
		Max.	698	692

Table 7.15
Summary of Open-Label Treatment Period PM PEF (L/min) by Genotype

Genotype: Gly/Gly

			Open-label Albuterol	Open-label Ipratropium Bromide
-----			-----	
Subjects in genotype			181	181
PM PEF (L/min)	Week 1	n	180	181
		Mean	379.9	382.4
		SE	6.92	7.33
		Median	370.6	372.3
		Min.	45	176
		Max.	632	715
	Week 2	n	181	181
		Mean	379.3	383.4
		SE	7.08	7.31
		Median	368.9	366.3
		Min.	34	221
		Max.	661	718
	Week 3	n	179	181
		Mean	379.2	382.6
		SE	7.38	7.35
		Median	365.7	370.0
		Min.	29	206
		Max.	642	721
	Week 4	n	181	181
		Mean	375.8	382.3
		SE	7.34	7.46
		Median	361.7	359.0
		Min.	27	202
		Max.	643	719

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Table 7.15
Summary of Open-Label Treatment Period PM PEF (L/min) by Genotype

Genotype: Gly/Gly

			Open-label Albuterol	Open-label Ipratropium Bromide

PM PEF (L/min)	Week 5	n	180	179
		Mean	379.5	379.6
		SE	6.87	7.41
		Median	367.1	363.7
		Min.	165	165
		Max.	639	734
	Week 6	n	179	180
		Mean	381.9	379.8
		SE	6.93	7.19
		Median	371.1	364.9
		Min.	161	211
		Max.	698	742
	Week 7	n	180	178
		Mean	378.2	380.9
		SE	7.04	7.35
		Median	368.1	364.6
		Min.	175	211
		Max.	700	747
	Week 8	n	173	174
		Mean	381.6	382.9
		SE	7.20	7.37
		Median	370.0	376.4
		Min.	186	204
		Max.	693	737

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Table 7.15
 Summary of Open-Label Treatment Period PM PEF (L/min) by Genotype

Genotype: Gly/Gly

			Open-label Albuterol	Open-label Ipratropium Bromide

PM PEF (L/min)	Weeks 1-4	n	181	181
		Mean	378.3	382.7
		SE	7.04	7.28
		Median	369.6	365.0
		Min.	33	210
		Max.	635	718
	Weeks 5-8	n	180	181
		Mean	380.5	380.0
		SE	6.87	7.15
		Median	370.0	370.5
		Min.	186	214
		Max.	683	740
	Overall	n	181	181
		Mean	379.3	381.4
		SE	6.81	7.17
		Median	367.5	364.1
		Min.	138	219
		Max.	636	729

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Table 7.16
Analysis of Open-Label Treatment Period PM PEF (L/min) by Genotype

		Arg/Arg 0-L Alb vs. 0-L Ipr	Arg/Gly 0-L Alb vs. 0-L Ipr	Gly/Gly 0-L Alb vs. 0-L Ipr
Weeks 1-4				
	p-value	0.008	0.274	0.165
	Mean Diff	-8.6	-3.0	-4.4
	95% CI for Diff	(-14.9, -2.3)	(-8.3, 2.4)	(-10.5, 1.8)
Weeks 5-8				
	p-value	0.053	0.312	0.899
	Mean Diff	-4.4	-2.3	0.3
	95% CI for Diff	(-8.9, 0.1)	(-6.7, 2.1)	(-4.6, 5.2)
Overall				
	p-value	0.006	0.298	0.380
	Mean Diff	-6.4	-2.1	-2.1
	95% CI for Diff	(-10.9, -1.8)	(-6.0, 1.8)	(-6.7, 2.6)

Note: P-values are from paired t-tests.

Mean differences are calculated as open-label albuterol - open-label ipratropium.

Table 7.17
 Summary of Open-Label Treatment Period Percent of Symptom-Free Days by Genotype

Genotype: Arg/Arg

			Open-label Albuterol	Open-label Ipratropium Bromide
-----			-----	
Subjects in genotype			173	173
% Symptom-free days	Week 1	n	168	168
		Mean	24.5	31.7
		SE	2.52	3.06
		Median	0.0	0.0
		Min.	0	0
		Max.	100	100
	Week 2	n	169	167
		Mean	28.0	33.2
		SE	2.80	3.04
		Median	0.0	0.0
		Min.	0	0
		Max.	100	100
	Week 3	n	171	168
		Mean	28.3	31.1
		SE	2.79	3.01
		Median	0.0	0.0
		Min.	0	0
		Max.	100	100
	Week 4	n	171	168
		Mean	30.0	29.5
		SE	2.94	2.96
		Median	0.0	0.0
		Min.	0	0
		Max.	100	100

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Table 7.17

Summary of Open-Label Treatment Period Percent of Symptom-Free Days by Genotype

Genotype: Arg/Arg

			Open-label Albuterol	Open-label Ipratropium Bromide

% Symptom-free days	Week 5	n	171	166
		Mean	30.2	31.3
		SE	2.95	3.05
		Median	0.0	0.0
		Min.	0	0
		Max.	100	100
	Week 6	n	169	166
		Mean	30.5	31.3
		SE	2.94	2.88
		Median	0.0	14.3
		Min.	0	0
		Max.	100	100
	Week 7	n	169	165
		Mean	31.0	31.2
		SE	3.01	2.99
		Median	0.0	14.3
		Min.	0	0
		Max.	100	100
	Week 8	n	165	160
		Mean	30.3	32.0
		SE	3.06	3.25
		Median	0.0	0.0
		Min.	0	0
		Max.	100	100

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Table 7.17
Summary of Open-Label Treatment Period Percent of Symptom-Free Days by Genotype

Genotype: Arg/Arg

			Open-label Albuterol	Open-label Ipratropium Bromide

% Symptom-free days	Weeks 1-4	n	171	169
		Mean	28.0	31.2
		SE	2.57	2.83
		Median	8.0	10.7
		Min.	0	0
		Max.	100	100
	Weeks 5-8	n	171	166
		Mean	30.1	31.7
		SE	2.79	2.82
		Median	7.1	14.3
		Min.	0	0
		Max.	100	100
	Overall	n	171	170
		Mean	29.2	31.3
		SE	2.61	2.73
		Median	12.5	11.8
		Min.	0	0
		Max.	100	100

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Table 7.17
 Summary of Open-Label Treatment Period Percent of Symptom-Free Days by Genotype

Genotype: Arg/Gly

			Open-label Albuterol	Open-label Ipratropium Bromide
-----			-----	
Subjects in genotype			180	180
% Symptom-free days	Week 1	n	176	176
		Mean	26.3	34.9
		SE	2.60	3.05
		Median	0.0	14.3
		Min.	0	0
		Max.	100	100
	Week 2	n	177	175
		Mean	27.6	32.8
		SE	2.65	2.98
		Median	0.0	0.0
		Min.	0	0
		Max.	100	100
	Week 3	n	176	176
		Mean	28.3	32.5
		SE	2.64	2.95
		Median	14.3	0.0
		Min.	0	0
		Max.	100	100
	Week 4	n	177	176
		Mean	29.7	34.0
		SE	2.67	2.99
		Median	14.3	14.3
		Min.	0	0
		Max.	100	100

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Table 7.17

Summary of Open-Label Treatment Period Percent of Symptom-Free Days by Genotype

Genotype: Arg/Gly

			Open-label Albuterol	Open-label Ipratropium Bromide

% Symptom-free days	Week 5	n	176	176
		Mean	32.3	32.1
		SE	2.90	2.90
		Median	14.3	14.3
		Min.	0	0
		Max.	100	100
	Week 6	n	176	176
		Mean	32.2	33.8
		SE	2.84	2.93
		Median	14.3	14.3
		Min.	0	0
		Max.	100	100
	Week 7	n	177	176
		Mean	34.1	34.6
		SE	2.91	2.96
		Median	14.3	14.3
		Min.	0	0
		Max.	100	100
	Week 8	n	170	172
		Mean	34.3	34.1
		SE	3.06	3.07
		Median	14.3	7.1
		Min.	0	0
		Max.	100	100

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Table 7.17

Summary of Open-Label Treatment Period Percent of Symptom-Free Days by Genotype

Genotype: Arg/Gly

			Open-label Albuterol	Open-label Ipratropium Bromide

% Symptom-free days	Weeks 1-4	n	178	176
		Mean	28.1	33.5
		SE	2.44	2.82
		Median	13.0	14.3
		Min.	0	0
		Max.	100	100
	Weeks 5-8	n	178	177
		Mean	33.0	33.7
		SE	2.69	2.78
		Median	21.4	17.9
		Min.	0	0
		Max.	100	100
	Overall	n	178	178
		Mean	30.5	33.8
		SE	2.47	2.72
		Median	17.8	20.4
		Min.	0	0
		Max.	100	100

Table 7.17
Summary of Open-Label Treatment Period Percent of Symptom-Free Days by Genotype

Genotype: Gly/Gly

			Open-label Albuterol	Open-label Ipratropium Bromide
-----			-----	
Subjects in genotype			181	181
% Symptom-free days	Week 1	n	179	179
		Mean	27.4	34.0
		SE	2.57	2.90
		Median	0.0	14.3
		Min.	0	0
		Max.	100	100
	Week 2	n	180	178
		Mean	29.5	32.2
		SE	2.67	2.87
		Median	14.3	14.3
		Min.	0	0
		Max.	100	100
	Week 3	n	179	181
		Mean	30.0	33.3
		SE	2.65	2.78
		Median	14.3	14.3
		Min.	0	0
		Max.	100	100
	Week 4	n	179	181
		Mean	29.8	33.8
		SE	2.62	2.92
		Median	14.3	14.3
		Min.	0	0
		Max.	100	100

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Table 7.17

Summary of Open-Label Treatment Period Percent of Symptom-Free Days by Genotype

Genotype: Gly/Gly

			Open-label Albuterol	Open-label Ipratropium Bromide

% Symptom-free days	Week 5	n	180	179
		Mean	32.6	33.0
		SE	2.80	2.97
		Median	14.3	0.0
		Min.	0	0
		Max.	100	100
	Week 6	n	179	178
		Mean	34.1	34.7
		SE	2.82	2.97
		Median	14.3	14.3
		Min.	0	0
		Max.	100	100
	Week 7	n	180	179
		Mean	32.4	33.0
		SE	2.80	2.83
		Median	14.3	14.3
		Min.	0	0
		Max.	100	100
	Week 8	n	174	174
		Mean	32.2	34.3
		SE	2.83	2.88
		Median	0.0	14.3
		Min.	0	0
		Max.	100	100

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Table 7.17
 Summary of Open-Label Treatment Period Percent of Symptom-Free Days by Genotype

Genotype: Gly/Gly

			Open-label Albuterol	Open-label Ipratropium Bromide

% Symptom-free days	Weeks 1-4	n	180	181
		Mean	29.2	33.3
		SE	2.41	2.70
		Median	17.9	16.7
		Min.	0	0
		Max.	100	100
	Weeks 5-8	n	180	181
		Mean	32.7	33.9
		SE	2.63	2.73
		Median	18.2	24.0
		Min.	0	0
		Max.	100	100
	Overall	n	181	181
		Mean	31.1	33.6
		SE	2.42	2.65
		Median	25.9	18.2
		Min.	0	0
		Max.	100	100

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Table 7.18
Analysis of Open-Label Treatment Period Percent of Symptom-Free Days by Genotype

		Arg/Arg 0-L Alb vs. 0-L Ipr	Arg/Gly 0-L Alb vs. 0-L Ipr	Gly/Gly 0-L Alb vs. 0-L Ipr
Weeks 1-4				
	p-value	0.040	0.002	0.011
	Mean Diff	-3.3	-5.3	-4.0
	95% CI for Diff	(-6.5, -0.2)	(-8.7, -1.9)	(-7.1, -0.9)
Weeks 5-8				
	p-value	0.327	0.481	0.405
	Mean Diff	-1.4	-1.1	-1.2
	95% CI for Diff	(-4.2, 1.4)	(-4.0, 1.9)	(-3.9, 1.6)
Overall				
	p-value	0.105	0.011	0.034
	Mean Diff	-2.0	-3.3	-2.5
	95% CI for Diff	(-4.4, 0.4)	(-5.8, -0.8)	(-4.9, -0.2)

Note: P-values are from paired t-tests.

Mean differences are calculated as open-label albuterol - open-label ipratropium.

Table 7.19
Summary of Percent of Subjects Requiring Albuterol

Treatment: FSC100/50

					Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)

Subjects in treatment group					87	91	90
Supplemental albuterol use	Albuterol	Weeks 1-4	n		87	91	90
			No use		6 (7%)	3 (3%)	2 (2%)
		Weeks 5-8	Use		81 (93%)	88 (97%)	88 (98%)
			n		87	91	89
		Overall	No use		8 (9%)	8 (9%)	5 (6%)
			Use		79 (91%)	83 (91%)	84 (94%)
	Ipratropium	Weeks 1-4	n		83	89	88
			No use		21 (25%)	24 (27%)	22 (25%)
		Weeks 5-8	Use		62 (75%)	65 (73%)	66 (75%)
			n		83	88	88
		Overall	No use		21 (25%)	21 (24%)	23 (26%)
			Use		62 (75%)	67 (76%)	65 (74%)
Double-blind	Baseline		n		84	90	88
			No use		12 (14%)	14 (16%)	15 (17%)
			Use		72 (86%)	76 (84%)	73 (83%)
			n		80	86	85
			No use		42 (53%)	41 (48%)	36 (42%)
			Use		38 (48%)	45 (52%)	49 (58%)

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Table 7.19
Summary of Percent of Subjects Requiring Albuterol

Treatment: FSC100/50

				Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)
Supplemental albuterol use	Double-blind	Weeks 1-4	n	85	89	86
			No use	33 (39%)	29 (33%)	34 (40%)
			Use	52 (61%)	60 (67%)	52 (60%)
		Weeks 5-8	n	83	84	83
			No use	32 (39%)	39 (46%)	34 (41%)
			Use	51 (61%)	45 (54%)	49 (59%)
		Weeks 9-12	n	78	85	78
			No use	30 (38%)	39 (46%)	36 (46%)
			Use	48 (62%)	46 (54%)	42 (54%)
		Weeks 13-16	n	78	83	77
Wash-out	Overall		No use	35 (45%)	39 (47%)	37 (48%)
			Use	43 (55%)	44 (53%)	40 (52%)
			n	86	91	88
			No use	23 (27%)	19 (21%)	21 (24%)
			Use	63 (73%)	72 (79%)	67 (76%)
	Overall		n	77	82	77
			No use	31 (40%)	25 (30%)	35 (45%)
			Use	46 (60%)	57 (70%)	42 (55%)

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Table 7.19
Summary of Percent of Subjects Requiring Albuterol

Treatment: Salmeterol

					Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)

Subjects in treatment group					86	89	91
Supplemental albuterol use	Albuterol	Weeks 1-4	n		84	87	90
			No use		3 (4%)	6 (7%)	5 (6%)
			Use		81 (96%)	81 (93%)	85 (94%)
		Weeks 5-8	n		84	85	90
			No use		4 (5%)	8 (9%)	11 (12%)
			Use		80 (95%)	77 (91%)	79 (88%)
	Ipratropium	Weeks 1-4	n		84	85	90
			No use		22 (26%)	17 (20%)	27 (30%)
			Use		62 (74%)	68 (80%)	63 (70%)
		Weeks 5-8	n		82	85	88
			No use		26 (32%)	26 (31%)	32 (36%)
			Use		56 (68%)	59 (69%)	56 (64%)
	Double-blind	Baseline	n		79	85	85
			No use		43 (54%)	37 (44%)	39 (46%)
			Use		36 (46%)	48 (56%)	46 (54%)

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Table 7.19
 Summary of Percent of Subjects Requiring Albuterol

Treatment: Salmeterol

				Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)
Supplemental albuterol use	Double-blind	Weeks 1-4	n	79	84	89
			No use	28 (35%)	27 (32%)	32 (36%)
			Use	51 (65%)	57 (68%)	57 (64%)
		Weeks 5-8	n	76	80	82
			No use	34 (45%)	29 (36%)	34 (41%)
			Use	42 (55%)	51 (64%)	48 (59%)
		Weeks 9-12	n	72	76	78
			No use	31 (43%)	32 (42%)	30 (38%)
			Use	41 (57%)	44 (58%)	48 (62%)
		Weeks 13-16	n	68	73	74
			No use	35 (51%)	33 (45%)	27 (36%)
			Use	33 (49%)	40 (55%)	47 (64%)
		Overall	n	81	85	89
			No use	21 (26%)	19 (22%)	18 (20%)
			Use	60 (74%)	66 (78%)	71 (80%)
	Wash-out	Overall	n	65	72	75
			No use	31 (48%)	26 (36%)	29 (39%)
			Use	34 (52%)	46 (64%)	46 (61%)

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Table 7.20
 Analysis of Percent of Subjects Requiring Albuterol

				Arg/Arg vs. Arg/Gly	Arg/Arg vs. Gly/Gly	Arg/Gly vs. Gly/Gly

FSC100/50	Double-blind	Overall	p-value	0.248	0.567	0.644
			Relative risk	0.91	0.95	1.04
			95% CI for RR	(0.77,1.07)	(0.80,1.13)	(0.89,1.21)

Note: P-values are from a Cochran-Mantel-Haenszel test controlling for ethnicity stratum.
 Relative risks are calculated as Arg/Arg / Arg/Gly, Arg/Arg / Gly/Gly and Arg/Gly / Gly/Gly.

[REDACTED]

Table 7.20
Analysis of Percent of Subjects Requiring Albuterol

				Arg/Arg vs. Arg/Gly	Arg/Arg vs. Gly/Gly	Arg/Gly vs. Gly/Gly
Salmeterol	Double-blind	Overall	p-value	0.780	0.392	0.729
			Relative risk	0.98	0.93	0.97
			95% CI for RR	(0.82,1.16)	(0.79,1.09)	(0.83,1.14)

Note: P-values are from a Cochran-Mantel-Haenszel test controlling for ethnicity stratum.
Relative risks are calculated as Arg/Arg / Arg/Gly, Arg/Arg / Gly/Gly and Arg/Gly / Gly/Gly.

[REDACTED]

Table 7.21
Summary of Supplemental Albuterol Use (puffs/day)

Treatment: FSC100/50

				Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)

Subjects in treatment group				87	91	90
Albuterol use (puffs/day)	Albuterol	Weeks 1-4	n	87	91	90
			Mean	1.43	1.35	1.43
			SE	0.149	0.122	0.111
			Median	1.00	1.07	1.38
			Min.	0.0	0.0	0.0
			Max.	6.1	5.9	4.8
		Weeks 5-8	n	87	91	89
			Mean	1.27	1.33	1.40
			SE	0.140	0.142	0.127
			Median	0.93	0.95	1.11
			Min.	0.0	0.0	0.0
			Max.	5.8	5.6	4.9
		Overall	n	87	91	90
			Mean	1.35	1.34	1.42
			SE	0.141	0.125	0.114
			Median	0.96	1.04	1.28
			Min.	0.0	0.0	0.0
			Max.	5.6	5.7	4.2
	Ipratropium	Weeks 1-4	n	83	89	88
			Mean	0.71	0.85	0.70
			SE	0.099	0.121	0.101
			Median	0.29	0.37	0.29
			Min.	0.0	0.0	0.0
			Max.	3.4	5.7	5.7
		Weeks 5-8	n	83	88	88
			Mean	0.61	0.75	0.66

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Table 7.21
Summary of Supplemental Albuterol Use (puffs/day)

Treatment: FSC100/50

				Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)
-----				-----		
Albuterol use (puffs/day)	Ipratropium	Weeks 5-8	SE	0.096	0.111	0.091
			Median	0.14	0.31	0.25
			Min.	0.0	0.0	0.0
			Max.	3.5	4.9	3.6
	Double-blind	Overall	n	84	90	88
			Mean	0.67	0.81	0.67
			SE	0.095	0.107	0.086
			Median	0.22	0.41	0.33
			Min.	0.0	0.0	0.0
			Max.	3.4	4.4	3.1
		Baseline	n	80	86	85
			Mean	0.60	0.81	0.62
			SE	0.104	0.136	0.093
			Median	0.00	0.29	0.29
			Min.	0.0	0.0	0.0
			Max.	3.4	6.3	3.4
		Weeks 1-4	n	85	89	86
			Mean	0.38	0.55	0.38
			SE	0.062	0.098	0.074
			Median	0.11	0.21	0.07
			Min.	0.0	0.0	0.0
			Max.	3.0	5.3	2.9
		Weeks 5-8	n	83	84	83
			Mean	0.39	0.35	0.38
			SE	0.073	0.066	0.070
			Median	0.11	0.07	0.07
			Min.	0.0	0.0	0.0
			Max.	3.4	2.6	2.6

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Table 7.21
Summary of Supplemental Albuterol Use (puffs/day)

Treatment: FSC100/50

				Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)
Albuterol use (puffs/day)	Double-blind	Weeks 9-12	n	78	85	78
			Mean	0.39	0.35	0.41
			SE	0.078	0.064	0.078
			Median	0.07	0.07	0.07
			Min.	0.0	0.0	0.0
			Max.	3.5	2.7	2.6
		Weeks 13-16	n	78	83	77
			Mean	0.36	0.40	0.34
			SE	0.074	0.069	0.074
			Median	0.07	0.07	0.04
			Min.	0.0	0.0	0.0
			Max.	3.6	2.5	3.4
		Overall	n	86	91	88
			Mean	0.38	0.50	0.37
			SE	0.063	0.088	0.063
			Median	0.15	0.13	0.08
			Min.	0.0	0.0	0.0
			Max.	3.4	4.5	2.6
	Wash-out	Overall	n	77	82	77
			Mean	0.66	0.80	0.69
			SE	0.114	0.114	0.126
			Median	0.22	0.43	0.07
			Min.	0.0	0.0	0.0
			Max.	4.2	4.6	4.8
Albuterol change	Double-blind	Weeks 1-4	n	79	86	82
			Mean	-0.22	-0.29	-0.22
			SE	0.082	0.128	0.079
			Median	0.00	0.00	0.00

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Table 7.21
Summary of Supplemental Albuterol Use (puffs/day)

Treatment: FSC100/50

				Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)
-----				-----		
Albuterol change	Double-blind	Weeks 1-4	Min. Max.	-2.9 0.9	-5.9 5.3	-2.6 2.1
		Weeks 5-8	n	77	81	79
			Mean	-0.22	-0.49	-0.25
			SE	0.092	0.124	0.085
			Median	0.00	0.00	0.00
			Min.	-3.2	-6.3	-2.6
			Max.	2.5	0.6	2.4
		Weeks 9-12	n	73	82	73
			Mean	-0.25	-0.49	-0.24
			SE	0.089	0.132	0.087
			Median	0.00	0.00	0.00
			Min.	-3.4	-6.3	-2.6
			Max.	1.8	2.0	1.8
		Weeks 13-16	n	73	80	73
			Mean	-0.27	-0.45	-0.30
			SE	0.086	0.129	0.089
			Median	0.00	0.00	-0.11
			Min.	-3.2	-6.1	-2.4
			Max.	1.3	2.0	3.1
		Overall	n	79	86	83
			Mean	-0.21	-0.36	-0.24
			SE	0.080	0.130	0.075
			Median	0.00	0.00	0.00
			Min.	-3.2	-6.2	-2.6
			Max.	0.9	4.5	2.3
	Wash-out	Overall	n	72	78	73

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Table 7.21
Summary of Supplemental Albuterol Use (puffs/day)

Treatment: FSC100/50

				Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)
-----				-----	-----	-----
Albuterol change	Wash-out	Overall	Mean	0.03	-0.08	0.04
			SE	0.095	0.123	0.087
			Median	0.00	0.00	0.00
			Min.	-2.4	-6.3	-1.9
			Max.	2.4	2.1	2.8

Table 7.21
Summary of Supplemental Albuterol Use (puffs/day)

Treatment: Salmeterol

				Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)	
Subjects in treatment group				86	89	91	
Albuterol use (puffs/day)	Albuterol	Weeks 1-4	n	84	87	90	
			Mean	1.54	1.70	1.55	
			SE	0.133	0.174	0.155	
			Median	1.32	1.11	1.04	
			Min.	0.0	0.0	0.0	
			Max.	4.9	7.3	7.3	
		Weeks 5-8	n	84	85	90	
			Mean	1.35	1.57	1.52	
			SE	0.141	0.173	0.148	
			Median	0.80	0.96	1.15	
			Min.	0.0	0.0	0.0	
			Max.	4.9	6.9	7.0	
		Overall	n	84	87	90	
			Mean	1.44	1.63	1.55	
			SE	0.131	0.168	0.150	
			Median	1.10	1.04	1.15	
			Min.	0.0	0.0	0.0	
			Max.	4.9	7.1	7.2	
	Ipratropium	Weeks 1-4	n	84	85	90	
			Mean	0.79	0.86	0.94	
			SE	0.119	0.129	0.126	
			Median	0.29	0.43	0.33	
			Min.	0.0	0.0	0.0	
			Max.	5.3	6.6	5.7	
		Weeks 5-8	n	82	85	88	
			Mean	0.70	0.76	0.89	

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Table 7.21
Summary of Supplemental Albuterol Use (puffs/day)

Treatment: Salmeterol

				Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)
-----				-----		
Albuterol use (puffs/day)	Ipratropium	Weeks 5-8	SE	0.102	0.121	0.126
			Median	0.29	0.32	0.38
			Min.	0.0	0.0	0.0
			Max.	4.1	6.6	6.1
	Double-blind	Overall	n	84	87	91
			Mean	0.73	0.79	0.92
			SE	0.104	0.121	0.121
			Median	0.26	0.33	0.40
			Min.	0.0	0.0	0.0
			Max.	4.1	6.6	5.9
		Baseline	n	79	85	85
			Mean	0.64	0.78	0.88
			SE	0.114	0.132	0.135
			Median	0.00	0.29	0.29
			Min.	0.0	0.0	0.0
			Max.	4.0	6.7	6.3
		Weeks 1-4	n	79	84	89
			Mean	0.54	0.60	0.73
			SE	0.087	0.093	0.110
			Median	0.21	0.21	0.21
			Min.	0.0	0.0	0.0
			Max.	3.1	3.3	6.2
		Weeks 5-8	n	76	80	82
			Mean	0.48	0.68	0.62
			SE	0.084	0.107	0.098
			Median	0.07	0.16	0.14
			Min.	0.0	0.0	0.0
			Max.	2.5	3.7	4.3

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Table 7.21
Summary of Supplemental Albuterol Use (puffs/day)

Treatment: Salmeterol

				Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)
Albuterol use (puffs/day)	Double-blind	Weeks 9-12	n	72	76	78
			Mean	0.51	0.57	0.62
			SE	0.099	0.093	0.102
			Median	0.07	0.15	0.18
			Min.	0.0	0.0	0.0
			Max.	3.4	3.4	5.0
		Weeks 13-16	n	68	73	74
			Mean	0.34	0.52	0.67
			SE	0.073	0.092	0.112
			Median	0.00	0.08	0.22
			Min.	0.0	0.0	0.0
			Max.	2.9	3.9	4.5
		Overall	n	81	85	89
			Mean	0.50	0.59	0.68
			SE	0.081	0.087	0.098
			Median	0.14	0.23	0.22
			Min.	0.0	0.0	0.0
			Max.	2.6	3.1	5.0
	Wash-out	Overall	n	65	72	75
			Mean	0.45	0.87	0.96
			SE	0.093	0.159	0.153
			Median	0.07	0.35	0.36
			Min.	0.0	0.0	0.0
			Max.	2.9	8.0	5.1
Albuterol change	Double-blind	Weeks 1-4	n	77	84	83
			Mean	-0.11	-0.19	-0.15
			SE	0.076	0.106	0.067
			Median	0.00	0.00	0.00

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Table 7.21
Summary of Supplemental Albuterol Use (puffs/day)

Treatment: Salmeterol

				Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)
-----				-----		
Albuterol change	Double-blind	Weeks 1-4	Min.	-2.4	-6.3	-2.6
			Max.	1.9	1.9	1.1
		Weeks 5-8	n	73	80	77
			Mean	-0.13	-0.11	-0.24
			SE	0.093	0.112	0.082
			Median	0.00	0.00	0.00
			Min.	-2.9	-6.2	-2.8
			Max.	2.0	2.6	1.1
		Weeks 9-12	n	70	75	74
			Mean	-0.10	-0.22	-0.21
			SE	0.100	0.104	0.084
			Median	0.00	0.00	0.00
			Min.	-2.9	-6.0	-3.2
			Max.	2.5	1.0	1.5
		Weeks 13-16	n	66	72	71
			Mean	-0.23	-0.27	-0.19
			SE	0.104	0.117	0.077
			Median	0.00	0.00	0.00
			Min.	-3.8	-5.6	-2.5
			Max.	1.7	1.4	1.6
		Overall	n	78	84	83
			Mean	-0.14	-0.19	-0.21
			SE	0.082	0.101	0.067
			Median	0.00	0.00	0.00
			Min.	-2.8	-6.0	-2.8
			Max.	1.9	1.7	1.0
	Wash-out	Overall	n	63	71	71

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Table 7.21
Summary of Supplemental Albuterol Use (puffs/day)

Treatment: Salmeterol

				Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)
-----	-----	-----	-----	-----	-----	-----
Albuterol change	Wash-out	Overall	Mean	-0.11	0.06	0.09
			SE	0.109	0.100	0.108
			Median	0.00	0.00	0.00
			Min.	-3.9	-3.0	-2.5
			Max.	1.4	2.9	3.7

Table 7.22
Summary of Maximum Albuterol Dose Response

Treatment: FSC100/50

			Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)

Subjects in treatment			87	91	90
Baseline FEV1 (L)	Visit 4 (Week -8)	n	87	91	90
		Mean	2.78	2.89	2.88
		SE	0.075	0.072	0.062
		Median	2.68	2.83	2.83
		Min.	1.57	1.30	1.62
		Max.	5.08	4.60	4.34
	Visit 6 (Day 1)	n	87	91	90
		Mean	2.76	2.87	2.86
		SE	0.076	0.073	0.066
		Median	2.68	2.77	2.83
		Min.	1.32	1.33	1.45
		Max.	4.95	4.77	4.34
	Visit 10 (Week 16)	n	77	83	79
		Mean	2.95	3.09	3.04
		SE	0.084	0.087	0.085
		Median	2.84	2.94	3.06
		Min.	1.62	1.15	1.62
		Max.	5.33	5.02	4.93
Max FEV1 post albuterol	Visit 4 (Week -8)	n	87	91	90
		Mean	3.08	3.20	3.21
		SE	0.083	0.081	0.077
		Median	3.00	3.09	3.23
		Min.	1.72	1.60	1.83
		Max.	5.69	4.87	4.98

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Table 7.22
 Summary of Maximum Albuterol Dose Response

Treatment: FSC100/50

			Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)
Max FEV1 post albuterol	Visit 6 (Day 1)	n	87	91	90
		Mean	3.06	3.18	3.20
		SE	0.079	0.081	0.078
		Median	3.01	3.09	3.16
		Min.	1.71	1.47	1.72
		Max.	5.21	4.99	4.87
	Visit 10 (Week 16)	n	77	83	79
		Mean	3.12	3.23	3.22
		SE	0.088	0.088	0.089
		Median	3.10	3.10	3.25
		Min.	1.67	1.26	1.73
Max % change	Visit 4 (Week -8)	n	87	91	90
		Mean	11.4	10.9	11.3
		SE	0.93	0.80	0.96
		Median	10.6	9.6	10.4
		Min.	-7	-1	-16
		Max.	48	43	43
	Visit 6 (Day 1)	n	87	91	90
		Mean	11.7	11.0	12.0
		SE	0.97	0.96	0.98
		Median	9.5	8.8	10.0
		Min.	-7	-1	0
		Max.	49	64	53

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Table 7.22
Summary of Maximum Albuterol Dose Response

Treatment: FSC100/50

		Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)
Max % change	Visit 10 (Week 16)			
	n	77	83	79
	Mean	6.2	4.9	6.1
	SE	0.78	0.59	0.71
	Median	5.4	3.9	4.5
	Min.	-12	-4	-5
	Max.	35	29	29

Table 7.22
 Summary of Maximum Albuterol Dose Response

Treatment: Salmeterol

			Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)

Subjects in treatment			86	89	91
Baseline FEV1 (L)	Visit 4 (Week -8)	n	86	89	91
		Mean	2.95	2.85	2.87
		SE	0.079	0.078	0.079
		Median	2.97	2.72	2.74
		Min.	1.58	1.44	1.62
		Max.	4.51	4.69	5.46
	Visit 6 (Day 1)	n	86	89	91
		Mean	2.89	2.84	2.88
		SE	0.080	0.081	0.077
		Median	2.81	2.76	2.79
		Min.	1.66	1.32	1.54
		Max.	4.53	4.73	4.93
	Visit 10 (Week 16)	n	66	73	75
		Mean	3.12	2.92	2.91
		SE	0.103	0.077	0.088
		Median	2.94	2.90	2.90
		Min.	1.52	1.22	1.43
		Max.	5.15	4.47	5.09
Max FEV1 post albuterol	Visit 4 (Week -8)	n	86	89	91
		Mean	3.28	3.21	3.24
		SE	0.094	0.088	0.085
		Median	3.20	3.12	3.13
		Min.	1.62	1.56	1.76
		Max.	5.42	5.67	5.91

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Table 7.22
Summary of Maximum Albuterol Dose Response

Treatment: Salmeterol

			Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)
Max FEV1 post albuterol	Visit 6 (Day 1)	n	86	89	91
		Mean	3.21	3.17	3.24
		SE	0.088	0.089	0.088
		Median	3.12	3.09	3.08
		Min.	1.71	1.38	1.91
		Max.	5.21	5.67	6.02
	Visit 10 (Week 16)	n	66	73	75
		Mean	3.25	3.16	3.17
		SE	0.100	0.086	0.092
		Median	3.13	3.11	3.15
		Min.	1.72	1.16	1.70
Max % change	Visit 4 (Week -8)	n	86	89	91
		Mean	11.0	12.8	13.5
		SE	0.88	0.98	1.13
		Median	9.8	10.8	11.7
		Min.	-8	0	-5
		Max.	44	51	46
	Visit 6 (Day 1)	n	86	89	91
		Mean	11.6	12.3	13.0
		SE	0.95	1.06	1.12
		Median	9.2	9.1	10.2
		Min.	-8	-2	-4
		Max.	48	57	66

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Table 7.22
Summary of Maximum Albuterol Dose Response

Treatment: Salmeterol

		Arg/Arg (N=173)	Arg/Gly (N=180)	Gly/Gly (N=181)
Max % change	Visit 10 (Week 16)			
	n	66	73	75
	Mean	5.1	8.3	9.7
	SE	0.89	0.99	1.05
	Median	4.8	6.3	6.6
	Min.	-38	-11	-2
	Max.	18	38	46

Table 7.23
Analysis of Maximum Albuterol Dose Response (% Change)

			Arg/Arg vs. Arg/Gly	Arg/Arg vs. Gly/Gly	Arg/Gly vs. Gly/Gly
FSC100/50	Visit 4 (Week -8)	p-value	0.695	0.920	0.765
		LS Means Diff	0.5	0.1	-0.4
		95% CI for Diff	(-2.0, 3.0)	(-2.4, 2.7)	(-2.9, 2.1)
	Visit 6 (Day 1)	p-value	0.544	0.919	0.469
		LS Means Diff	0.8	-0.1	-1.0
		95% CI for Diff	(-1.9, 3.5)	(-2.8, 2.6)	(-3.6, 1.7)
	Visit 10 (Week 16)	p-value	0.250	0.997	0.242
		LS Means Diff	1.1	-0.0	-1.1
		95% CI for Diff	(-0.8, 3.0)	(-1.9, 1.9)	(-3.0, 0.8)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum and Arg16Gly genotype. Least squares mean differences are calculated as Arg/Arg-Arg/Gly, Arg/Arg-Gly/Gly and Arg/Gly-Gly/Gly.

Table 7.23
Analysis of Maximum Albuterol Dose Response (% Change)

			Arg/Arg vs. Arg/Gly	Arg/Arg vs. Gly/Gly	Arg/Gly vs. Gly/Gly
Salmeterol	Visit 4 (Week -8)	p-value	0.298	0.121	0.607
		LS Means Diff	-1.5	-2.2	-0.7
		95% CI for Diff	(-4.4, 1.3)	(-5.1, 0.6)	(-3.5, 2.0)
	Visit 6 (Day 1)	p-value	0.661	0.336	0.596
		LS Means Diff	-0.7	-1.4	-0.8
		95% CI for Diff	(-3.6, 2.3)	(-4.4, 1.5)	(-3.6, 2.1)
	Visit 10 (Week 16)	p-value	0.087	0.008	0.317
		LS Means Diff	-2.4	-3.8	-1.3
		95% CI for Diff	(-5.2, 0.4)	(-6.5, -1.0)	(-4.0, 1.3)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum and Arg16Gly genotype. Least squares mean differences are calculated as Arg/Arg-Arg/Gly, Arg/Arg-Gly/Gly and Arg/Gly-Gly/Gly.

Table 7.24
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS1432623

Treatment: FSC100/50

				C, C	C, T	T, T
-----				-----		
Subjects in treatment				37	95	110
AM PEF (L/min)	Double-blind	Baseline	n	37	93	108
			Mean	336.5	387.0	355.8
			SE	11.51	9.22	9.01
			Median	360.0	387.1	352.5
			Min.	121	192	183
			Max.	449	663	658
		Weeks 1-4	n	35	95	110
			Mean	355.6	404.5	381.2
			SE	10.58	9.66	9.62
			Median	348.8	402.4	373.3
			Min.	228	214	149
			Max.	493	634	703
		Weeks 5-8	n	33	92	106
			Mean	357.7	413.2	381.2
			SE	10.44	10.72	9.65
			Median	361.2	402.1	366.8
			Min.	247	254	150
			Max.	478	678	682
		Weeks 9-12	n	31	89	103
			Mean	353.6	413.9	388.5
			SE	11.60	11.22	9.91
			Median	367.9	400.3	375.3
			Min.	244	239	152
			Max.	488	667	680
		Weeks 13-16	n	30	89	101
			Mean	354.8	413.6	390.3
			SE	11.44	10.74	10.18

Table 7.24
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS1432623

Treatment: FSC100/50

				C, C	C, T	T, T
AM PEF (L/min)	Double-blind	Weeks 13-16	Median	372.4	390.3	374.9
			Min.	242	257	158
			Max.	472	648	675
		Overall	n	35	95	110
			Mean	357.4	411.6	385.2
			SE	10.19	10.16	9.42
			Median	367.6	398.8	372.5
			Min.	246	241	152
			Max.	483	647	685
	Wash-out	Overall	n	29	88	99
			Mean	348.4	402.3	374.9
			SE	10.73	10.27	9.90
			Median	357.1	387.0	356.9
			Min.	262	226	144
			Max.	441	645	655
AM PEF change	Double-blind	Weeks 1-4	n	35	93	108
			Mean	22.3	19.5	27.2
			SE	6.89	4.79	4.12
			Median	11.8	15.1	19.6
			Min.	-39	-139	-103
			Max.	126	172	188
		Weeks 5-8	n	33	90	104
			Mean	26.4	29.0	27.8
			SE	7.31	5.35	4.53
			Median	10.8	16.8	19.1
			Min.	-27	-113	-85
			Max.	148	172	199
		Weeks 9-12	n	31	87	101

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Table 7.24
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS1432623

Treatment: FSC100/50

				C, C	C, T	T, T
AM PEF change	Double-blind	Weeks 9-12	Mean	23.0	28.7	35.4
			SE	8.43	5.62	4.96
			Median	7.9	16.0	26.3
			Min.	-46	-94	-98
			Max.	162	180	178
		Weeks 13-16	n	30	87	99
			Mean	23.3	29.1	35.6
			SE	9.17	5.61	5.29
			Median	8.4	17.8	22.6
			Min.	-38	-87	-94
			Max.	175	167	210
		Overall	n	35	93	108
			Mean	24.2	26.6	30.6
			SE	7.16	4.84	4.32
			Median	14.9	15.7	19.9
			Min.	-30	-108	-89
			Max.	153	166	194
	Wash-out	Overall	n	29	86	97
			Mean	15.1	17.8	21.1
			SE	6.36	4.61	4.10
			Median	2.7	13.3	11.7
			Min.	-21	-77	-70
			Max.	157	147	123

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Table 7.24
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS1432623

Treatment: Salmeterol

				C, C	C, T	T, T
-----				-----		
Subjects in treatment				34	98	100
AM PEF (L/min)	Double-blind	Baseline	n	33	96	98
			Mean	380.3	361.0	383.7
			SE	14.30	10.21	9.62
			Median	385.0	331.1	374.9
			Min.	203	180	213
			Max.	533	643	685
		Weeks 1-4	n	33	97	97
			Mean	395.9	379.4	398.6
			SE	13.91	10.42	10.63
			Median	375.9	346.1	386.0
			Min.	240	182	220
			Max.	563	699	675
		Weeks 5-8	n	31	94	93
			Mean	396.0	381.0	402.4
			SE	14.65	11.22	10.98
			Median	395.5	352.1	383.4
			Min.	201	183	221
			Max.	561	827	679
		Weeks 9-12	n	28	91	88
			Mean	394.0	387.2	398.9
			SE	15.75	11.89	10.73
			Median	394.5	361.2	385.8
			Min.	206	209	237
			Max.	566	943	640
		Weeks 13-16	n	27	87	84
			Mean	394.2	391.5	397.8
			SE	15.06	12.40	10.91

Table 7.24
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS1432623

Treatment: Salmeterol

				C, C	C, T	T, T
AM PEF (L/min)	Double-blind	Weeks 13-16	Median	378.1	363.6	386.4
			Min.	242	212	242
			Max.	548	975	628
		Overall	n	33	97	97
			Mean	393.9	383.3	403.2
			SE	14.11	10.89	10.62
			Median	376.7	350.3	387.0
			Min.	216	211	235
			Max.	560	859	677
	Wash-out	Overall	n	27	86	83
			Mean	390.3	375.7	385.8
			SE	14.55	12.63	10.59
			Median	378.5	339.6	375.1
			Min.	259	211	225
			Max.	540	980	625
AM PEF change	Double-blind	Weeks 1-4	n	33	95	97
			Mean	15.7	17.5	15.3
			SE	5.05	4.05	3.29
			Median	13.0	12.9	6.9
			Min.	-69	-83	-106
			Max.	76	174	135
		Weeks 5-8	n	31	92	93
			Mean	9.3	19.7	21.2
			SE	6.46	4.41	4.03
			Median	8.3	13.5	8.7
			Min.	-87	-55	-91
			Max.	102	302	180
		Weeks 9-12	n	28	90	88

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Table 7.24
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS1432623

Treatment: Salmeterol

				C, C	C, T	T, T
AM PEF change	Double-blind	Weeks 9-12	Mean	15.3	25.6	24.5
			SE	7.23	5.65	5.09
			Median	16.9	14.0	14.2
			Min.	-75	-40	-116
			Max.	124	418	319
		Weeks 13-16	n	27	86	84
			Mean	9.0	27.0	21.7
			SE	8.78	6.19	4.57
			Median	14.6	20.3	16.7
			Min.	-95	-92	-110
			Max.	124	451	186
		Overall	n	33	95	97
			Mean	13.7	21.2	19.9
			SE	5.82	4.57	3.61
			Median	14.8	14.4	13.3
			Min.	-73	-83	-106
			Max.	107	334	152
	Wash-out	Overall	n	27	85	83
			Mean	5.1	13.4	12.0
			SE	9.21	6.47	4.26
			Median	8.1	6.4	11.1
			Min.	-102	-98	-139
			Max.	91	456	128

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Table 7.25
Analysis of AM PEF (L/min) - ADRB2 Gene SNP RS1432623

			C/C vs. C/T	C/C vs. T/T	C/T vs. T/T
FSC100/50	Double-blind	Weeks 1-4	p-value	0.767	0.439
			LS Means Diff	-2.6	-4.8
			95% CI for Diff	(-19.7, 14.5)	(-17.1, 7.4)
		Weeks 5-8	p-value	0.404	0.667
			LS Means Diff	-8.1	3.0
			95% CI for Diff	(-27.2, 11.0)	(-10.6, 16.5)
		Weeks 9-12	p-value	0.268	0.562
			LS Means Diff	-11.8	-4.3
			95% CI for Diff	(-32.9, 9.2)	(-19.1, 10.4)
		Weeks 13-16	p-value	0.255	0.587
			LS Means Diff	-12.6	-4.2
			95% CI for Diff	(-34.3, 9.2)	(-19.3, 10.9)
	Wash-out	Overall	p-value	0.382	0.751
			LS Means Diff	-7.9	-2.0
			95% CI for Diff	(-25.6, 9.9)	(-14.8, 10.7)
		Overall	p-value	0.378	0.682
			LS Means Diff	-7.7	-2.5
			95% CI for Diff	(-24.9, 9.5)	(-14.5, 9.5)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS1432623. Least squares mean differences are calculated as C/C-C/T, C/C-T/T and C/T-T/T.

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Table 7.25
Analysis of AM PEF (L/min) - ADRB2 Gene SNP RS1432623

				C/C vs. C/T	C/C vs. T/T	C/T vs. T/T
Salmeterol	Double-blind	Weeks 1-4	p-value	0.936	0.995	0.906
			LS Means Diff	-0.6	0.0	0.6
			95% CI for Diff	(-14.1,13.0)	(-14.0,14.1)	(-9.4,10.6)
		Weeks 5-8	p-value	0.229	0.161	0.737
			LS Means Diff	-9.8	-11.8	-2.0
			95% CI for Diff	(-25.9,6.2)	(-28.5,4.8)	(-13.8,9.7)
		Weeks 9-12	p-value	0.449	0.523	0.894
			LS Means Diff	-8.0	-7.0	1.0
			95% CI for Diff	(-28.8,12.8)	(-28.6,14.6)	(-13.8,15.8)
		Weeks 13-16	p-value	0.166	0.352	0.556
			LS Means Diff	-14.9	-10.4	4.5
			95% CI for Diff	(-36.2,6.3)	(-32.4,11.6)	(-10.6,19.7)
	Overall	p-value	0.428	0.467	0.953	
		LS Means Diff	-6.1	-5.8	0.3	
95% CI for Diff		(-21.3,9.1)	(-21.5,9.9)	(-10.8,11.5)		
Wash-out	Overall	p-value	0.638	0.837	0.722	
		LS Means Diff	-5.2	-2.4	2.8	
		95% CI for Diff	(-26.9,16.5)	(-24.9,20.2)	(-12.9,18.5)	

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS1432623. Least squares mean differences are calculated as C/C-C/T, C/C-T/T and C/T-T/T.

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Table 7.26
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS1042711

Treatment: FSC100/50

				C, C	C, T	T, T
-----				-----		
Subjects in treatment				23	72	141
AM PEF (L/min)	Double-blind	Baseline	n	23	71	138
			Mean	348.5	385.3	360.4
			SE	12.23	10.08	8.05
			Median	365.6	388.1	355.9
			Min.	213	222	121
			Max.	448	663	658
		Weeks 1-4	n	22	72	140
			Mean	368.6	403.6	384.6
			SE	10.87	10.86	8.43
			Median	381.4	403.7	376.3
			Min.	279	214	149
			Max.	437	634	703
		Weeks 5-8	n	20	69	136
			Mean	368.2	411.3	388.0
			SE	11.44	12.03	8.58
			Median	374.4	404.6	373.0
			Min.	283	254	150
			Max.	445	678	682
		Weeks 9-12	n	19	66	133
			Mean	369.5	412.9	391.2
			SE	12.05	12.87	8.80
			Median	391.1	405.2	375.3
			Min.	282	239	152
			Max.	445	667	680
		Weeks 13-16	n	19	66	130
			Mean	369.9	414.1	392.2
			SE	11.73	12.37	8.92

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Table 7.26
 Summary of AM PEF (L/min) - ADRB2 Gene SNP RS1042711

Treatment: FSC100/50

				C, C	C, T	T, T
AM PEF (L/min)	Double-blind	Weeks 13-16	Median	388.2	405.9	375.0
			Min.	283	242	158
			Max.	444	648	675
		Overall	n	22	72	140
			Mean	370.4	409.9	389.5
			SE	10.56	11.43	8.36
			Median	380.5	403.3	375.4
			Min.	282	241	152
			Max.	443	647	685
	Wash-out	Overall	n	18	66	127
			Mean	360.4	400.6	378.9
			SE	12.45	11.67	8.57
			Median	374.9	389.6	372.0
			Min.	262	226	144
			Max.	440	645	655
AM PEF change	Double-blind	Weeks 1-4	n	22	71	137
			Mean	21.2	21.0	25.9
			SE	8.12	5.39	3.84
			Median	9.8	16.5	18.6
			Min.	-36	-139	-103
			Max.	126	172	188
		Weeks 5-8	n	20	68	133
			Mean	22.6	29.6	29.8
			SE	8.75	5.95	4.22
			Median	10.4	21.8	17.0
			Min.	-10	-113	-85
			Max.	148	172	199
		Weeks 9-12	n	19	65	130

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Table 7.26
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS1042711

Treatment: FSC100/50

				C, C	C, T	T, T
AM PEF change	Double-blind	Weeks 9-12	Mean	21.5	29.5	34.0
			SE	9.71	6.39	4.54
			Median	6.4	20.2	22.8
			Min.	-5	-94	-98
			Max.	162	180	180
		Weeks 13-16	n	19	65	127
			Mean	22.0	27.9	35.2
			SE	10.23	6.44	4.80
			Median	8.7	21.2	19.9
			Min.	-12	-87	-94
			Max.	175	167	210
		Overall	n	22	71	137
			Mean	23.0	27.0	30.5
			SE	8.35	5.39	4.00
			Median	14.9	18.9	17.5
			Min.	-16	-108	-89
			Max.	153	166	194
	Wash-out	Overall	n	18	65	124
			Mean	8.6	14.7	22.6
			SE	4.58	5.34	3.75
			Median	0.9	11.5	13.4
			Min.	-15	-77	-70
			Max.	49	147	157

Table 7.26
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS1042711

Treatment: Salmeterol

				C, C	C, T	T, T
-----				-----		
Subjects in treatment				25	71	133
AM PEF (L/min)	Double-blind	Baseline	n	25	70	129
			Mean	387.2	365.7	373.8
			SE	14.39	11.45	8.81
			Median	394.3	335.6	364.1
			Min.	228	226	180
			Max.	533	628	685
		Weeks 1-4	n	25	70	129
			Mean	404.7	387.4	387.2
			SE	15.00	11.73	9.37
			Median	394.9	360.0	371.4
			Min.	266	232	182
			Max.	563	699	675
		Weeks 5-8	n	23	67	125
			Mean	411.1	388.7	389.3
			SE	14.74	13.29	9.58
			Median	412.4	356.7	377.1
			Min.	246	228	183
			Max.	561	827	679
		Weeks 9-12	n	20	66	118
			Mean	406.2	395.0	388.2
			SE	16.47	14.24	9.40
			Median	401.8	365.4	375.9
			Min.	251	231	206
			Max.	566	943	651
		Weeks 13-16	n	20	64	111
			Mean	402.0	395.2	391.0
			SE	17.54	14.93	9.42

Table 7.26
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS1042711

Treatment: Salmeterol

				C, C	C, T	T, T
AM PEF (L/min)	Double-blind	Weeks 13-16	Median	387.9	364.8	371.6
			Min.	242	226	212
			Max.	548	975	667
		Overall	n	25	70	129
			Mean	405.0	391.2	390.9
			SE	15.00	12.85	9.26
			Median	396.0	361.6	374.5
			Min.	251	229	211
			Max.	560	859	677
	Wash-out	Overall	n	20	64	109
			Mean	395.9	379.5	378.9
			SE	16.73	15.05	9.30
			Median	378.8	343.9	368.6
			Min.	267	212	211
			Max.	540	980	664
AM PEF change	Double-blind	Weeks 1-4	n	25	69	128
			Mean	17.6	19.1	14.5
			SE	5.46	5.14	2.84
			Median	9.8	14.4	8.5
			Min.	-35	-83	-106
			Max.	76	174	135
		Weeks 5-8	n	23	66	124
			Mean	14.6	21.2	18.4
			SE	7.28	5.91	3.28
			Median	14.6	13.6	8.6
			Min.	-42	-87	-91
			Max.	102	302	180
		Weeks 9-12	n	20	65	118

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Table 7.26
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS1042711

Treatment: Salmeterol

				C, C	C, T	T, T
AM PEF change	Double-blind	Weeks 9-12	Mean	19.5	28.7	21.8
			SE	8.53	7.59	4.01
			Median	17.5	19.8	12.8
			Min.	-43	-75	-116
			Max.	124	418	319
		Weeks 13-16	n	20	63	111
			Mean	15.3	27.6	20.4
			SE	9.61	8.24	3.78
			Median	15.6	20.2	17.3
			Min.	-44	-92	-110
			Max.	124	451	186
		Overall	n	25	69	128
			Mean	17.8	22.8	18.1
			SE	6.57	6.12	2.93
			Median	15.4	14.5	13.1
			Min.	-38	-83	-106
			Max.	107	334	152
	Wash-out	Overall	n	20	63	109
			Mean	9.2	12.7	11.2
			SE	8.86	8.73	3.56
			Median	8.3	4.3	9.4
			Min.	-78	-102	-139
			Max.	81	456	128

Table 7.27
Analysis of AM PEF (L/min) - ADRB2 Gene SNP RS1042711

				C/C vs. C/T	C/C vs. T/T	C/T vs. T/T
FSC100/50	Double-blind	Weeks 1-4	p-value	0.440	0.121	0.233
			LS Means Diff	-8.2	-16.0	-7.7
			95% CI for Diff	(-29.2,12.8)	(-36.2,4.2)	(-20.5,5.0)
		Weeks 5-8	p-value	0.220	0.130	0.694
			LS Means Diff	-14.9	-17.7	-2.8
			95% CI for Diff	(-38.7,9.0)	(-40.6,5.2)	(-17.0,11.4)
		Weeks 9-12	p-value	0.205	0.062	0.375
			LS Means Diff	-16.8	-23.7	-6.9
			95% CI for Diff	(-42.8,9.2)	(-48.6,1.2)	(-22.2,8.4)
		Weeks 13-16	p-value	0.244	0.056	0.255
			LS Means Diff	-15.8	-24.9	-9.1
			95% CI for Diff	(-42.4,10.9)	(-50.4,0.6)	(-24.8,6.6)
	Overall	p-value	0.276	0.086	0.354	
		LS Means Diff	-12.1	-18.3	-6.2	
95% CI for Diff		(-33.8,9.7)	(-39.2,2.6)	(-19.4,7.0)		
Wash-out	Overall	p-value	0.240	0.045	0.191	
		LS Means Diff	-12.6	-20.8	-8.2	
		95% CI for Diff	(-33.8,8.5)	(-41.2,-0.5)	(-20.5,4.1)	

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS1042711. Least squares mean differences are calculated as C/C-C/T, C/C-T/T and C/T-T/T.

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Table 7.27
Analysis of AM PEF (L/min) - ADRB2 Gene SNP RS1042711

				C/C vs. C/T	C/C vs. T/T	C/T vs. T/T
Salmeterol	Double-blind	Weeks 1-4	p-value	0.861	0.779	0.884
			LS Means Diff	-1.4	-2.2	-0.8
			95% CI for Diff	(-17.1, 14.3)	(-17.6, 13.2)	(-11.4, 9.8)
		Weeks 5-8	p-value	0.414	0.259	0.669
			LS Means Diff	-7.8	-10.5	-2.7
			95% CI for Diff	(-26.6, 11.0)	(-28.8, 7.8)	(-15.2, 9.8)
	Weeks 9-12		p-value	0.426	0.497	0.846
			LS Means Diff	-9.9	-8.4	1.6
			95% CI for Diff	(-34.5, 14.6)	(-32.7, 15.9)	(-14.1, 17.2)
	Weeks 13-16		p-value	0.294	0.388	0.765
			LS Means Diff	-13.1	-10.7	2.4
			95% CI for Diff	(-37.7, 11.5)	(-35.0, 13.6)	(-13.6, 18.5)
	Overall		p-value	0.559	0.462	0.839
			LS Means Diff	-5.2	-6.4	-1.2
			95% CI for Diff	(-22.7, 12.3)	(-23.6, 10.8)	(-13.0, 10.6)
	Wash-out	Overall	p-value	0.768	0.825	0.908
			LS Means Diff	-3.8	-2.8	1.0
			95% CI for Diff	(-29.0, 21.4)	(-27.8, 22.2)	(-15.6, 17.5)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS1042711. Least squares mean differences are calculated as C/C-C/T, C/C-T/T and C/T-T/T.

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Table 7.28
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS1042713

Treatment: FSC100/50

				A, A	A, G	G, G

Subjects in treatment				81	85	77
AM PEF (L/min)	Double-blind	Baseline	n	78	85	76
			Mean	354.1	367.4	373.3
			SE	11.05	9.36	9.84
			Median	350.2	365.1	366.6
			Min.	121	183	213
			Max.	658	614	663
		Weeks 1-4	n	80	85	76
			Mean	379.1	390.2	391.1
			SE	10.90	10.73	9.95
			Median	371.0	384.0	383.6
			Min.	180	149	214
			Max.	703	619	653
		Weeks 5-8	n	77	83	72
			Mean	384.1	394.0	394.4
			SE	11.04	11.25	11.10
			Median	368.1	383.8	381.5
			Min.	222	150	233
			Max.	682	632	678
		Weeks 9-12	n	73	83	68
			Mean	388.7	393.2	400.1
			SE	11.46	11.54	11.75
			Median	372.7	383.0	392.3
			Min.	223	152	235
			Max.	680	665	667
		Weeks 13-16	n	72	81	68
			Mean	387.7	394.1	403.5
			SE	11.43	11.53	11.54

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Table 7.28
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS1042713

Treatment: FSC100/50

				A, A	A, G	G, G
AM PEF (L/min)	Double-blind	Weeks 13-16	Median	366.4	383.1	389.6
			Min.	218	158	241
			Max.	671	636	675
		Overall	n	80	85	76
			Mean	385.7	392.9	396.7
			SE	10.69	10.91	10.41
			Median	371.4	385.7	393.8
			Min.	221	152	235
			Max.	685	633	659
	Wash-out	Overall	n	71	79	67
			Mean	375.8	384.7	387.0
			SE	10.94	11.11	11.31
			Median	362.4	376.9	380.2
			Min.	216	144	225
			Max.	655	600	645
AM PEF change	Double-blind	Weeks 1-4	n	77	85	75
			Mean	27.8	22.8	20.2
			SE	4.89	4.74	5.20
			Median	19.2	15.8	13.0
			Min.	-80	-103	-139
			Max.	157	172	188
		Weeks 5-8	n	74	83	71
			Mean	33.6	27.5	24.1
			SE	5.45	5.31	5.57
			Median	20.2	18.7	11.5
			Min.	-46	-85	-113
			Max.	145	172	199
		Weeks 9-12	n	70	83	67

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Table 7.28
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS1042713

Treatment: FSC100/50

				A, A	A, G	G, G
-----				-----		
AM PEF change	Double-blind	Weeks 9-12	Mean	39.4	26.6	27.8
			SE	5.83	5.61	6.19
			Median	26.2	14.7	16.0
			Min.	-66	-98	-94
			Max.	166	180	178
		Weeks 13-16	n	69	81	67
			Mean	40.9	25.9	28.1
			SE	6.01	5.78	6.54
			Median	33.6	14.6	12.8
			Min.	-44	-94	-87
			Max.	154	168	210
		Overall	n	77	85	75
			Mean	33.9	25.5	25.5
			SE	4.98	5.00	5.24
			Median	19.0	15.0	14.9
			Min.	-49	-89	-108
			Max.	140	166	194
	Wash-out	Overall	n	68	79	66
			Mean	29.3	17.4	10.3
			SE	5.31	4.73	3.96
			Median	19.7	11.5	3.4
			Min.	-56	-70	-77
			Max.	157	147	103

Table 7.28
 Summary of AM PEF (L/min) - ADRB2 Gene SNP RS1042713

Treatment: Salmeterol

				A, A	A, G	G, G
-----				-----		
Subjects in treatment				72	79	81
AM PEF (L/min)	Double-blind	Baseline	n	69	77	81
			Mean	390.1	362.6	369.9
			SE	12.95	9.92	10.25
			Median	374.3	342.3	353.0
			Min.	203	180	220
			Max.	658	685	628
		Weeks 1-4	n	69	77	81
			Mean	405.5	383.4	383.1
			SE	13.48	11.39	10.02
			Median	377.9	369.0	360.7
			Min.	210	182	220
			Max.	665	699	667
		Weeks 5-8	n	67	75	76
			Mean	403.6	389.5	385.0
			SE	13.58	12.74	10.47
			Median	381.5	367.4	367.6
			Min.	201	183	238
			Max.	654	827	652
		Weeks 9-12	n	63	71	73
			Mean	406.2	391.3	383.6
			SE	14.19	12.69	10.93
			Median	379.5	378.5	369.2
			Min.	206	231	237
			Max.	651	943	645
		Weeks 13-16	n	60	68	70
			Mean	410.5	392.9	382.4
			SE	13.96	13.25	11.38

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Table 7.28
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS1042713

Treatment: Salmeterol

				A, A	A, G	G, G
AM PEF (L/min)	Double-blind	Weeks 13-16	Median	386.4	377.2	363.1
			Min.	212	226	242
			Max.	667	975	630
		Overall	n	69	77	81
			Mean	408.7	389.1	384.4
			SE	13.44	12.08	10.09
			Median	382.0	366.9	369.7
			Min.	211	229	235
			Max.	659	859	649
		Wash-out	n	58	68	70
			Mean	400.5	377.4	371.1
			SE	14.26	13.26	10.97
			Median	379.7	351.5	355.2
			Min.	211	212	238
			Max.	664	980	603
AM PEF change	Double-blind	Weeks 1-4	n	68	76	81
			Mean	17.4	18.4	13.3
			SE	3.71	5.10	3.08
			Median	16.8	4.9	8.6
			Min.	-106	-72	-83
			Max.	119	174	76
		Weeks 5-8	n	66	74	76
			Mean	19.3	22.1	15.3
			SE	4.38	6.01	3.38
			Median	12.4	7.9	12.2
			Min.	-91	-87	-42
			Max.	133	302	102
		Weeks 9-12	n	63	70	73

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Table 7.28
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS1042713

Treatment: Salmeterol

				A, A	A, G	G, G
-----				-----		
AM PEF change	Double-blind	Weeks 9-12	Mean	24.8	29.2	17.6
			SE	6.58	7.25	3.62
			Median	13.9	20.3	13.9
			Min.	-116	-75	-43
			Max.	319	418	124
		Weeks 13-16	n	60	67	70
			Mean	22.5	29.2	15.4
			SE	6.03	7.83	4.07
			Median	23.9	22.6	14.0
			Min.	-110	-92	-62
			Max.	186	451	124
		Overall	n	68	76	81
			Mean	20.5	24.0	14.5
			SE	4.35	5.75	3.22
			Median	14.7	14.5	9.9
			Min.	-106	-73	-83
			Max.	152	334	107
	Wash-out	Overall	n	58	67	70
			Mean	12.9	18.5	4.1
			SE	5.69	8.22	3.82
			Median	14.3	8.6	4.3
			Min.	-139	-102	-78
			Max.	128	456	84

Table 7.29
Analysis of AM PEF (L/min) - ADRB2 Gene SNP RS1042713

				A/A vs. A/G	A/A vs. G/G	A/G vs. G/G
FSC100/50	Double-blind	Weeks 1-4	p-value	0.332	0.208	0.742
			LS Means Diff	6.6	8.8	2.2
			95% CI for Diff	(-6.7, 19.9)	(-4.9, 22.6)	(-11.1, 15.5)
		Weeks 5-8	p-value	0.363	0.184	0.637
			LS Means Diff	6.8	10.4	3.6
			95% CI for Diff	(-8.0, 21.6)	(-5.0, 25.8)	(-11.3, 18.4)
		Weeks 9-12	p-value	0.091	0.170	0.808
			LS Means Diff	13.7	11.7	-2.0
			95% CI for Diff	(-2.2, 29.6)	(-5.0, 28.5)	(-18.0, 14.0)
		Weeks 13-16	p-value	0.072	0.169	0.721
			LS Means Diff	15.1	12.1	-3.0
			95% CI for Diff	(-1.4, 31.5)	(-5.2, 29.4)	(-19.5, 13.5)
	Wash-out	Overall	p-value	0.168	0.187	0.987
			LS Means Diff	9.7	9.6	-0.1
			95% CI for Diff	(-4.1, 23.5)	(-4.7, 23.8)	(-13.9, 13.7)
		Overall	p-value	0.097	0.012	0.325
			LS Means Diff	10.9	17.3	6.5
			95% CI for Diff	(-2.0, 23.7)	(3.8, 30.8)	(-6.4, 19.3)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS1042713. Least squares mean differences are calculated as A/A-A/G, A/A-G/G and A/G-G/G.

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Table 7.29
Analysis of AM PEF (L/min) - ADRB2 Gene SNP RS1042713

				A/A vs. A/G	A/A vs. G/G	A/G vs. G/G
Salmeterol	Double-blind	Weeks 1-4	p-value	0.596	0.129	0.300
			LS Means Diff	3.1	8.7	5.7
			95% CI for Diff	(-8.3,14.4)	(-2.5,19.9)	(-5.1,16.4)
		Weeks 5-8	p-value	0.840	0.303	0.385
			LS Means Diff	1.4	7.0	5.6
			95% CI for Diff	(-12.0,14.7)	(-6.3,20.3)	(-7.1,18.3)
		Weeks 9-12	p-value	0.920	0.150	0.108
			LS Means Diff	-0.9	12.2	13.1
			95% CI for Diff	(-17.6,15.9)	(-4.5,28.9)	(-2.9,29.1)
		Weeks 13-16	p-value	0.672	0.240	0.094
			LS Means Diff	-3.7	10.3	14.0
			95% CI for Diff	(-20.9,13.5)	(-6.9,27.4)	(-2.4,30.3)
	Overall	p-value	0.910	0.096	0.104	
		LS Means Diff	0.7	10.7	9.9	
95% CI for Diff		(-11.9,13.4)	(-1.9,23.2)	(-2.1,21.9)		
Wash-out	Overall	p-value	0.604	0.290	0.097	
		LS Means Diff	-4.7	9.5	14.1	
		95% CI for Diff	(-22.4,13.0)	(-8.2,27.1)	(-2.6,30.8)	

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS1042713. Least squares mean differences are calculated as A/A-A/G, A/A-G/G and A/G-G/G.

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Table 7.30
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS1042714

Treatment: FSC100/50

				C, C	C, G	G, G
-----				-----		
Subjects in treatment				147	73	23
AM PEF (L/min)	Double-blind	Baseline	n	144	72	23
			Mean	357.3	385.5	348.5
			SE	7.88	10.15	12.23
			Median	354.1	386.3	365.6
			Min.	121	222	213
			Max.	658	663	448
		Weeks 1-4	n	146	73	22
			Mean	381.5	403.1	368.6
			SE	8.25	10.84	10.87
			Median	374.4	403.3	381.4
			Min.	149	214	279
			Max.	703	634	437
		Weeks 5-8	n	142	70	20
			Mean	384.8	409.6	368.2
			SE	8.47	11.90	11.44
			Median	369.5	404.4	374.4
			Min.	150	254	283
			Max.	682	678	445
		Weeks 9-12	n	138	67	19
			Mean	388.8	411.1	369.5
			SE	8.68	12.77	12.05
			Median	373.9	402.9	391.1
			Min.	152	239	282
			Max.	680	667	445
		Weeks 13-16	n	135	67	19
			Mean	389.8	412.3	369.9
			SE	8.79	12.28	11.73

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Table 7.30
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS1042714

Treatment: FSC100/50

				C, C	C, G	G, G
AM PEF (L/min)	Double-blind	Weeks 13-16	Median	372.8	403.9	388.2
			Min.	158	242	283
			Max.	675	648	444
		Overall	n	146	73	22
			Mean	386.5	408.5	370.4
			SE	8.22	11.36	10.56
			Median	373.4	399.4	380.5
			Min.	152	241	282
			Max.	685	647	443
	Wash-out	Overall	n	132	67	18
			Mean	375.6	402.0	360.4
			SE	8.40	11.81	12.45
			Median	365.7	391.7	374.9
			Min.	144	226	262
			Max.	655	645	440
AM PEF change	Double-blind	Weeks 1-4	n	143	72	22
			Mean	25.7	20.2	21.2
			SE	3.68	5.34	8.12
			Median	18.9	14.5	9.8
			Min.	-103	-139	-36
			Max.	188	172	126
		Weeks 5-8	n	139	69	20
			Mean	29.6	27.7	22.6
			SE	4.08	5.87	8.75
			Median	17.0	19.8	10.4
			Min.	-85	-113	-10
			Max.	199	172	148
		Weeks 9-12	n	135	66	19

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Table 7.30
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS1042714

Treatment: FSC100/50

				C, C	C, G	G, G
-----				-----		
AM PEF change	Double-blind	Weeks 9-12	Mean	34.1	27.6	21.5
			SE	4.40	6.28	9.71
			Median	23.0	17.4	6.4
			Min.	-98	-94	-5
			Max.	180	180	162
		Weeks 13-16	n	132	66	19
			Mean	35.4	26.0	22.0
			SE	4.64	6.32	10.23
			Median	20.4	15.5	8.7
			Min.	-94	-87	-12
			Max.	210	167	175
		Overall	n	143	72	22
			Mean	30.4	25.4	23.0
			SE	3.85	5.33	8.35
			Median	18.7	14.7	14.9
			Min.	-89	-108	-16
			Max.	194	166	153
	Wash-out	Overall	n	129	66	18
			Mean	22.0	16.0	8.6
			SE	3.65	5.20	4.58
			Median	13.4	12.1	0.9
			Min.	-70	-77	-15
			Max.	157	147	49

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Table 7.30
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS1042714

Treatment: Salmeterol

				C, C	C, G	G, G
-----				-----		
Subjects in treatment				133	71	25
AM PEF (L/min)	Double-blind	Baseline	n	129	70	25
			Mean	374.0	365.7	387.2
			SE	8.57	11.45	14.39
			Median	366.3	335.6	394.3
			Min.	180	226	228
			Max.	685	628	533
		Weeks 1-4	n	129	70	25
			Mean	387.5	387.4	404.7
			SE	9.18	11.73	15.00
			Median	371.4	360.0	394.9
			Min.	182	232	266
			Max.	675	699	563
		Weeks 5-8	n	125	67	23
			Mean	390.0	388.7	411.1
			SE	9.42	13.29	14.74
			Median	378.3	356.7	412.4
			Min.	183	228	246
			Max.	679	827	561
		Weeks 9-12	n	119	66	20
			Mean	391.1	395.0	406.2
			SE	9.40	14.24	16.47
			Median	378.5	365.4	401.8
			Min.	206	231	251
			Max.	651	943	566
		Weeks 13-16	n	113	64	20
			Mean	393.2	395.2	402.0
			SE	9.42	14.93	17.54

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Table 7.30
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS1042714

Treatment: Salmeterol

				C, C	C, G	G, G
AM PEF (L/min)	Double-blind	Weeks 13-16	Median	372.8	364.8	387.9
			Min.	212	226	242
			Max.	667	975	548
		Overall	n	129	70	25
			Mean	391.4	391.2	405.0
			SE	9.10	12.85	15.00
			Median	376.3	361.6	396.0
			Min.	211	229	251
			Max.	677	859	560
	Wash-out	Overall	n	110	64	20
			Mean	382.3	379.5	395.9
			SE	9.35	15.05	16.73
			Median	369.6	343.9	378.8
			Min.	211	212	267
			Max.	664	980	540
AM PEF change	Double-blind	Weeks 1-4	n	128	69	25
			Mean	14.5	19.1	17.6
			SE	2.83	5.14	5.46
			Median	8.9	14.4	9.8
			Min.	-106	-83	-35
			Max.	135	174	76
		Weeks 5-8	n	124	66	23
			Mean	18.9	21.2	14.6
			SE	3.29	5.91	7.28
			Median	8.6	13.6	14.6
			Min.	-91	-87	-42
			Max.	180	302	102
		Weeks 9-12	n	119	65	20

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Table 7.30
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS1042714

Treatment: Salmeterol

				C, C	C, G	G, G
AM PEF change	Double-blind	Weeks 9-12	Mean	22.0	28.7	19.5
			SE	4.02	7.59	8.53
			Median	13.5	19.8	17.5
			Min.	-116	-75	-43
			Max.	319	418	124
		Weeks 13-16	n	113	63	20
			Mean	20.6	27.6	15.3
			SE	3.81	8.24	9.61
			Median	16.1	20.2	15.6
			Min.	-110	-92	-44
			Max.	186	451	124
		Overall	n	128	69	25
			Mean	18.5	22.8	17.8
			SE	2.96	6.12	6.57
			Median	13.1	14.5	15.4
			Min.	-106	-83	-38
			Max.	152	334	107
	Wash-out	Overall	n	110	63	20
			Mean	11.7	12.7	9.2
			SE	3.60	8.73	8.86
			Median	10.2	4.3	8.3
			Min.	-139	-102	-78
			Max.	128	456	81

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Table 7.31
Analysis of AM PEF (L/min) - ADRB2 Gene SNP RS1042714

			C/C vs. C/G	C/C vs. G/G	C/G vs. G/G
FSC100/50	Double-blind	Weeks 1-4	p-value	0.213	0.136
			LS Means Diff	7.9	15.1
			95% CI for Diff	(-4.6, 20.4)	(-4.8, 35.0)
		Weeks 5-8	p-value	0.537	0.140
			LS Means Diff	4.4	17.0
			95% CI for Diff	(-9.6, 18.3)	(-5.6, 39.7)
		Weeks 9-12	p-value	0.258	0.066
			LS Means Diff	8.7	23.0
			95% CI for Diff	(-6.4, 23.7)	(-1.5, 47.6)
		Weeks 13-16	p-value	0.169	0.059
FSC100/50	Double-blind		LS Means Diff	10.8	24.3
			95% CI for Diff	(-4.6, 26.3)	(-0.9, 49.4)
		Overall	p-value	0.259	0.093
			LS Means Diff	7.4	17.7
			95% CI for Diff	(-5.5, 20.4)	(-3.0, 38.3)
	Wash-out	Overall	p-value	0.334	0.056
			LS Means Diff	6.0	19.6
			95% CI for Diff	(-6.2, 18.1)	(-0.5, 39.6)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS1042714. Least squares mean differences are calculated as C/C-C/G, C/C-G/G and C/G-G/G.

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Table 7.31
Analysis of AM PEF (L/min) - ADRB2 Gene SNP RS1042714

				C/C vs. C/G	C/C vs. G/G	C/G vs. G/G
Salmeterol	Double-blind	Weeks 1-4	p-value	0.951	0.834	0.870
			LS Means Diff	0.3	1.6	1.3
			95% CI for Diff	(-10.2,10.8)	(-13.7,17.0)	(-14.4,17.0)
		Weeks 5-8	p-value	0.729	0.283	0.415
			LS Means Diff	2.2	10.0	7.8
			95% CI for Diff	(-10.3,14.7)	(-8.3,28.3)	(-11.0,26.6)
		Weeks 9-12	p-value	0.763	0.552	0.437
			LS Means Diff	-2.4	7.3	9.7
			95% CI for Diff	(-18.0,13.2)	(-17.0,31.6)	(-14.9,34.4)
		Weeks 13-16	p-value	0.674	0.440	0.302
			LS Means Diff	-3.4	9.5	12.9
			95% CI for Diff	(-19.4,12.6)	(-14.8,33.8)	(-11.7,37.6)
	Overall	p-value	0.914	0.516	0.574	
		LS Means Diff	0.6	5.7	5.0	
95% CI for Diff		(-11.2,12.5)	(-11.5,22.9)	(-12.6,22.7)		
Wash-out	Overall	p-value	0.875	0.849	0.772	
		LS Means Diff	-1.3	2.4	3.7	
		95% CI for Diff	(-17.8,15.1)	(-22.5,27.3)	(-21.5,29.0)	

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS1042714. Least squares mean differences are calculated as C/C-C/G, C/C-G/G and C/G-G/G.

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Table 7.32
 Summary of AM PEF (L/min) - ADRB2 Gene SNP RS1042718

Treatment: FSC100/50

				A, A	A, C	C, C
-----				-----		
Subjects in treatment				17	78	148
AM PEF (L/min)	Double-blind	Baseline	n	17	78	144
			Mean	357.1	374.3	360.8
			SE	23.90	10.42	7.33
			Median	354.0	376.7	360.0
			Min.	231	183	121
			Max.	663	608	658
		Weeks 1-4	n	17	78	146
			Mean	371.4	396.1	383.7
			SE	16.55	12.01	7.50
			Median	375.5	392.0	376.3
			Min.	232	149	180
			Max.	524	653	703
		Weeks 5-8	n	17	75	140
			Mean	373.1	398.3	389.0
			SE	17.46	13.05	7.76
			Median	366.3	399.4	373.1
			Min.	233	150	222
			Max.	551	678	682
		Weeks 9-12	n	17	72	135
			Mean	387.2	400.2	391.3
			SE	19.54	13.51	8.11
			Median	378.8	392.7	376.7
			Min.	235	152	223
			Max.	569	667	680
		Weeks 13-16	n	16	72	133
			Mean	392.4	403.3	390.7
			SE	21.07	13.25	8.04

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Table 7.32
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS1042718

Treatment: FSC100/50

				A, A	A, C	C, C
AM PEF (L/min)	Double-blind	Weeks 13-16	Median	378.2	388.8	375.1
			Min.	241	158	218
			Max.	576	675	671
		Overall	n	17	78	146
			Mean	379.8	399.4	389.0
			SE	18.12	12.35	7.47
			Median	374.7	397.5	374.4
			Min.	235	152	221
			Max.	555	659	685
	Wash-out	Overall	n	16	70	131
			Mean	363.7	391.6	379.9
			SE	20.75	12.77	7.75
			Median	362.4	385.6	371.5
			Min.	225	144	216
			Max.	587	645	655
AM PEF change	Double-blind	Weeks 1-4	n	17	78	142
			Mean	14.3	21.8	25.7
			SE	12.02	4.94	3.64
			Median	22.2	12.1	17.6
			Min.	-139	-91	-103
			Max.	80	188	172
		Weeks 5-8	n	17	75	136
			Mean	16.0	25.4	31.6
			SE	11.25	5.68	3.99
			Median	28.7	14.5	17.7
			Min.	-113	-85	-72
			Max.	68	199	172
		Weeks 9-12	n	17	72	131

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Table 7.32
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS1042718

Treatment: FSC100/50

				A, A	A, C	C, C
AM PEF change	Double-blind	Weeks 9-12	Mean	30.2	26.0	34.0
			SE	13.73	5.90	4.35
			Median	26.7	15.8	20.2
			Min.	-94	-81	-98
			Max.	159	180	180
		Weeks 13-16	n	16	72	129
			Mean	30.2	26.7	34.1
			SE	16.03	5.96	4.54
			Median	17.2	17.7	18.5
			Min.	-87	-66	-94
			Max.	181	210	175
		Overall	n	17	78	142
			Mean	22.8	25.1	30.6
			SE	12.52	5.06	3.75
			Median	28.8	13.6	17.3
			Min.	-108	-80	-89
			Max.	120	194	166
	Wash-out	Overall	n	16	70	127
			Mean	1.4	15.7	23.0
			SE	7.67	4.68	3.70
			Median	-3.4	12.9	13.3
			Min.	-77	-77	-69
			Max.	57	112	157

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Table 7.32
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS1042718

Treatment: Salmeterol

				A, A	A, C	C, C
-----				-----		
Subjects in treatment				21	68	143
AM PEF (L/min)	Double-blind	Baseline	n	21	67	139
			Mean	335.2	366.0	383.0
			SE	17.45	11.20	8.37
			Median	300.9	348.6	361.1
			Min.	220	180	203
			Max.	479	628	685
		Weeks 1-4	n	21	67	139
			Mean	347.7	377.2	402.6
			SE	18.65	11.57	8.78
			Median	337.4	351.6	389.1
			Min.	220	182	210
			Max.	524	667	699
		Weeks 5-8	n	20	64	134
			Mean	350.1	381.7	403.6
			SE	19.28	12.45	9.26
			Median	351.3	361.6	384.6
			Min.	238	183	201
			Max.	531	652	827
		Weeks 9-12	n	20	62	125
			Mean	349.6	383.2	404.9
			SE	19.44	12.09	9.76
			Median	338.5	357.7	387.5
			Min.	237	240	206
			Max.	543	645	943
		Weeks 13-16	n	18	59	121
			Mean	349.0	383.4	406.8
			SE	21.71	12.17	9.91

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Table 7.32
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS1042718

Treatment: Salmeterol

				A, A	A, C	C, C
AM PEF (L/min)	Double-blind	Weeks 13-16	Median	315.6	363.7	389.9
			Min.	242	244	212
			Max.	559	630	975
		Overall	n	21	67	139
			Mean	350.9	380.4	406.1
			SE	18.76	11.48	9.08
			Median	336.0	359.3	382.0
			Min.	235	229	211
			Max.	539	649	859
	Wash-out	Overall	n	18	59	119
			Mean	337.0	369.5	395.0
			SE	20.31	11.59	10.10
			Median	330.9	347.8	378.5
			Min.	238	225	211
			Max.	492	603	980
AM PEF change	Double-blind	Weeks 1-4	n	21	67	137
			Mean	12.4	11.3	19.3
			SE	5.03	4.31	3.09
			Median	4.2	6.9	13.0
			Min.	-21	-83	-106
			Max.	59	135	174
		Weeks 5-8	n	20	64	132
			Mean	18.6	16.9	19.8
			SE	6.20	4.55	3.77
			Median	8.2	9.7	12.8
			Min.	-21	-45	-91
			Max.	74	180	302
		Weeks 9-12	n	20	62	124

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Table 7.32
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS1042718

Treatment: Salmeterol

				A, A	A, C	C, C
AM PEF change	Double-blind	Weeks 9-12	Mean	18.0	18.2	27.5
			SE	5.19	4.21	5.22
			Median	10.2	12.0	16.9
			Min.	-8	-45	-116
			Max.	71	122	418
		Weeks 13-16	n	18	59	120
			Mean	17.7	17.3	25.4
			SE	6.76	4.12	5.37
			Median	14.6	11.8	22.6
			Min.	-36	-51	-110
			Max.	80	104	451
		Overall	n	21	67	137
			Mean	15.6	14.4	22.7
			SE	5.06	3.86	3.77
			Median	8.9	9.8	15.4
			Min.	-13	-83	-106
			Max.	65	113	334
	Wash-out	Overall	n	18	59	118
			Mean	5.7	8.0	14.4
			SE	6.09	4.23	5.44
			Median	6.0	5.5	13.0
			Min.	-40	-64	-139
			Max.	84	87	456

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Table 7.33
Analysis of AM PEF (L/min) - ADRB2 Gene SNP RS1042718

			A/A vs. A/C	A/A vs. C/C	A/C vs. C/C
FSC100/50	Double-blind	Weeks 1-4	p-value	0.871	0.756
			LS Means Diff	-1.9	-3.5
			95% CI for Diff	(-25.0, 21.2)	(-25.8, 18.8)
		Weeks 5-8	p-value	0.692	0.492
			LS Means Diff	-5.1	-8.5
			95% CI for Diff	(-30.4, 20.2)	(-32.9, 15.9)
		Weeks 9-12	p-value	0.487	0.711
			LS Means Diff	9.6	4.9
			95% CI for Diff	(-17.5, 36.6)	(-21.2, 31.0)
		Weeks 13-16	p-value	0.478	0.648
			LS Means Diff	10.2	6.4
			95% CI for Diff	(-18.1, 38.5)	(-21.1, 33.8)
	Wash-out	Overall	p-value	0.815	0.990
			LS Means Diff	2.8	-0.1
			95% CI for Diff	(-21.1, 26.8)	(-23.3, 23.0)
		Overall	p-value	0.278	0.123
			LS Means Diff	-12.2	-16.8
			95% CI for Diff	(-34.2, 9.9)	(-38.1, 4.6)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS1042718. Least squares mean differences are calculated as A/A-A/C, A/A-C/C and A/C-C/C.

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Table 7.33
Analysis of AM PEF (L/min) - ADRB2 Gene SNP RS1042718

				A/A vs. A/C	A/A vs. C/C	A/C vs. C/C
Salmeterol	Double-blind	Weeks 1-4	p-value	0.746	0.486	0.094
			LS Means Diff	2.8	-5.8	-8.6
			95% CI for Diff	(-14.2,19.8)	(-22.3,10.6)	(-18.7,1.5)
		Weeks 5-8	p-value	0.627	0.781	0.713
			LS Means Diff	5.0	2.8	-2.2
			95% CI for Diff	(-15.2,25.2)	(-16.8,22.3)	(-14.2,9.7)
	Weeks 9-12	p-value	0.995	0.415	0.192	
		LS Means Diff	-0.1	-10.0	-9.9	
		95% CI for Diff	(-25.1,25.0)	(-34.2,14.1)	(-24.9,5.0)	
	Weeks 13-16	p-value	0.952	0.613	0.347	
		LS Means Diff	0.8	-6.5	-7.3	
		95% CI for Diff	(-25.5,27.1)	(-31.9,18.9)	(-22.7,8.0)	
	Overall	p-value	0.745	0.539	0.122	
LS Means Diff		3.2	-5.8	-8.9		
95% CI for Diff		(-15.9,22.2)	(-24.2,12.7)	(-20.2,2.4)		
Wash-out	Overall	p-value	0.695	0.380	0.433	
		LS Means Diff	-5.3	-11.6	-6.3	
		95% CI for Diff	(-32.0,21.4)	(-37.5,14.4)	(-22.0,9.5)	

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS1042718. Least squares mean differences are calculated as A/A-A/C, A/A-C/C and A/C-C/C.

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Table 7.34
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS1042719

Treatment: FSC100/50

				C, C	C, G	G, G
-----				-----		
Subjects in treatment				28	99	116
AM PEF (L/min)	Double-blind	Baseline	n	28	98	113
			Mean	375.1	372.4	356.0
			SE	18.34	9.88	7.57
			Median	360.9	367.6	360.0
			Min.	231	183	121
			Max.	663	617	658
		Weeks 1-4	n	28	99	114
			Mean	392.3	395.8	377.7
			SE	16.40	10.55	8.09
			Median	380.6	383.9	373.2
			Min.	232	149	180
			Max.	592	653	703
		Weeks 5-8	n	27	96	109
			Mean	387.0	398.2	385.3
			SE	16.27	11.15	8.66
			Median	373.2	383.8	371.4
			Min.	233	150	222
			Max.	572	678	682
		Weeks 9-12	n	27	92	105
			Mean	395.5	401.2	386.9
			SE	17.16	11.52	9.10
			Median	394.9	391.4	375.3
			Min.	235	152	223
			Max.	576	667	680
		Weeks 13-16	n	27	91	103
			Mean	398.7	405.8	384.3
			SE	17.83	11.43	8.89

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Table 7.34
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS1042719

Treatment: FSC100/50

				C, C	C, G	G, G
AM PEF (L/min)	Double-blind	Weeks 13-16	Median	385.4	388.2	372.8
			Min.	241	158	218
			Max.	587	675	671
		Overall	n	28	99	114
			Mean	397.1	399.3	383.7
			SE	16.84	10.67	8.17
			Median	390.7	386.0	373.2
			Min.	235	152	221
			Max.	582	659	685
	Wash-out	Overall	n	27	88	102
			Mean	379.4	391.1	375.9
			SE	18.27	11.25	8.30
			Median	374.9	382.8	370.6
			Min.	225	144	216
			Max.	600	645	655
AM PEF change	Double-blind	Weeks 1-4	n	28	98	111
			Mean	17.2	25.2	23.8
			SE	8.34	4.71	3.92
			Median	21.8	16.6	15.5
			Min.	-139	-103	-83
			Max.	111	188	172
		Weeks 5-8	n	27	95	106
			Mean	16.7	28.5	31.3
			SE	8.50	5.08	4.49
			Median	16.6	16.0	17.7
			Min.	-113	-85	-72
			Max.	115	199	172
		Weeks 9-12	n	27	91	102

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Table 7.34
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS1042719

Treatment: FSC100/50

				C, C	C, G	G, G
AM PEF change	Double-blind	Weeks 9-12	Mean	25.2	29.7	33.8
			SE	9.93	5.42	4.86
			Median	22.8	19.4	19.9
			Min.	-94	-98	-66
			Max.	159	180	180
		Weeks 13-16	n	27	90	100
			Mean	28.4	31.2	32.3
			SE	10.65	5.67	5.00
			Median	17.3	20.0	16.5
			Min.	-87	-94	-54
			Max.	181	210	167
		Overall	n	28	98	111
			Mean	22.1	28.6	29.5
			SE	8.75	4.72	4.13
			Median	15.7	18.8	16.3
			Min.	-108	-89	-65
			Max.	120	194	166
	Wash-out	Overall	n	27	87	99
			Mean	9.1	17.4	23.0
			SE	6.31	4.08	4.42
			Median	6.2	13.1	12.9
			Min.	-77	-77	-69
			Max.	82	120	157

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Table 7.34
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS1042719

Treatment: Salmeterol

				C, C	C, G	G, G
-----				-----		
Subjects in treatment				25	90	117
AM PEF (L/min)	Double-blind	Baseline	n	25	89	113
			Mean	347.1	372.5	380.2
			SE	16.08	10.14	9.28
			Median	361.7	352.4	361.1
			Min.	220	180	203
			Max.	495	685	658
		Weeks 1-4	n	25	89	113
			Mean	366.5	383.4	400.4
			SE	18.90	10.34	9.76
			Median	351.6	360.4	389.1
			Min.	220	182	210
			Max.	544	675	699
		Weeks 5-8	n	24	85	109
			Mean	373.2	385.3	401.9
			SE	20.45	10.75	10.41
			Median	362.4	366.0	385.3
			Min.	238	183	201
			Max.	588	679	827
		Weeks 9-12	n	24	82	101
			Mean	369.3	384.1	406.0
			SE	19.37	10.13	11.38
			Median	362.4	362.5	387.5
			Min.	237	240	206
			Max.	543	645	943
		Weeks 13-16	n	21	80	97
			Mean	367.0	384.8	408.5
			SE	21.87	10.00	11.66

Table 7.34
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS1042719

Treatment: Salmeterol

				C, C	C, G	G, G
AM PEF (L/min)	Double-blind	Weeks 13-16	Median	344.2	365.5	387.3
			Min.	242	242	212
			Max.	559	630	975
		Overall	n	25	89	113
			Mean	371.1	386.3	403.9
			SE	19.04	10.22	10.21
			Median	359.3	364.9	378.9
			Min.	235	229	211
			Max.	539	677	859
	Wash-out	Overall	n	21	80	95
			Mean	355.8	371.3	396.8
			SE	20.28	9.72	11.93
			Median	364.3	350.0	379.2
			Min.	238	225	211
			Max.	506	603	980
AM PEF change	Double-blind	Weeks 1-4	n	25	89	111
			Mean	19.4	10.9	19.8
			SE	6.47	3.45	3.52
			Median	5.7	6.9	13.0
			Min.	-21	-83	-106
			Max.	135	119	174
		Weeks 5-8	n	24	85	107
			Mean	28.6	15.4	19.4
			SE	8.57	3.56	4.30
			Median	14.3	11.0	10.9
			Min.	-21	-45	-91
			Max.	180	133	302
		Weeks 9-12	n	24	82	100

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Table 7.34
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS1042719

Treatment: Salmeterol

				C, C	C, G	G, G
AM PEF change	Double-blind	Weeks 9-12	Mean	24.8	17.8	28.4
			SE	6.35	3.67	6.19
			Median	11.6	12.0	16.9
			Min.	-8	-45	-116
			Max.	122	126	418
		Weeks 13-16	n	21	80	96
			Mean	24.6	17.2	26.1
			SE	7.43	3.68	6.41
			Median	15.2	12.1	22.9
			Min.	-36	-62	-110
			Max.	104	116	451
		Overall	n	25	89	111
			Mean	23.9	13.7	23.2
			SE	6.32	3.24	4.38
			Median	13.8	9.8	15.4
			Min.	-13	-83	-106
			Max.	113	124	334
	Wash-out	Overall	n	21	80	94
			Mean	13.3	6.9	15.3
			SE	6.83	3.48	6.63
			Median	6.8	5.2	13.6
			Min.	-40	-64	-139
			Max.	84	110	456

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Table 7.35
Analysis of AM PEF (L/min) - ADRB2 Gene SNP RS1042719

				C/C vs. C/G	C/C vs. G/G	C/G vs. G/G
FSC100/50	Double-blind	Weeks 1-4	p-value	0.656	0.907	0.611
			LS Means Diff	-4.1	-1.1	3.0
			95% CI for Diff	(-22.3, 14.1)	(-19.2, 17.0)	(-8.7, 14.8)
		Weeks 5-8	p-value	0.450	0.356	0.802
			LS Means Diff	-7.8	-9.4	-1.7
	Wash-out	Weeks 9-12	95% CI for Diff	(-28.0, 12.4)	(-29.5, 10.7)	(-14.7, 11.4)
			p-value	0.955	0.782	0.739
		Weeks 13-16	LS Means Diff	-0.6	-3.0	-2.4
			95% CI for Diff	(-22.3, 21.0)	(-24.6, 18.5)	(-16.6, 11.8)
			p-value	0.886	0.794	0.860
FSC100/50	Double-blind	Weeks 1-4	LS Means Diff	1.6	2.9	1.3
			95% CI for Diff	(-20.6, 23.8)	(-19.2, 25.0)	(-13.4, 16.1)
			p-value	0.800	0.848	0.923
		Weeks 5-8	LS Means Diff	-2.4	-1.8	0.6
			95% CI for Diff	(-21.3, 16.4)	(-20.6, 16.9)	(-11.6, 12.8)
	Wash-out	Weeks 9-12	p-value	0.509	0.285	0.547
			LS Means Diff	-5.8	-9.4	-3.5
			95% CI for Diff	(-23.2, 11.5)	(-26.6, 7.9)	(-15.1, 8.0)
		Weeks 13-16	p-value	0.886	0.794	0.860
			LS Means Diff	1.6	2.9	1.3
			95% CI for Diff	(-20.6, 23.8)	(-19.2, 25.0)	(-13.4, 16.1)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS1042719. Least squares mean differences are calculated as C/C-C/G, C/C-G/G and C/G-G/G.

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Table 7.35
Analysis of AM PEF (L/min) - ADRB2 Gene SNP RS1042719

				C/C vs. C/G	C/C vs. G/G	C/G vs. G/G
Salmeterol	Double-blind	Weeks 1-4	p-value	0.253	0.849	0.032
			LS Means Diff	9.0	-1.5	-10.5
			95% CI for Diff	(-6.5,24.5)	(-16.8,13.8)	(-20.0,-0.9)
		Weeks 5-8	p-value	0.123	0.271	0.460
			LS Means Diff	14.4	10.1	-4.3
			95% CI for Diff	(-3.9,32.7)	(-7.9,28.2)	(-15.6,7.1)
		Weeks 9-12	p-value	0.680	0.513	0.094
			LS Means Diff	4.8	-7.5	-12.2
			95% CI for Diff	(-18.0,27.6)	(-30.0,15.0)	(-26.6,2.1)
		Weeks 13-16	p-value	0.730	0.701	0.236
			LS Means Diff	4.2	-4.6	-8.9
			95% CI for Diff	(-19.8,28.2)	(-28.4,19.2)	(-23.5,5.8)
		Overall	p-value	0.239	0.938	0.043
	LS Means Diff		10.4	-0.7	-11.1	
95% CI for Diff	(-7.0,27.8)		(-17.8,16.5)	(-21.8,-0.4)		
Wash-out	Overall	p-value	0.968	0.563	0.317	
		LS Means Diff	0.5	-7.2	-7.7	
		95% CI for Diff	(-24.0,24.9)	(-31.5,17.2)	(-22.7,7.4)	

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS1042719. Least squares mean differences are calculated as C/C-C/G, C/C-G/G and C/G-G/G.

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Table 7.36
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS17778257

Treatment: FSC100/50

				A, A	A, T	T, T
-----				-----		
Subjects in treatment				100	88	55
AM PEF (L/min)	Double-blind	Baseline	n	99	87	53
			Mean	363.4	375.2	350.8
			SE	8.73	9.72	12.90
			Median	363.0	378.7	343.9
			Min.	121	183	187
			Max.	663	614	658
		Weeks 1-4	n	98	88	55
			Mean	381.7	395.9	381.4
			SE	8.56	10.94	13.24
			Median	382.0	391.5	365.7
			Min.	214	149	180
			Max.	634	653	703
		Weeks 5-8	n	94	86	52
			Mean	385.5	402.1	381.9
			SE	9.41	11.52	13.01
			Median	374.8	386.6	369.6
			Min.	233	150	222
			Max.	678	664	682
		Weeks 9-12	n	89	86	49
			Mean	388.8	399.7	392.6
			SE	10.25	11.48	13.66
			Median	384.1	380.2	379.1
			Min.	235	152	223
			Max.	667	643	680
		Weeks 13-16	n	88	84	49
			Mean	391.8	399.9	392.0
			SE	9.93	11.67	13.65

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Table 7.36
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS17778257

Treatment: FSC100/50

				A, A	A, T	T, T
AM PEF (L/min)	Double-blind	Weeks 13-16	Median	386.4	378.8	372.8
			Min.	241	158	218
			Max.	648	675	671
		Overall	n	98	88	55
			Mean	386.9	400.0	387.0
			SE	9.00	11.05	12.72
			Median	382.3	384.6	371.9
			Min.	235	152	221
			Max.	647	659	685
	Wash-out	Overall	n	87	81	49
			Mean	379.0	388.3	379.1
			SE	9.67	11.14	13.33
			Median	374.9	375.4	369.0
			Min.	225	144	216
			Max.	645	621	655
AM PEF change	Double-blind	Weeks 1-4	n	97	87	53
			Mean	20.6	20.5	34.3
			SE	4.32	5.02	5.48
			Median	13.0	14.4	26.1
			Min.	-139	-103	-28
			Max.	126	188	157
		Weeks 5-8	n	93	85	50
			Mean	25.3	27.5	35.8
			SE	4.70	5.49	6.46
			Median	11.5	18.7	27.0
			Min.	-113	-85	-46
			Max.	149	199	138
		Weeks 9-12	n	88	85	47

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Table 7.36
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS17778257

Treatment: FSC100/50

				A, A	A, T	T, T
-----				-----		
AM PEF change	Double-blind	Weeks 9-12	Mean	27.8	25.3	47.6
			SE	5.42	5.48	6.77
			Median	14.9	13.2	43.3
			Min.	-94	-98	-66
			Max.	180	180	166
		Weeks 13-16	n	87	83	47
			Mean	27.7	26.6	46.4
			SE	5.48	6.08	6.62
			Median	12.8	13.3	37.4
			Min.	-87	-94	-44
			Max.	181	210	154
		Overall	n	97	87	53
			Mean	25.5	24.8	38.7
			SE	4.47	5.10	5.75
			Median	14.9	12.8	30.0
			Min.	-108	-89	-46
			Max.	153	194	140
	Wash-out	Overall	n	86	80	47
			Mean	14.1	15.8	33.3
			SE	3.86	4.78	6.10
			Median	5.6	10.2	30.3
			Min.	-77	-70	-56
			Max.	157	147	123

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Table 7.36
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS17778257

Treatment: Salmeterol

				A, A	A, T	T, T
-----				-----		
Subjects in treatment				100	86	46
AM PEF (L/min)	Double-blind	Baseline	n	99	83	45
			Mean	365.3	363.3	410.7
			SE	9.23	10.61	14.27
			Median	351.3	335.6	389.9
			Min.	180	205	213
			Max.	628	685	658
		Weeks 1-4	n	99	84	44
			Mean	377.6	383.8	429.8
			SE	9.03	11.53	15.92
			Median	359.7	347.0	418.3
			Min.	182	210	223
			Max.	667	699	663
		Weeks 5-8	n	94	82	42
			Mean	377.9	389.7	429.4
			SE	9.44	12.52	16.26
			Median	364.5	359.7	409.3
			Min.	183	211	221
			Max.	652	827	643
		Weeks 9-12	n	91	76	40
			Mean	377.9	392.7	428.4
			SE	9.56	13.06	16.82
			Median	365.6	368.5	405.7
			Min.	206	209	242
			Max.	645	943	640
		Weeks 13-16	n	87	71	40
			Mean	378.5	397.7	423.9
			SE	9.67	13.82	16.68

Table 7.36
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS17778257

Treatment: Salmeterol

				A, A	A, T	T, T
AM PEF (L/min)	Double-blind	Weeks 13-16	Median	362.5	371.1	406.1
			Min.	242	212	246
			Max.	630	975	628
		Overall	n	99	84	44
			Mean	378.6	388.9	435.2
			SE	8.97	12.15	15.84
			Median	363.9	360.0	426.3
			Min.	216	211	238
			Max.	649	859	653
	Wash-out	Overall	n	87	70	39
			Mean	369.4	378.7	416.1
			SE	9.42	14.06	16.55
			Median	354.5	351.5	396.5
			Min.	238	211	245
			Max.	603	980	625
AM PEF change	Double-blind	Weeks 1-4	n	99	82	44
			Mean	12.3	19.5	19.1
			SE	2.98	4.55	5.02
			Median	8.6	4.9	17.4
			Min.	-83	-45	-106
			Max.	90	174	119
		Weeks 5-8	n	94	80	42
			Mean	13.0	23.0	24.1
			SE	3.08	5.56	5.89
			Median	8.4	11.6	15.9
			Min.	-87	-55	-91
			Max.	102	302	133
		Weeks 9-12	n	91	75	40

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Table 7.36
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS17778257

Treatment: Salmeterol

				A, A	A, T	T, T
AM PEF change	Double-blind	Weeks 9-12	Mean	16.1	29.4	30.5
			SE	3.29	6.73	9.72
			Median	11.9	20.3	16.4
			Min.	-75	-45	-116
			Max.	124	418	319
		Weeks 13-16	n	87	70	40
			Mean	14.2	30.3	26.0
			SE	3.80	7.47	7.93
			Median	14.1	26.8	25.5
			Min.	-95	-92	-110
			Max.	124	451	186
		Overall	n	99	82	44
			Mean	13.2	24.5	24.6
			SE	2.90	5.33	6.02
			Median	9.9	14.4	19.5
			Min.	-83	-46	-106
			Max.	107	334	152
	Wash-out	Overall	n	87	69	39
			Mean	5.0	17.7	15.8
			SE	3.83	7.77	7.52
			Median	5.9	8.6	18.8
			Min.	-102	-98	-139
			Max.	91	456	128

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Table 7.37
Analysis of AM PEF (L/min) - ADRB2 Gene SNP RS17778257

				A/A vs. A/T	A/A vs. T/T	A/T vs. T/T
FSC100/50	Double-blind	Weeks 1-4	p-value	0.804	0.173	0.121
			LS Means Diff	1.6	-10.1	-11.6
			95% CI for Diff	(-10.9, 14.0)	(-24.6, 4.4)	(-26.4, 3.1)
		Weeks 5-8	p-value	0.922	0.331	0.380
			LS Means Diff	-0.7	-8.1	-7.4
	Wash-out	Weeks 9-12	95% CI for Diff	(-14.6, 13.2)	(-24.4, 8.3)	(-23.9, 9.2)
			p-value	0.530	0.067	0.019
		Weeks 13-16	LS Means Diff	4.7	-16.6	-21.4
			95% CI for Diff	(-10.1, 19.6)	(-34.5, 1.2)	(-39.2, -3.6)
			p-value	0.655	0.101	0.044
FSC100/50	Double-blind	Weeks 1-4	LS Means Diff	3.5	-15.4	-18.9
			95% CI for Diff	(-11.9, 18.9)	(-33.8, 3.0)	(-37.2, -0.5)
		Weeks 5-8	p-value	0.732	0.160	0.095
			LS Means Diff	2.2	-10.8	-13.0
			95% CI for Diff	(-10.7, 15.2)	(-25.8, 4.3)	(-28.3, 2.3)
	Wash-out	Weeks 9-12	p-value	0.876	0.013	0.019
			LS Means Diff	-1.0	-18.2	-17.2
			95% CI for Diff	(-13.1, 11.2)	(-32.5, -3.8)	(-31.5, -2.9)
		Weeks 13-16	p-value	0.876	0.013	0.019
			LS Means Diff	-1.0	-18.2	-17.2
			95% CI for Diff	(-13.1, 11.2)	(-32.5, -3.8)	(-31.5, -2.9)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS17778257. Least squares mean differences are calculated as A/A-A/T, A/A-T/T and A/T-T/T.

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Table 7.37
Analysis of AM PEF (L/min) - ADRB2 Gene SNP RS17778257

				A/A vs. A/T	A/A vs. T/T	A/T vs. T/T
Salmeterol	Double-blind	Weeks 1-4	p-value	0.203	0.197	0.796
			LS Means Diff	-6.5	-8.2	-1.7
			95% CI for Diff	(-16.6,3.5)	(-20.7,4.3)	(-14.3,11.0)
		Weeks 5-8	p-value	0.230	0.205	0.767
			LS Means Diff	-7.3	-9.5	-2.2
			95% CI for Diff	(-19.2,4.6)	(-24.2,5.2)	(-17.0,12.6)
		Weeks 9-12	p-value	0.109	0.123	0.811
			LS Means Diff	-12.3	-14.5	-2.3
			95% CI for Diff	(-27.3,2.8)	(-33.1,4.0)	(-21.0,16.4)
		Weeks 13-16	p-value	0.101	0.234	0.862
			LS Means Diff	-13.0	-11.3	1.7
			95% CI for Diff	(-28.5,2.5)	(-30.0,7.4)	(-17.3,20.7)
		Overall	p-value	0.082	0.100	0.810
	LS Means Diff		-10.0	-11.7	-1.7	
95% CI for Diff	(-21.2,1.3)		(-25.6,2.2)	(-15.8,12.4)		
Wash-out	Overall	p-value	0.247	0.339	0.996	
		LS Means Diff	-9.4	-9.3	0.0	
		95% CI for Diff	(-25.4,6.6)	(-28.6,9.9)	(-19.6,19.7)	

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS17778257. Least squares mean differences are calculated as A/A-A/T, A/A-T/T and A/T-T/T.

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Table 7.38
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS11168070

Treatment: FSC100/50

				C, C	C, G	G, G
-----				-----		
Subjects in treatment				147	73	23
AM PEF (L/min)	Double-blind	Baseline	n	144	72	23
			Mean	357.3	385.5	348.5
			SE	7.88	10.15	12.23
			Median	354.1	386.3	365.6
			Min.	121	222	213
			Max.	658	663	448
		Weeks 1-4	n	146	73	22
			Mean	381.5	403.1	368.6
			SE	8.25	10.84	10.87
			Median	374.4	403.3	381.4
			Min.	149	214	279
			Max.	703	634	437
		Weeks 5-8	n	142	70	20
			Mean	384.8	409.6	368.2
			SE	8.47	11.90	11.44
			Median	369.5	404.4	374.4
			Min.	150	254	283
			Max.	682	678	445
		Weeks 9-12	n	138	67	19
			Mean	388.8	411.1	369.5
			SE	8.68	12.77	12.05
			Median	373.9	402.9	391.1
			Min.	152	239	282
			Max.	680	667	445
		Weeks 13-16	n	135	67	19
			Mean	389.8	412.3	369.9
			SE	8.79	12.28	11.73

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Table 7.38
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS11168070

Treatment: FSC100/50

				C, C	C, G	G, G
AM PEF (L/min)	Double-blind	Weeks 13-16	Median	372.8	403.9	388.2
			Min.	158	242	283
			Max.	675	648	444
		Overall	n	146	73	22
			Mean	386.5	408.5	370.4
			SE	8.22	11.36	10.56
			Median	373.4	399.4	380.5
			Min.	152	241	282
			Max.	685	647	443
	Wash-out	Overall	n	132	67	18
			Mean	375.6	402.0	360.4
			SE	8.40	11.81	12.45
			Median	365.7	391.7	374.9
			Min.	144	226	262
			Max.	655	645	440
AM PEF change	Double-blind	Weeks 1-4	n	143	72	22
			Mean	25.7	20.2	21.2
			SE	3.68	5.34	8.12
			Median	18.9	14.5	9.8
			Min.	-103	-139	-36
			Max.	188	172	126
		Weeks 5-8	n	139	69	20
			Mean	29.6	27.7	22.6
			SE	4.08	5.87	8.75
			Median	17.0	19.8	10.4
			Min.	-85	-113	-10
			Max.	199	172	148
		Weeks 9-12	n	135	66	19

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Table 7.38
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS11168070

Treatment: FSC100/50

				C, C	C, G	G, G
AM PEF change	Double-blind	Weeks 9-12	Mean	34.1	27.6	21.5
			SE	4.40	6.28	9.71
			Median	23.0	17.4	6.4
			Min.	-98	-94	-5
			Max.	180	180	162
		Weeks 13-16	n	132	66	19
			Mean	35.4	26.0	22.0
			SE	4.64	6.32	10.23
			Median	20.4	15.5	8.7
			Min.	-94	-87	-12
			Max.	210	167	175
		Overall	n	143	72	22
			Mean	30.4	25.4	23.0
			SE	3.85	5.33	8.35
			Median	18.7	14.7	14.9
			Min.	-89	-108	-16
			Max.	194	166	153
	Wash-out	Overall	n	129	66	18
			Mean	22.0	16.0	8.6
			SE	3.65	5.20	4.58
			Median	13.4	12.1	0.9
			Min.	-70	-77	-15
			Max.	157	147	49

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Table 7.38
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS11168070

Treatment: Salmeterol

				C, C	C, G	G, G
-----				-----		
Subjects in treatment				136	71	25
AM PEF (L/min)	Double-blind	Baseline	n	132	70	25
			Mean	375.2	365.7	387.2
			SE	8.69	11.45	14.39
			Median	365.2	335.6	394.3
			Min.	180	226	228
			Max.	685	628	533
		Weeks 1-4	n	132	70	25
			Mean	388.6	387.4	404.7
			SE	9.25	11.73	15.00
			Median	371.7	360.0	394.9
			Min.	182	232	266
			Max.	675	699	563
		Weeks 5-8	n	128	67	23
			Mean	390.8	388.7	411.1
			SE	9.45	13.29	14.74
			Median	377.7	356.7	412.4
			Min.	183	228	246
			Max.	679	827	561
		Weeks 9-12	n	121	66	20
			Mean	389.9	395.0	406.2
			SE	9.30	14.24	16.47
			Median	376.9	365.4	401.8
			Min.	206	231	251
			Max.	651	943	566
		Weeks 13-16	n	114	64	20
			Mean	392.9	395.2	402.0
			SE	9.34	14.93	17.54

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Table 7.38
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS11168070

Treatment: Salmeterol

				C, C	C, G	G, G
AM PEF (L/min)	Double-blind	Weeks 13-16	Median	372.2	364.8	387.9
			Min.	212	226	242
			Max.	667	975	548
		Overall	n	132	70	25
			Mean	392.3	391.2	405.0
			SE	9.15	12.85	15.00
			Median	375.4	361.6	396.0
			Min.	211	229	251
			Max.	677	859	560
	Wash-out	Overall	n	112	64	20
			Mean	381.0	379.5	395.9
			SE	9.24	15.05	16.73
			Median	368.8	343.9	378.8
			Min.	211	212	267
			Max.	664	980	540
AM PEF change	Double-blind	Weeks 1-4	n	131	69	25
			Mean	14.5	19.1	17.6
			SE	2.78	5.14	5.46
			Median	8.6	14.4	9.8
			Min.	-106	-83	-35
			Max.	135	174	76
		Weeks 5-8	n	127	66	23
			Mean	18.4	21.2	14.6
			SE	3.23	5.91	7.28
			Median	8.6	13.6	14.6
			Min.	-91	-87	-42
			Max.	180	302	102
		Weeks 9-12	n	121	65	20

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Table 7.38
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS11168070

Treatment: Salmeterol

				C, C	C, G	G, G
AM PEF change	Double-blind	Weeks 9-12	Mean	21.8	28.7	19.5
			SE	3.95	7.59	8.53
			Median	12.0	19.8	17.5
			Min.	-116	-75	-43
			Max.	319	418	124
		Weeks 13-16	n	114	63	20
			Mean	20.6	27.6	15.3
			SE	3.77	8.24	9.61
			Median	16.7	20.2	15.6
			Min.	-110	-92	-44
			Max.	186	451	124
		Overall	n	131	69	25
			Mean	18.2	22.8	17.8
			SE	2.90	6.12	6.57
			Median	12.9	14.5	15.4
			Min.	-106	-83	-38
			Max.	152	334	107
	Wash-out	Overall	n	112	63	20
			Mean	11.5	12.7	9.2
			SE	3.54	8.73	8.86
			Median	9.5	4.3	8.3
			Min.	-139	-102	-78
			Max.	128	456	81

Table 7.39
Analysis of AM PEF (L/min) - ADRB2 Gene SNP RS11168070

			C/C vs. C/G	C/C vs. G/G	C/G vs. G/G
FSC100/50	Double-blind	Weeks 1-4	p-value	0.213	0.136
			LS Means Diff	7.9	15.1
			95% CI for Diff	(-4.6, 20.4)	(-4.8, 35.0)
		Weeks 5-8	p-value	0.537	0.140
			LS Means Diff	4.4	17.0
			95% CI for Diff	(-9.6, 18.3)	(-5.6, 39.7)
		Weeks 9-12	p-value	0.258	0.066
			LS Means Diff	8.7	23.0
			95% CI for Diff	(-6.4, 23.7)	(-1.5, 47.6)
		Weeks 13-16	p-value	0.169	0.059
FSC100/50	Double-blind		LS Means Diff	10.8	24.3
			95% CI for Diff	(-4.6, 26.3)	(-0.9, 49.4)
		Overall	p-value	0.259	0.093
			LS Means Diff	7.4	17.7
			95% CI for Diff	(-5.5, 20.4)	(-3.0, 38.3)
	Wash-out	Overall	p-value	0.334	0.056
			LS Means Diff	6.0	19.6
			95% CI for Diff	(-6.2, 18.1)	(-0.5, 39.6)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS11168070. Least squares mean differences are calculated as C/C-C/G, C/C-G/G and C/G-G/G.

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Table 7.39
Analysis of AM PEF (L/min) - ADRB2 Gene SNP RS11168070

				C/C vs. C/G	C/C vs. G/G	C/G vs. G/G
Salmeterol	Double-blind	Weeks 1-4	p-value	0.927	0.814	0.867
			LS Means Diff	0.5	1.8	1.3
			95% CI for Diff	(-10.0,11.0)	(-13.4,17.1)	(-14.3,17.0)
		Weeks 5-8	p-value	0.737	0.289	0.419
			LS Means Diff	2.1	9.8	7.7
	95% CI for Diff		(-10.3,14.5)	(-8.4,28.0)	(-11.0,26.4)	
	Weeks 9-12	p-value	0.758	0.551	0.434	
		LS Means Diff	-2.4	7.3	9.7	
		95% CI for Diff	(-18.0,13.1)	(-16.8,31.5)	(-14.8,34.2)	
	Weeks 13-16	p-value	0.681	0.435	0.301	
		LS Means Diff	-3.3	9.6	12.9	
95% CI for Diff		(-19.3,12.6)	(-14.6,33.8)	(-11.7,37.5)		
Wash-out	Overall	p-value	0.913	0.513	0.572	
		LS Means Diff	0.7	5.7	5.0	
		95% CI for Diff	(-11.1,12.4)	(-11.4,22.8)	(-12.5,22.5)	
		p-value	0.872	0.850	0.770	
		LS Means Diff	-1.3	2.4	3.7	
95% CI for Diff	(-17.7,15.0)	(-22.4,27.2)	(-21.4,28.8)			

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS11168070. Least squares mean differences are calculated as C/C-C/G, C/C-G/G and C/G-G/G.

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Table 7.40
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS9325122

Treatment: FSC100/50

				C, C	C, T	T, T
-----				-----		
Subjects in treatment				23	65	145
AM PEF (L/min)	Double-blind	Baseline	n	23	64	142
			Mean	349.8	389.9	357.8
			SE	11.06	10.82	7.97
			Median	365.6	388.4	355.0
			Min.	265	222	121
			Max.	448	663	658
		Weeks 1-4	n	22	65	144
			Mean	366.2	404.9	381.9
			SE	11.19	11.30	8.34
			Median	381.4	404.0	374.4
			Min.	279	214	149
			Max.	437	634	703
		Weeks 5-8	n	20	62	140
			Mean	365.0	411.6	385.1
			SE	11.89	12.62	8.55
			Median	374.4	405.7	369.5
			Min.	283	254	150
			Max.	445	678	682
		Weeks 9-12	n	19	59	136
			Mean	364.8	413.0	389.5
			SE	12.64	13.61	8.78
			Median	391.1	407.6	373.9
			Min.	282	239	152
			Max.	445	667	680
		Weeks 13-16	n	19	60	133
			Mean	365.7	413.0	390.5
			SE	12.02	13.10	8.88

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Table 7.40
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS9325122

Treatment: FSC100/50

				C, C	C, T	T, T
AM PEF (L/min)	Double-blind	Weeks 13-16	Median	385.9	405.9	372.8
			Min.	283	242	158
			Max.	444	648	675
		Overall	n	22	65	144
			Mean	367.2	410.5	387.0
			SE	10.97	11.99	8.30
			Median	380.5	407.1	373.4
			Min.	282	241	152
			Max.	443	647	685
	Wash-out	Overall	n	18	60	130
			Mean	361.6	404.3	376.3
			SE	11.75	12.73	8.51
			Median	374.9	392.8	365.7
			Min.	289	226	144
			Max.	440	645	655
AM PEF change	Double-blind	Weeks 1-4	n	22	64	141
			Mean	17.5	18.0	25.6
			SE	6.48	5.39	3.72
			Median	9.8	15.3	18.9
			Min.	-36	-139	-103
			Max.	118	109	188
		Weeks 5-8	n	20	61	137
			Mean	18.0	25.5	29.4
			SE	5.90	5.97	4.10
			Median	10.4	18.3	17.0
			Min.	-10	-113	-85
			Max.	105	153	199
		Weeks 9-12	n	19	58	133

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Table 7.40
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS9325122

Treatment: FSC100/50

				C, C	C, T	T, T
-----				-----		
AM PEF change	Double-blind	Weeks 9-12	Mean	15.4	24.8	34.3
			SE	5.86	6.40	4.45
			Median	6.4	13.3	23.0
			Min.	-5	-94	-98
			Max.	105	166	180
		Weeks 13-16	n	19	59	130
			Mean	16.2	23.1	35.6
			SE	6.05	6.50	4.70
			Median	8.7	13.3	20.4
			Min.	-12	-87	-94
			Max.	97	167	210
		Overall	n	22	64	141
			Mean	18.5	23.2	30.4
			SE	5.72	5.36	3.89
			Median	15.1	14.3	18.7
			Min.	-16	-108	-89
			Max.	106	146	194
	Wash-out	Overall	n	18	59	127
			Mean	8.3	14.8	22.1
			SE	4.24	5.65	3.70
			Median	0.9	10.3	13.4
			Min.	-15	-77	-70
			Max.	46	147	157

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Table 7.40
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS9325122

Treatment: Salmeterol

				C, C	C, T	T, T
-----				-----		
Subjects in treatment				27	63	129
AM PEF (L/min)	Double-blind	Baseline	n	26	63	125
			Mean	387.1	367.9	378.3
			SE	13.78	12.46	8.90
			Median	390.9	335.7	366.7
			Min.	228	226	180
			Max.	533	628	685
		Weeks 1-4	n	27	62	125
			Mean	411.9	383.8	393.0
			SE	14.91	11.86	9.44
			Median	398.1	360.0	376.4
			Min.	266	232	182
			Max.	563	667	675
		Weeks 5-8	n	25	60	121
			Mean	419.7	380.6	393.6
			SE	15.09	12.42	9.74
			Median	414.9	352.1	378.3
			Min.	246	228	183
			Max.	568	652	679
		Weeks 9-12	n	23	58	114
			Mean	420.1	383.6	392.6
			SE	16.34	12.45	9.60
			Median	411.1	361.9	377.7
			Min.	251	231	206
			Max.	566	645	651
		Weeks 13-16	n	23	57	108
			Mean	416.6	381.7	394.4
			SE	17.34	12.61	9.66

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Table 7.40
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS9325122

Treatment: Salmeterol

				C, C	C, T	T, T
AM PEF (L/min)	Double-blind	Weeks 13-16	Median	408.4	351.8	372.2
			Min.	242	226	212
			Max.	555	630	667
		Overall	n	27	62	125
			Mean	413.1	384.7	395.7
			SE	15.12	11.88	9.39
			Median	407.5	361.5	376.3
			Min.	251	229	211
			Max.	560	649	677
	Wash-out	Overall	n	23	57	106
			Mean	407.0	365.6	382.3
			SE	16.09	12.57	9.58
			Median	401.9	339.2	368.8
			Min.	267	212	211
			Max.	540	603	664
AM PEF change	Double-blind	Weeks 1-4	n	26	62	124
			Mean	19.9	15.4	15.8
			SE	5.57	4.97	2.81
			Median	11.4	12.8	9.3
			Min.	-35	-83	-106
			Max.	76	174	135
		Weeks 5-8	n	24	60	120
			Mean	17.6	14.4	18.5
			SE	7.41	4.21	3.33
			Median	15.6	10.3	8.6
			Min.	-42	-87	-91
			Max.	102	113	180
		Weeks 9-12	n	22	58	114

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Table 7.40
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS9325122

Treatment: Salmeterol

				C, C	C, T	T, T
AM PEF change	Double-blind	Weeks 9-12	Mean	22.0	20.9	21.8
			SE	8.44	4.84	4.13
			Median	17.5	16.2	12.8
			Min.	-43	-75	-116
			Max.	124	118	319
		Weeks 13-16	n	22	57	108
			Mean	17.9	18.8	19.9
			SE	9.46	4.81	3.91
			Median	15.6	16.5	15.7
			Min.	-44	-92	-110
			Max.	124	101	186
		Overall	n	26	62	124
			Mean	20.7	16.4	18.5
			SE	6.74	4.30	2.98
			Median	16.1	13.6	12.7
			Min.	-38	-83	-106
			Max.	107	102	152
	Wash-out	Overall	n	22	57	106
			Mean	10.9	2.7	10.8
			SE	8.14	5.43	3.64
			Median	12.7	0.0	9.4
			Min.	-78	-102	-139
			Max.	81	94	128

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Table 7.41
Analysis of AM PEF (L/min) - ADRB2 Gene SNP RS9325122

				C/C vs. C/T	C/C vs. T/T	C/T vs. T/T
FSC100/50	Double-blind	Weeks 1-4	p-value	0.424	0.053	0.096
			LS Means Diff	-8.3	-19.1	-10.8
			95% CI for Diff	(-28.7,12.1)	(-38.5,0.3)	(-23.6,1.9)
		Weeks 5-8	p-value	0.207	0.055	0.357
			LS Means Diff	-14.9	-21.6	-6.7
			95% CI for Diff	(-38.1,8.3)	(-43.6,0.4)	(-20.9,7.6)
		Weeks 9-12	p-value	0.174	0.015	0.117
			LS Means Diff	-17.5	-29.9	-12.3
			95% CI for Diff	(-42.9,7.8)	(-53.8,-6.0)	(-27.8,3.1)
		Weeks 13-16	p-value	0.223	0.015	0.070
			LS Means Diff	-16.1	-30.8	-14.7
			95% CI for Diff	(-42.1,9.9)	(-55.4,-6.2)	(-30.5,1.2)
	Overall	p-value	0.250	0.027	0.124	
		LS Means Diff	-12.4	-22.7	-10.3	
95% CI for Diff		(-33.5,8.8)	(-42.7,-2.6)	(-23.5,2.9)		
Wash-out	Overall	p-value	0.227	0.055	0.299	
		LS Means Diff	-13.2	-20.0	-6.8	
		95% CI for Diff	(-34.7,8.3)	(-40.4,0.4)	(-19.7,6.1)	

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS9325122. Least squares mean differences are calculated as C/C-C/T, C/C-T/T and C/T-T/T.

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Table 7.41
Analysis of AM PEF (L/min) - ADRB2 Gene SNP RS9325122

				C/C vs. C/T	C/C vs. T/T	C/T vs. T/T
Salmeterol	Double-blind	Weeks 1-4	p-value	0.661	0.917	0.438
			LS Means Diff	3.3	-0.8	-4.1
			95% CI for Diff	(-11.6,18.3)	(-15.4,13.8)	(-14.5,6.3)
		Weeks 5-8	p-value	0.825	0.414	0.143
			LS Means Diff	1.8	-6.7	-8.5
	95% CI for Diff		(-14.6,18.3)	(-22.7,9.4)	(-19.9,2.9)	
	Weeks 9-12	p-value	0.975	0.670	0.510	
		LS Means Diff	0.3	-4.3	-4.6	
		95% CI for Diff	(-19.7,20.4)	(-24.0,15.4)	(-18.3,9.1)	
	Weeks 13-16	p-value	0.850	0.519	0.521	
LS Means Diff		-1.8	-6.1	-4.3		
95% CI for Diff		(-20.8,17.1)	(-24.7,12.5)	(-17.4,8.8)		
Wash-out	Overall	p-value	0.701	0.680	0.260	
		LS Means Diff	2.9	-3.0	-5.9	
		95% CI for Diff	(-11.9,17.7)	(-17.5,11.4)	(-16.2,4.4)	
	Overall	p-value	0.369	0.945	0.232	
		LS Means Diff	8.6	0.6	-8.0	
95% CI for Diff		(-10.3,27.5)	(-17.9,19.2)	(-21.1,5.2)		

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS9325122. Least squares mean differences are calculated as C/C-C/T, C/C-T/T and C/T-T/T.

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Table 7.42
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS1800888

Treatment: FSC100/50

				C, C	C, T
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Subjects in treatment				240	3
AM PEF (L/min)	Double-blind	Baseline	n	236	3
			Mean	365.1	351.1
			SE	5.88	38.26
			Median	360.0	388.7
			Min.	121	275
			Max.	663	390
		Weeks 1-4	n	238	3
			Mean	387.2	358.3
			SE	6.16	22.28
			Median	380.4	378.9
			Min.	149	314
			Max.	703	382
		Weeks 5-8	n	229	3
			Mean	391.3	356.1
			SE	6.50	26.45
			Median	373.9	381.4
			Min.	150	303
			Max.	682	384
		Weeks 9-12	n	221	3
			Mean	394.2	363.1
			SE	6.77	17.91
			Median	383.0	377.9
			Min.	152	328
			Max.	680	384
		Weeks 13-16	n	219	2
			Mean	395.0	385.2
			SE	6.70	3.70

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Table 7.42
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS1800888

Treatment: FSC100/50

				C, C	C, T
AM PEF (L/min)	Double-blind	Weeks 13-16	Median	379.3	385.2
			Min.	158	381
			Max.	675	389
		Overall	n	238	3
			Mean	392.1	359.8
			SE	6.23	22.48
			Median	379.9	381.5
			Min.	152	315
			Max.	685	383
	Wash-out	Overall	n	215	2
			Mean	382.5	384.6
			SE	6.47	0.02
			Median	372.9	384.6
			Min.	144	385
			Max.	655	385
AM PEF change	Double-blind	Weeks 1-4	n	234	3
			Mean	23.8	7.2
			SE	2.87	16.06
			Median	16.6	-6.5
			Min.	-139	-11
			Max.	188	39
		Weeks 5-8	n	225	3
			Mean	28.7	5.0
			SE	3.17	11.87
			Median	16.9	-5.0
			Min.	-113	-9
			Max.	199	29
		Weeks 9-12	n	217	3

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Protocol: SFA100062

Population: ITT Excluding Investigator

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Table 7.42
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS1800888

Treatment: FSC100/50

CG100/00

			C, C	C, T	
AM PEF change	Double-blind	Weeks 9-12	Mean	31.3	12.0
			SE	3.43	20.49
			Median	20.0	-5.9
			Min.	-98	-11
			Max.	180	53
		Weeks 13-16	n	215	2
			Mean	31.7	-4.2
			SE	3.56	4.35
			Median	18.5	-4.2
			Min.	-94	-9
			Max.	210	0
		Overall	n	234	3
			Mean	28.5	8.7
			SE	2.96	15.81
			Median	16.8	-5.6
			Min.	-108	-9
			Max.	194	40
	Wash-out	Overall	n	211	2
			Mean	19.2	-4.8
			SE	2.79	0.62
			Median	12.1	-4.8
			Min.	-77	-5
			Max.	157	-4

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Table 7.42
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS1800888

Treatment: Salmeterol

				C, C	C, T
-----				-----	
Subjects in treatment				226	6
AM PEF (L/min)	Double-blind	Baseline	n	221	6
			Mean	372.7	404.1
			SE	6.40	50.67
			Median	354.0	385.2
			Min.	180	281
			Max.	685	596
		Weeks 1-4	n	221	6
			Mean	389.4	412.1
			SE	6.74	49.57
			Median	371.4	375.9
			Min.	182	297
			Max.	699	600
		Weeks 5-8	n	213	5
			Mean	391.8	413.6
			SE	7.11	57.97
			Median	375.1	361.6
			Min.	183	293
			Max.	827	589
		Weeks 9-12	n	202	5
			Mean	392.4	420.2
			SE	7.30	57.17
			Median	378.6	365.6
			Min.	206	312
			Max.	943	602
		Weeks 13-16	n	193	5
			Mean	394.0	416.4
			SE	7.48	56.48

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Table 7.42
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS1800888

Treatment: Salmeterol

				C, C	C, T
AM PEF (L/min)	Double-blind	Weeks 13-16	Median	373.3	351.6
			Min.	212	306
			Max.	975	593
		Overall	n	221	6
			Mean	392.8	414.9
			SE	6.90	47.18
			Median	372.8	380.0
			Min.	211	309
			Max.	859	596
	Wash-out	Overall	n	191	5
			Mean	381.2	410.9
			SE	7.47	51.41
			Median	364.9	368.4
			Min.	211	307
			Max.	980	580
AM PEF change	Double-blind	Weeks 1-4	n	219	6
			Mean	16.5	8.0
			SE	2.39	7.20
			Median	9.4	9.2
			Min.	-106	-21
			Max.	174	30
		Weeks 5-8	n	211	5
			Mean	19.0	10.4
			SE	2.78	6.79
			Median	11.0	11.7
			Min.	-91	-7
			Max.	302	33
		Weeks 9-12	n	201	5

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Table 7.42
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS1800888

Treatment: Salmeterol

				C, C	C, T

AM PEF change	Double-blind	Weeks 9-12	Mean	23.9	17.0
			SE	3.51	6.62
			Median	14.5	9.9
			Min.	-116	4
			Max.	418	35
		Weeks 13-16	n	192	5
			Mean	22.5	13.3
			SE	3.62	17.53
			Median	18.0	11.8
			Min.	-110	-36
			Max.	451	70
		Overall	n	219	6
			Mean	19.8	10.9
			SE	2.68	7.39
			Median	14.4	8.2
			Min.	-106	-13
			Max.	334	36
	Wash-out	Overall	n	190	5
			Mean	11.8	7.7
			SE	3.66	11.97
			Median	8.5	6.8
			Min.	-139	-20
			Max.	456	43

Table 7.43
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS3729943

Treatment: FSC100/50

				C, C	C, G

Subjects in treatment				241	2
AM PEF (L/min)	Double-blind	Baseline	n	237	2
			Mean	365.1	345.2
			SE	5.86	17.79
			Median	360.0	345.2
			Min.	121	327
			Max.	663	363
		Weeks 1-4	n	239	2
			Mean	387.0	366.8
			SE	6.14	17.21
			Median	379.4	366.8
			Min.	149	350
			Max.	703	384
		Weeks 5-8	n	230	2
			Mean	391.0	371.4
			SE	6.48	5.08
			Median	374.5	371.4
			Min.	150	366
			Max.	682	377
		Weeks 9-12	n	222	2
			Mean	394.0	377.0
			SE	6.74	14.87
			Median	381.0	377.0
			Min.	152	362
			Max.	680	392
		Weeks 13-16	n	219	2
			Mean	395.1	374.7
			SE	6.70	15.59

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Table 7.43
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS3729943

Treatment: FSC100/50

				C, C	C, G
AM PEF (L/min)	Double-blind	Weeks 13-16	Median	381.0	374.7
			Min.	158	359
			Max.	675	390
		Overall	n	239	2
			Mean	391.9	372.4
			SE	6.21	13.27
			Median	380.3	372.4
			Min.	152	359
			Max.	685	386
	Wash-out	Overall	n	215	2
			Mean	382.9	344.5
			SE	6.46	42.24
			Median	373.5	344.5
			Min.	144	302
			Max.	655	387
AM PEF change	Double-blind	Weeks 1-4	n	235	2
			Mean	23.6	21.6
			SE	2.87	0.57
			Median	15.8	21.6
			Min.	-139	21
			Max.	188	22
		Weeks 5-8	n	226	2
			Mean	28.4	26.2
			SE	3.17	12.71
			Median	16.9	26.2
			Min.	-113	14
			Max.	199	39
		Weeks 9-12	n	218	2

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Protocol: SFA100062

Population: ITT Excluding Investigator

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Table 7.43
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS3729943

Treatment: FSC100/50

				C, C	C, G
AM PEF change	Double-blind	Weeks 9-12	Mean	31.1	31.8
			SE	3.43	2.91
			Median	19.5	31.8
			Min.	-98	29
			Max.	180	35
		Weeks 13-16	n	215	2
			Mean	31.4	29.5
			SE	3.57	2.20
			Median	17.8	29.5
			Min.	-94	27
			Max.	210	32
		Overall	n	235	2
			Mean	28.2	27.2
			SE	2.95	4.52
			Median	16.3	27.2
			Min.	-108	23
			Max.	194	32
	Wash-out	Overall	n	211	2
			Mean	19.2	-0.7
			SE	2.79	24.46
			Median	11.7	-0.7
			Min.	-77	-25
			Max.	157	24

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Table 7.43
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS3729943

Treatment: Salmeterol

				C, C	C, G
Subjects in treatment				231	1
AM PEF (L/min)	Double-blind	Baseline	n	226	1
			Mean	373.8	312.8
			SE	6.38	
			Median	356.0	312.8
			Min.	180	313
			Max.	685	313
		Weeks 1-4	n	226	1
			Mean	390.4	311.6
			SE	6.70	
			Median	371.5	311.6
			Min.	182	312
			Max.	699	312
		Weeks 5-8	n	217	1
			Mean	392.7	302.9
			SE	7.07	
			Median	375.1	302.9
			Min.	183	303
			Max.	827	303
		Weeks 9-12	n	206	1
			Mean	393.5	309.9
			SE	7.26	
			Median	378.6	309.9
			Min.	206	310
			Max.	943	310
Weeks 13-16	n	197	1		
	Mean	394.9	323.4		
	SE	7.44			

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Table 7.43
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS3729943

Treatment: Salmeterol

				C, C	C, G
AM PEF (L/min)	Double-blind	Weeks 13-16	Median	373.3	323.4
			Min.	212	323
			Max.	975	323
		Overall	n	226	1
			Mean	393.7	311.9
			SE	6.84	
			Median	373.7	311.9
			Min.	211	312
			Max.	859	312
	Wash-out	Overall	n	195	1
			Mean	382.3	330.3
			SE	7.42	
			Median	367.8	330.3
			Min.	211	330
			Max.	980	330
AM PEF change	Double-blind	Weeks 1-4	n	224	1
			Mean	16.3	-1.3
			SE	2.34	
			Median	9.6	-1.3
			Min.	-106	-1
			Max.	174	-1
		Weeks 5-8	n	215	1
			Mean	19.0	-10.0
			SE	2.73	
			Median	11.5	-10.0
			Min.	-91	-10
			Max.	302	-10
		Weeks 9-12	n	205	1

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Table 7.43
Summary of AM PEF (L/min) - ADRB2 Gene SNP RS3729943

Treatment: Salmeterol

				C, C	C, G
AM PEF change	Double-blind	Weeks 9-12	Mean	23.9	-3.0
			SE	3.44	
			Median	14.5	-3.0
			Min.	-116	-3
			Max.	418	-3
		Weeks 13-16	n	196	1
			Mean	22.3	10.5
			SE	3.57	
			Median	18.0	10.5
			Min.	-110	11
			Max.	451	11
		Overall	n	224	1
			Mean	19.6	-0.9
			SE	2.63	
			Median	14.1	-0.9
			Min.	-106	-1
			Max.	334	-1
	Wash-out	Overall	n	194	1
			Mean	11.6	17.5
			SE	3.59	
			Median	8.3	17.5
			Min.	-139	17
			Max.	456	17

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Table 7.44
Summary of AM PEF (L/min) - Poly-C Repeat Group

Treatment: FSC100/50

				<12 Repeats	>=12 Repeats

Subjects in treatment				102	137
AM PEF (L/min)	Double-blind	Baseline	n	102	133
			Mean	359.0	369.7
			SE	7.97	8.47
			Median	361.5	364.7
			Min.	121	183
			Max.	663	658
		Weeks 1-4	n	100	137
			Mean	381.3	391.0
			SE	8.55	8.69
			Median	379.1	378.7
			Min.	228	149
			Max.	653	703
		Weeks 5-8	n	97	132
			Mean	382.6	396.8
			SE	9.00	9.11
			Median	371.4	377.4
			Min.	227	150
			Max.	664	682
		Weeks 9-12	n	93	128
			Mean	383.1	402.0
			SE	9.49	9.38
			Median	378.8	382.3
			Min.	235	152
			Max.	665	680
		Weeks 13-16	n	93	125
			Mean	383.9	403.5

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Table 7.44
Summary of AM PEF (L/min) - Poly-C Repeat Group

Treatment: FSC100/50

				<12 Repeats	>=12 Repeats
AM PEF (L/min)	Double-blind	Weeks 13-16	SE	9.75	9.17
			Median	372.8	383.4
			Min.	241	158
			Max.	675	671
		Overall	n	100	137
			Mean	384.6	397.0
			SE	8.82	8.69
			Median	378.3	379.5
			Min.	235	152
			Max.	659	685
	Wash-out	Overall	n	90	124
			Mean	374.3	388.7
			SE	9.09	9.04
			Median	363.1	377.4
			Min.	225	144
			Max.	600	655
AM PEF change	Double-blind	Weeks 1-4	n	100	133
			Mean	22.9	24.0
			SE	4.44	3.80
			Median	13.5	18.6
			Min.	-139	-103
			Max.	188	172
		Weeks 5-8	n	97	128
			Mean	26.4	29.2
			SE	4.83	4.19
			Median	14.6	20.8
			Min.	-113	-85
			Max.	199	172

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Table 7.44
Summary of AM PEF (L/min) - Poly-C Repeat Group

Treatment: FSC100/50

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				<12 Repeats	>=12 Repeats
AM PEF change	Double-blind	Weeks 9-12	n	93	124
			Mean	27.3	33.7
			SE	5.29	4.52
			Median	11.4	25.4
			Min.	-94	-98
			Max.	180	180
		Weeks 13-16	n	93	121
			Mean	28.1	33.6
			SE	5.66	4.59
			Median	10.4	24.5
			Min.	-87	-94
			Max.	210	175
		Overall	n	100	133
			Mean	26.3	29.6
			SE	4.65	3.85
			Median	14.2	20.5
			Min.	-108	-89
			Max.	194	166
	Wash-out	Overall	n	90	120
			Mean	18.4	19.0
			SE	4.48	3.58
			Median	8.9	15.2
			Min.	-77	-77
			Max.	157	123

Table 7.44
Summary of AM PEF (L/min) - Poly-C Repeat Group

Treatment: Salmeterol

				<12 Repeats	>=12 Repeats

Subjects in treatment				91	139
AM PEF (L/min)	Double-blind	Baseline	n	89	136
			Mean	354.8	386.2
			SE	8.74	8.73
			Median	351.3	357.5
			Min.	180	205
			Max.	539	685
		Weeks 1-4	n	88	137
			Mean	379.8	397.1
			SE	10.37	8.74
			Median	369.8	371.7
			Min.	182	223
			Max.	699	675
		Weeks 5-8	n	84	132
			Mean	380.6	400.5
			SE	11.49	8.99
			Median	368.8	376.1
			Min.	183	216
			Max.	827	679
		Weeks 9-12	n	81	124
			Mean	382.0	401.1
			SE	12.17	9.00
			Median	368.3	379.2
			Min.	206	209
			Max.	943	651
		Weeks 13-16	n	77	120
			Mean	382.8	401.9

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Table 7.44
 Summary of AM PEF (L/min) - Poly-C Repeat Group

Treatment: Salmeterol

				<12 Repeats	>=12 Repeats
AM PEF (L/min)	Double-blind	Weeks 13-16	SE	12.84	9.00
			Median	362.5	381.4
			Min.	212	226
			Max.	975	667
		Overall	n	88	137
			Mean	383.0	400.7
			SE	11.08	8.70
			Median	370.6	374.5
			Min.	211	225
			Max.	859	677
	Wash-out	Overall	n	77	118
			Mean	371.8	388.3
			SE	12.64	9.06
			Median	354.5	370.0
			Min.	211	212
			Max.	980	664
AM PEF change	Double-blind	Weeks 1-4	n	87	136
			Mean	23.7	11.8
			SE	4.27	2.66
			Median	13.0	9.3
			Min.	-72	-106
			Max.	174	119
		Weeks 5-8	n	83	131
			Mean	24.7	15.7
			SE	5.14	3.03
			Median	13.6	11.5
			Min.	-55	-91
			Max.	302	133

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Table 7.44
Summary of AM PEF (L/min) - Poly-C Repeat Group

Treatment: Salmeterol

				<12 Repeats	>=12 Repeats
AM PEF change	Double-blind	Weeks 9-12	n	80	124
			Mean	29.1	20.8
			SE	6.24	4.00
			Median	15.2	14.5
			Min.	-31	-116
			Max.	418	319
		Weeks 13-16	n	76	120
			Mean	28.1	18.9
			SE	7.02	3.73
			Median	19.3	16.9
			Min.	-95	-110
			Max.	451	186
		Overall	n	87	136
			Mean	26.8	15.3
			SE	4.92	2.91
			Median	15.4	13.0
			Min.	-38	-106
			Max.	334	152
	Wash-out	Overall	n	76	118
			Mean	17.8	7.9
			SE	7.20	3.63
			Median	8.3	9.0
			Min.	-98	-139
			Max.	456	128

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Table 7.45
Analysis of AM PEF (L/min) - Poly-C Repeat Group

				<12 vs. ≥12

FSC100/50	Double-blind	Weeks 1-4	p-value	0.967
			LS Means Diff	0.2
			95% CI for Diff	(-11.2,11.6)
		Weeks 5-8	p-value	0.631
			LS Means Diff	-3.1
			95% CI for Diff	(-15.7,9.5)
		Weeks 9-12	p-value	0.345
			LS Means Diff	-6.6
			95% CI for Diff	(-20.3,7.1)
		Weeks 13-16	p-value	0.438
			LS Means Diff	-5.6
			95% CI for Diff	(-19.7,8.6)
		Overall	p-value	0.633
			LS Means Diff	-2.9
			95% CI for Diff	(-14.7,8.9)
	Wash-out	Overall	p-value	0.746
			LS Means Diff	-1.8
			95% CI for Diff	(-12.9,9.3)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and Poly-C repeat group. Least squares mean differences are calculated as <12 Repeats - ≥12 Repeats.

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Table 7.45
Analysis of AM PEF (L/min) - Poly-C Repeat Group

				<12 vs. ≥12

Salmeterol	Double-blind	Weeks 1-4	p-value	0.040
			LS Means Diff	9.7
			95% CI for Diff	(0.4,19.0)
		Weeks 5-8	p-value	0.125
			LS Means Diff	8.5
			95% CI for Diff	(-2.4,19.5)
		Weeks 9-12	p-value	0.301
			LS Means Diff	7.3
			95% CI for Diff	(-6.6,21.2)
		Weeks 13-16	p-value	0.252
			LS Means Diff	8.3
			95% CI for Diff	(-5.9,22.5)
		Overall	p-value	0.070
			LS Means Diff	9.6
			95% CI for Diff	(-0.8,20.0)
Wash-out	Overall	p-value	0.181	
		LS Means Diff	9.8	
		95% CI for Diff	(-4.6,24.3)	

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and Poly-C repeat group. Least squares mean differences are calculated as <12 Repeats - ≥12 Repeats.

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Table 7.46
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1432623

Treatment: FSC100/50

			C, C	C, T	T, T
-----			-----		
Subjects in treatment			37	95	110
FEV1 (L)	Visit 2 (Week -16)	n	37	95	110
		Mean	2.59	3.03	2.73
		SE	0.088	0.068	0.068
		Median	2.63	2.95	2.68
		Min.	1.44	1.89	1.25
		Max.	4.03	4.70	5.03
	Visit 3 (Week -12)	n	37	95	110
		Mean	2.63	3.03	2.75
		SE	0.083	0.064	0.068
		Median	2.69	2.97	2.69
		Min.	1.48	1.68	1.45
		Max.	3.68	4.63	5.02
	Visit 4 (Week -8)	n	37	95	110
		Mean	2.66	3.01	2.76
		SE	0.086	0.062	0.069
		Median	2.72	3.04	2.68
		Min.	1.57	1.80	1.30
		Max.	3.55	4.34	5.08
	Visit 5 (Week -4)	n	37	95	110
		Mean	2.64	3.01	2.77
		SE	0.081	0.062	0.069
		Median	2.76	3.01	2.73
		Min.	1.63	1.95	1.46
		Max.	3.55	4.52	4.74

Table 7.46
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1432623

Treatment: FSC100/50

			C, C	C, T	T, T
FEV1 (L)	Visit 6 (Day 1)	n	37	95	110
		Mean	2.59	3.01	2.75
		SE	0.081	0.065	0.070
		Median	2.64	2.99	2.69
		Min.	1.32	1.86	1.33
		Max.	3.45	4.38	4.95
	Visit 7 (Week 4)	n	33	94	105
		Mean	2.73	3.23	2.94
		SE	0.095	0.072	0.080
		Median	2.74	3.18	2.87
		Min.	1.63	1.87	1.36
		Max.	3.74	4.73	5.98
	Visit 8 (Week 8)	n	31	91	103
		Mean	2.72	3.21	2.96
		SE	0.101	0.075	0.080
		Median	2.78	3.07	2.95
		Min.	1.64	1.92	1.20
		Max.	3.78	4.89	5.68
	Visit 9 (Week 12)	n	30	89	101
		Mean	2.71	3.21	2.97
		SE	0.105	0.077	0.081
		Median	2.80	3.07	2.90
		Min.	1.43	2.05	1.22
		Max.	3.84	4.90	5.75

Table 7.46
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1432623

Treatment: FSC100/50

			C, C	C, T	T, T
-----			-----		
FEV1 (L)	Visit 10 (Week 16)	n	30	88	100
		Mean	2.72	3.24	2.93
		SE	0.103	0.075	0.081
		Median	2.73	3.12	2.93
		Min.	1.62	2.06	1.15
		Max.	3.56	4.93	5.33
	Endpoint	n	33	94	105
		Mean	2.74	3.25	2.92
		SE	0.096	0.072	0.079
		Median	2.75	3.13	2.93
		Min.	1.62	2.06	1.15
		Max.	3.56	4.93	5.33
	Overall	n	33	94	105
		Mean	2.73	3.24	2.94
		SE	0.094	0.071	0.078
		Median	2.80	3.22	2.88
		Min.	1.61	2.05	1.23
		Max.	3.68	4.86	5.69
	Visit 11 (Wash-out)	n	30	87	99
		Mean	2.62	3.04	2.78
		SE	0.104	0.072	0.079
		Median	2.77	2.90	2.75
		Min.	1.37	1.95	1.20
		Max.	3.99	4.69	4.78

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Table 7.46
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1432623

Treatment: FSC100/50

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		C, C	C, T	T, T	
FEV1 change	Visit 7 (Week 4)	n	33	94	105
		Mean	0.18	0.23	0.22
		SE	0.037	0.037	0.030
		Median	0.18	0.15	0.18
		Min.	-0.35	-0.67	-0.80
		Max.	0.80	1.55	1.62
		Visit 8 (Week 8)	n	31	91
	Mean		0.20	0.23	0.22
	SE		0.043	0.034	0.029
	Median		0.18	0.10	0.19
	Min.		-0.20	-0.51	-0.54
	Max.		0.85	1.50	1.41
	Visit 9 (Week 12)		n	30	89
		Mean	0.19	0.24	0.22
		SE	0.042	0.037	0.031
		Median	0.18	0.14	0.22
		Min.	-0.23	-0.60	-0.64
		Max.	0.61	1.56	1.44
		Visit 10 (Week 16)	n	30	88
	Mean		0.20	0.26	0.19
	SE		0.048	0.042	0.036
	Median		0.19	0.19	0.16
	Min.		-0.37	-0.74	-0.68
	Max.		0.88	1.65	1.59

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Table 7.46
 Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1432623

Treatment: FSC100/50

		C, C		C, T	T, T
-----		-----		-----	-----
FEV1 change	Endpoint	n	33	94	105
		Mean	0.19	0.25	0.19
		SE	0.044	0.040	0.034
		Median	0.19	0.19	0.16
		Min.	-0.37	-0.74	-0.68
		Max.	0.88	1.65	1.59
	Overall	n	33	94	105
		Mean	0.19	0.23	0.21
		SE	0.034	0.031	0.028
		Median	0.19	0.15	0.19
		Min.	-0.14	-0.28	-0.41
		Max.	0.72	1.44	1.52
	Visit 11 (Wash-out)	n	30	87	99
		Mean	0.10	0.06	0.05
		SE	0.046	0.027	0.033
		Median	0.10	0.05	0.04
		Min.	-0.57	-0.63	-1.03
		Max.	0.88	0.81	1.53

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Table 7.46
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1432623

Treatment: Salmeterol

			C, C	C, T	T, T
-----			-----		
Subjects in treatment			34	98	100
FEV1 (L)	Visit 2 (Week -16)	n	34	98	100
		Mean	2.79	2.81	2.95
		SE	0.086	0.074	0.077
		Median	2.85	2.70	2.84
		Min.	1.68	1.55	1.44
		Max.	3.95	5.09	4.76
	Visit 3 (Week -12)	n	34	98	100
		Mean	2.78	2.84	2.99
		SE	0.093	0.080	0.076
		Median	2.77	2.69	2.90
		Min.	1.77	1.64	1.39
		Max.	4.39	5.46	4.66
	Visit 4 (Week -8)	n	34	98	100
		Mean	2.80	2.85	2.99
		SE	0.093	0.081	0.077
		Median	2.83	2.67	2.89
		Min.	1.75	1.70	1.44
		Max.	3.99	5.46	4.63
	Visit 5 (Week -4)	n	34	98	100
		Mean	2.76	2.89	3.00
		SE	0.085	0.081	0.079
		Median	2.75	2.75	2.84
		Min.	1.81	1.65	1.51
		Max.	4.01	5.66	4.93

Table 7.46
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1432623

Treatment: Salmeterol

		C, C	C, T	T, T
FEV1 (L)	Visit 6 (Day 1)	n	34	98
		Mean	2.79	2.85
		SE	0.086	0.082
		Median	2.84	2.75
		Min.	1.69	1.65
		Max.	4.00	4.93
	Visit 7 (Week 4)	n	32	96
		Mean	3.02	2.99
		SE	0.118	0.082
		Median	2.94	2.91
		Min.	1.76	1.80
		Max.	4.87	5.35
	Visit 8 (Week 8)	n	29	92
		Mean	2.94	2.97
		SE	0.103	0.083
		Median	3.05	2.81
		Min.	1.62	1.67
		Max.	4.29	5.36
	Visit 9 (Week 12)	n	28	87
		Mean	2.88	2.98
		SE	0.109	0.078
		Median	2.95	2.94
		Min.	1.72	1.66
		Max.	4.36	4.99

Table 7.46
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1432623

Treatment: Salmeterol

			C, C	C, T	T, T
-----			-----		
FEV1 (L)	Visit 10 (Week 16)	n	27	86	84
		Mean	2.87	2.98	3.01
		SE	0.110	0.085	0.089
		Median	3.00	2.88	2.91
		Min.	1.67	1.43	1.22
		Max.	4.10	5.13	5.15
	Endpoint	n	32	96	94
		Mean	2.88	2.99	3.07
		SE	0.111	0.087	0.087
		Median	2.99	2.88	2.92
		Min.	1.67	1.43	1.22
		Max.	4.28	5.36	5.15
	Overall	n	32	96	94
		Mean	2.96	2.98	3.10
		SE	0.102	0.080	0.082
		Median	3.00	2.86	2.94
		Min.	1.74	1.73	1.22
		Max.	4.28	5.16	4.89
	Visit 11 (Wash-out)	n	27	85	83
		Mean	2.74	2.81	2.92
		SE	0.116	0.079	0.088
		Median	2.84	2.75	2.83
		Min.	1.46	1.54	1.10
		Max.	4.17	4.65	5.32

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Table 7.46
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1432623

Treatment: Salmeterol

			C, C	C, T	T, T
FEV1 change	Visit 7 (Week 4)	n	32	96	94
		Mean	0.21	0.14	0.17
		SE	0.087	0.031	0.035
		Median	0.09	0.15	0.13
		Min.	-0.33	-1.33	-0.78
		Max.	2.38	1.30	1.47
	Visit 8 (Week 8)	n	29	92	89
		Mean	0.15	0.11	0.15
		SE	0.034	0.030	0.039
		Median	0.15	0.10	0.07
		Min.	-0.20	-0.90	-0.84
		Max.	0.58	0.99	1.73
	Visit 9 (Week 12)	n	28	87	85
		Mean	0.08	0.12	0.14
		SE	0.037	0.030	0.037
		Median	0.06	0.11	0.09
		Min.	-0.47	-0.61	-0.61
		Max.	0.44	1.25	1.27
	Visit 10 (Week 16)	n	27	86	84
		Mean	0.03	0.14	0.12
		SE	0.045	0.040	0.040
		Median	0.09	0.09	0.06
		Min.	-0.62	-0.38	-0.90
		Max.	0.47	2.54	1.63

Table 7.46
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1432623

Treatment: Salmeterol

			C, C	C, T	T, T
FEV1 change	Endpoint	n	32	96	94
		Mean	0.06	0.14	0.12
		SE	0.044	0.037	0.038
		Median	0.09	0.10	0.07
		Min.	-0.62	-0.38	-0.90
		Max.	0.65	2.54	1.63
	Overall	n	32	96	94
		Mean	0.14	0.13	0.14
		SE	0.040	0.024	0.032
		Median	0.10	0.10	0.09
		Min.	-0.41	-0.35	-0.47
		Max.	0.72	1.08	1.19
	Visit 11 (Wash-out)	n	27	85	83
		Mean	-0.10	-0.03	0.04
		SE	0.051	0.026	0.043
		Median	-0.04	-0.02	0.03
		Min.	-0.75	-0.49	-1.54
		Max.	0.33	0.86	1.03

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Table 7.47
Analysis of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1432623

			C/C vs. C/T	C/C vs. T/T	C/T vs. T/T
FSC100/50	Visit 7 (Week 4)	p-value	0.526	0.476	0.936
		LS Means Diff	-0.04	-0.05	-0.00
		95% CI for Diff	(-0.17, 0.09)	(-0.17, 0.08)	(-0.10, 0.09)
	Visit 8 (Week 8)	p-value	0.575	0.487	0.867
		LS Means Diff	-0.04	-0.04	-0.01
		95% CI for Diff	(-0.16, 0.09)	(-0.16, 0.08)	(-0.09, 0.08)
	Visit 9 (Week 12)	p-value	0.416	0.322	0.826
		LS Means Diff	-0.05	-0.06	-0.01
		95% CI for Diff	(-0.18, 0.08)	(-0.19, 0.06)	(-0.10, 0.08)
	Visit 10 (Week 16)	p-value	0.256	0.586	0.379
		LS Means Diff	-0.09	-0.04	0.05
		95% CI for Diff	(-0.23, 0.06)	(-0.18, 0.10)	(-0.06, 0.15)
	Endpoint	p-value	0.251	0.534	0.437
		LS Means Diff	-0.08	-0.04	0.04
		95% CI for Diff	(-0.22, 0.06)	(-0.18, 0.09)	(-0.06, 0.14)
	Overall	p-value	0.386	0.407	0.927
		LS Means Diff	-0.05	-0.05	0.00
		95% CI for Diff	(-0.16, 0.06)	(-0.16, 0.06)	(-0.08, 0.08)
	Visit 11 (Wash-out)	p-value	0.714	0.661	0.933
		LS Means Diff	0.02	0.03	0.00
		95% CI for Diff	(-0.10, 0.15)	(-0.09, 0.15)	(-0.08, 0.09)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS1432623. Least squares mean differences are calculated as C/C-C/T, C/C-T/T and C/T-T/T.

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Table 7.47
Analysis of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1432623

			C/C vs. C/T	C/C vs. T/T	C/T vs. T/T
Salmeterol	Visit 7 (Week 4)	p-value	0.491	0.753	0.623
		LS Means Diff	0.05	0.02	-0.03
		95% CI for Diff	(-0.09, 0.19)	(-0.12, 0.17)	(-0.13, 0.08)
	Visit 8 (Week 8)	p-value	0.837	0.476	0.186
		LS Means Diff	0.01	-0.05	-0.06
		95% CI for Diff	(-0.12, 0.14)	(-0.19, 0.09)	(-0.16, 0.03)
	Visit 9 (Week 12)	p-value	0.399	0.248	0.616
		LS Means Diff	-0.05	-0.07	-0.02
		95% CI for Diff	(-0.17, 0.07)	(-0.20, 0.05)	(-0.11, 0.07)
	Visit 10 (Week 16)	p-value	0.143	0.200	0.860
		LS Means Diff	-0.11	-0.10	0.01
		95% CI for Diff	(-0.26, 0.04)	(-0.26, 0.06)	(-0.10, 0.12)
	Endpoint	p-value	0.187	0.305	0.732
		LS Means Diff	-0.09	-0.08	0.02
		95% CI for Diff	(-0.23, 0.05)	(-0.22, 0.07)	(-0.08, 0.12)
	Overall	p-value	0.994	0.721	0.620
		LS Means Diff	-0.00	-0.02	-0.02
		95% CI for Diff	(-0.10, 0.10)	(-0.13, 0.09)	(-0.10, 0.06)
	Visit 11 (Wash-out)	p-value	0.199	0.023	0.127
		LS Means Diff	-0.09	-0.16	-0.07
		95% CI for Diff	(-0.22, 0.05)	(-0.30, -0.02)	(-0.17, 0.02)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS1432623. Least squares mean differences are calculated as C/C-C/T, C/C-T/T and C/T-T/T.

Table 7.48
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042711

Treatment: FSC100/50

			C, C	C, T	T, T
-----			-----		
Subjects in treatment			23	72	141
FEV1 (L)	Visit 2 (Week -16)	n	23	72	141
		Mean	2.73	3.05	2.73
		SE	0.111	0.073	0.060
		Median	2.70	2.96	2.67
		Min.	1.87	1.93	1.25
		Max.	4.03	4.48	5.03
	Visit 3 (Week -12)	n	23	72	141
		Mean	2.78	3.02	2.77
		SE	0.107	0.070	0.060
		Median	2.77	2.97	2.70
		Min.	1.72	1.68	1.45
		Max.	3.68	4.63	5.02
	Visit 4 (Week -8)	n	23	72	141
		Mean	2.84	3.03	2.76
		SE	0.101	0.064	0.061
		Median	2.83	3.04	2.68
		Min.	1.86	2.11	1.30
		Max.	3.55	4.34	5.08
	Visit 5 (Week -4)	n	23	72	141
		Mean	2.79	3.04	2.76
		SE	0.102	0.066	0.059
		Median	2.88	3.01	2.69
		Min.	1.66	2.08	1.46
		Max.	3.55	4.52	4.74

Table 7.48
 Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042711

Treatment: FSC100/50

			C, C	C, T	T, T
FEV1 (L)	Visit 6 (Day 1)	n	23	72	141
		Mean	2.75	3.04	2.74
		SE	0.093	0.068	0.062
		Median	2.68	2.99	2.61
		Min.	1.84	2.07	1.32
		Max.	3.45	4.34	4.95
	Visit 7 (Week 4)	n	21	71	134
		Mean	2.92	3.26	2.94
		SE	0.113	0.081	0.070
		Median	2.96	3.23	2.86
		Min.	1.83	1.87	1.36
		Max.	3.74	4.73	5.98
	Visit 8 (Week 8)	n	19	68	133
		Mean	2.88	3.22	2.95
		SE	0.137	0.084	0.069
		Median	2.95	3.10	2.88
		Min.	1.64	2.13	1.20
		Max.	3.78	4.89	5.68
	Visit 9 (Week 12)	n	19	66	130
		Mean	2.88	3.26	2.95
		SE	0.131	0.089	0.070
		Median	3.09	3.08	2.86
		Min.	1.61	2.05	1.22
		Max.	3.84	4.90	5.75

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Table 7.48
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042711

Treatment: FSC100/50

			C, C	C, T	T, T
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FEV1 (L)	Visit 10 (Week 16)	n	19	66	128
		Mean	2.88	3.28	2.92
		SE	0.121	0.083	0.070
		Median	2.99	3.18	2.84
		Min.	1.71	2.13	1.15
		Max.	3.56	4.93	5.33
	Endpoint	n	21	71	134
		Mean	2.90	3.28	2.92
		SE	0.112	0.080	0.068
		Median	2.99	3.21	2.84
		Min.	1.71	2.13	1.15
		Max.	3.56	4.93	5.33
	Overall	n	21	71	134
		Mean	2.91	3.26	2.94
		SE	0.115	0.080	0.068
		Median	2.98	3.20	2.87
		Min.	1.70	2.10	1.23
		Max.	3.68	4.86	5.69
	Visit 11 (Wash-out)	n	19	65	127
		Mean	2.80	3.05	2.78
		SE	0.125	0.076	0.069
		Median	2.85	2.94	2.64
		Min.	1.76	1.99	1.20
		Max.	3.99	4.69	4.78

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Table 7.48
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042711

Treatment: FSC100/50

			C, C	C, T	T, T
-----			-----		
FEV1 change	Visit 7 (Week 4)	n	21	71	134
		Mean	0.22	0.23	0.21
		SE	0.044	0.043	0.026
		Median	0.19	0.13	0.18
		Min.	-0.01	-0.47	-0.80
		Max.	0.80	1.55	1.62
	Visit 8 (Week 8)	n	19	68	133
		Mean	0.20	0.23	0.22
		SE	0.060	0.040	0.024
		Median	0.12	0.09	0.20
		Min.	-0.20	-0.51	-0.54
		Max.	0.85	1.50	1.41
	Visit 9 (Week 12)	n	19	66	130
		Mean	0.20	0.24	0.22
		SE	0.059	0.045	0.027
		Median	0.17	0.13	0.22
		Min.	-0.23	-0.35	-0.64
		Max.	0.61	1.56	1.44
	Visit 10 (Week 16)	n	19	66	128
		Mean	0.20	0.27	0.19
		SE	0.071	0.049	0.030
		Median	0.16	0.19	0.17
		Min.	-0.37	-0.74	-0.68
		Max.	0.88	1.65	1.59

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Table 7.48
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042711

Treatment: FSC100/50

			C, C	C, T	T, T
-----			-----		
FEV1 change	Endpoint	n	21	71	134
		Mean	0.20	0.25	0.19
		SE	0.064	0.046	0.029
		Median	0.19	0.19	0.17
		Min.	-0.37	-0.74	-0.68
		Max.	0.88	1.65	1.59
	Overall	n	21	71	134
		Mean	0.21	0.23	0.21
		SE	0.048	0.038	0.024
		Median	0.21	0.11	0.19
		Min.	-0.14	-0.28	-0.41
		Max.	0.72	1.44	1.52
	Visit 11 (Wash-out)	n	19	65	127
		Mean	0.13	0.03	0.06
		SE	0.054	0.032	0.027
		Median	0.15	0.03	0.06
		Min.	-0.14	-0.63	-1.03
		Max.	0.88	0.81	1.53

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Table 7.48
 Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042711

Treatment: Salmeterol

			C, C	C, T	T, T
-----			-----		
Subjects in treatment			25	71	133
FEV1 (L)	Visit 2 (Week -16)	n	25	71	133
		Mean	2.88	2.84	2.86
		SE	0.092	0.089	0.063
		Median	2.93	2.69	2.83
		Min.	1.99	1.55	1.44
		Max.	3.95	5.09	4.76
	Visit 3 (Week -12)	n	25	71	133
		Mean	2.90	2.86	2.90
		SE	0.103	0.094	0.064
		Median	2.87	2.70	2.79
		Min.	1.96	1.65	1.39
		Max.	4.39	5.46	4.66
	Visit 4 (Week -8)	n	25	71	133
		Mean	2.87	2.91	2.89
		SE	0.094	0.099	0.064
		Median	2.87	2.71	2.87
		Min.	2.15	1.70	1.44
		Max.	3.99	5.46	4.63
	Visit 5 (Week -4)	n	25	71	133
		Mean	2.82	2.92	2.91
		SE	0.096	0.097	0.065
		Median	2.76	2.75	2.82
		Min.	1.92	1.66	1.51
		Max.	4.01	5.66	4.88

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Table 7.48
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042711

Treatment: Salmeterol

			C, C	C, T	T, T
FEV1 (L)	Visit 6 (Day 1)	n	25	71	133
		Mean	2.93	2.89	2.87
		SE	0.089	0.093	0.068
		Median	2.91	2.80	2.76
		Min.	2.11	1.65	1.32
		Max.	4.00	4.93	4.71
	Visit 7 (Week 4)	n	23	69	127
		Mean	3.09	3.01	3.05
		SE	0.108	0.098	0.072
		Median	2.99	2.89	2.96
		Min.	1.96	1.80	1.22
		Max.	4.28	5.35	4.89
	Visit 8 (Week 8)	n	20	67	120
		Mean	3.12	2.99	2.96
		SE	0.101	0.096	0.068
		Median	3.17	2.93	2.81
		Min.	2.09	1.72	1.24
		Max.	4.29	5.36	5.11
	Visit 9 (Week 12)	n	20	64	113
		Mean	3.05	2.93	2.99
		SE	0.114	0.087	0.071
		Median	3.02	2.91	2.92
		Min.	1.82	1.70	1.20
		Max.	4.36	4.99	4.83

Table 7.48
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042711

Treatment: Salmeterol

			C, C	C, T	T, T
FEV1 (L)	Visit 10 (Week 16)	n	20	64	110
		Mean	3.01	2.92	2.98
		SE	0.114	0.090	0.077
		Median	3.06	2.89	2.89
		Min.	1.67	1.43	1.22
		Max.	4.10	5.09	5.13
	Endpoint	n	23	69	127
		Mean	3.06	2.98	2.99
		SE	0.116	0.098	0.075
		Median	3.07	2.89	2.88
		Min.	1.67	1.43	1.22
		Max.	4.28	5.36	5.13
	Overall	n	23	69	127
		Mean	3.10	2.99	3.01
		SE	0.108	0.094	0.069
		Median	3.00	2.95	2.92
		Min.	1.89	1.73	1.22
		Max.	4.28	5.16	4.89
	Visit 11 (Wash-out)	n	20	63	109
		Mean	2.88	2.78	2.86
		SE	0.110	0.091	0.074
		Median	2.88	2.65	2.78
		Min.	1.67	1.46	1.10
		Max.	4.17	4.65	5.32

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Table 7.48
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042711

Treatment: Salmeterol

			C, C	C, T	T, T
-----			-----		
FEV1 change	Visit 7 (Week 4)	n	23	69	127
		Mean	0.12	0.11	0.20
		SE	0.045	0.033	0.035
		Median	0.09	0.14	0.13
		Min.	-0.33	-1.33	-0.78
		Max.	0.65	0.73	2.38
	Visit 8 (Week 8)	n	20	67	120
		Mean	0.16	0.10	0.14
		SE	0.046	0.032	0.032
		Median	0.14	0.11	0.08
		Min.	-0.20	-0.78	-0.90
		Max.	0.58	0.82	1.73
	Visit 9 (Week 12)	n	20	64	113
		Mean	0.09	0.08	0.15
		SE	0.051	0.030	0.030
		Median	0.07	0.09	0.10
		Min.	-0.47	-0.61	-0.61
		Max.	0.44	0.86	1.25
	Visit 10 (Week 16)	n	20	64	110
		Mean	0.05	0.07	0.14
		SE	0.055	0.028	0.039
		Median	0.09	0.08	0.07
		Min.	-0.62	-0.41	-0.90
		Max.	0.47	0.60	2.54

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Table 7.48
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042711

Treatment: Salmeterol

			C, C	C, T	T, T
-----			-----		
FEV1 change	Endpoint	n	23	69	127
		Mean	0.09	0.09	0.14
		SE	0.055	0.027	0.035
		Median	0.10	0.09	0.07
		Min.	-0.62	-0.41	-0.90
		Max.	0.65	0.63	2.54
	Overall	n	23	69	127
		Mean	0.13	0.09	0.16
		SE	0.043	0.022	0.026
		Median	0.12	0.08	0.10
		Min.	-0.41	-0.35	-0.47
		Max.	0.65	0.58	1.16
	Visit 11 (Wash-out)	n	20	63	109
		Mean	-0.08	-0.06	0.03
		SE	0.049	0.030	0.035
		Median	-0.04	-0.02	0.02
		Min.	-0.62	-0.75	-1.54
		Max.	0.33	0.52	1.03

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Table 7.49
Analysis of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042711

			C/C vs. C/T	C/C vs. T/T	C/T vs. T/T
FSC100/50	Visit 7 (Week 4)	p-value	0.762	0.711	0.929
		LS Means Diff	-0.02	-0.03	-0.00
		95% CI for Diff	(-0.18,0.13)	(-0.18,0.12)	(-0.10,0.09)
	Visit 8 (Week 8)	p-value	0.498	0.291	0.561
		LS Means Diff	-0.05	-0.08	-0.03
		95% CI for Diff	(-0.20,0.10)	(-0.22,0.07)	(-0.11,0.06)
	Visit 9 (Week 12)	p-value	0.337	0.264	0.848
		LS Means Diff	-0.08	-0.09	-0.01
		95% CI for Diff	(-0.24,0.08)	(-0.24,0.07)	(-0.10,0.08)
	Visit 10 (Week 16)	p-value	0.209	0.541	0.255
		LS Means Diff	-0.11	-0.05	0.06
		95% CI for Diff	(-0.29,0.06)	(-0.23,0.12)	(-0.04,0.17)
	Endpoint	p-value	0.251	0.595	0.286
		LS Means Diff	-0.10	-0.04	0.05
		95% CI for Diff	(-0.27,0.07)	(-0.21,0.12)	(-0.05,0.16)
	Overall	p-value	0.435	0.429	0.973
		LS Means Diff	-0.05	-0.05	0.00
		95% CI for Diff	(-0.19,0.08)	(-0.19,0.08)	(-0.08,0.08)
	Visit 11 (Wash-out)	p-value	0.362	0.594	0.495
		LS Means Diff	0.07	0.04	-0.03
		95% CI for Diff	(-0.08,0.22)	(-0.11,0.18)	(-0.12,0.06)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS1042711. Least squares mean differences are calculated as C/C-C/T, C/C-T/T and C/T-T/T.

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Table 7.49
Analysis of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042711

			C/C vs. C/T	C/C vs. T/T	C/T vs. T/T
Salmeterol	Visit 7 (Week 4)	p-value	0.923	0.547	0.294
		LS Means Diff	0.01	-0.05	-0.06
		95% CI for Diff	(-0.15, 0.17)	(-0.21, 0.11)	(-0.16, 0.05)
	Visit 8 (Week 8)	p-value	0.535	0.915	0.251
		LS Means Diff	0.05	-0.01	-0.06
		95% CI for Diff	(-0.11, 0.20)	(-0.16, 0.15)	(-0.16, 0.04)
	Visit 9 (Week 12)	p-value	0.930	0.436	0.185
		LS Means Diff	0.01	-0.05	-0.06
		95% CI for Diff	(-0.13, 0.14)	(-0.19, 0.08)	(-0.15, 0.03)
	Visit 10 (Week 16)	p-value	0.770	0.304	0.264
		LS Means Diff	-0.03	-0.09	-0.06
		95% CI for Diff	(-0.19, 0.14)	(-0.26, 0.08)	(-0.17, 0.05)
	Endpoint	p-value	0.917	0.582	0.506
		LS Means Diff	-0.01	-0.04	-0.03
		95% CI for Diff	(-0.17, 0.15)	(-0.20, 0.11)	(-0.14, 0.07)
	Overall	p-value	0.621	0.734	0.207
		LS Means Diff	0.03	-0.02	-0.05
		95% CI for Diff	(-0.09, 0.15)	(-0.14, 0.10)	(-0.13, 0.03)
	Visit 11 (Wash-out)	p-value	0.787	0.230	0.160
		LS Means Diff	-0.02	-0.09	-0.07
		95% CI for Diff	(-0.18, 0.13)	(-0.25, 0.06)	(-0.17, 0.03)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS1042711. Least squares mean differences are calculated as C/C-C/T, C/C-T/T and C/T-T/T.

Table 7.50
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042713

Treatment: FSC100/50

			A, A	A, G	G, G
-----			-----		
Subjects in treatment			81	85	77
FEV1 (L)	Visit 2 (Week -16)	n	81	85	77
		Mean	2.79	2.81	2.87
		SE	0.078	0.076	0.075
		Median	2.80	2.74	2.80
		Min.	1.44	1.25	1.62
		Max.	5.03	4.52	4.48
	Visit 3 (Week -12)	n	81	85	77
		Mean	2.82	2.80	2.90
		SE	0.079	0.071	0.073
		Median	2.73	2.72	2.89
		Min.	1.48	1.45	1.68
		Max.	5.02	4.61	4.63
	Visit 4 (Week -8)	n	81	85	77
		Mean	2.79	2.83	2.89
		SE	0.080	0.073	0.067
		Median	2.70	2.82	2.82
		Min.	1.57	1.30	1.62
		Max.	5.08	4.60	4.34
	Visit 5 (Week -4)	n	81	85	77
		Mean	2.81	2.84	2.88
		SE	0.076	0.072	0.071
		Median	2.69	2.84	2.89
		Min.	1.63	1.46	1.62
		Max.	4.74	4.63	4.52

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Table 7.50
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042713

Treatment: FSC100/50

			A, A	A, G	G, G
-----			-----		
FEV1 (L)	Visit 6 (Day 1)	n	81	85	77
		Mean	2.77	2.82	2.88
		SE	0.081	0.073	0.072
		Median	2.70	2.73	2.85
		Min.	1.32	1.33	1.45
		Max.	4.95	4.77	4.34
	Visit 7 (Week 4)	n	75	83	75
		Mean	2.99	3.02	3.07
		SE	0.091	0.084	0.085
		Median	2.87	2.94	3.01
		Min.	1.63	1.36	1.75
		Max.	5.98	4.86	4.79
	Visit 8 (Week 8)	n	73	83	70
		Mean	2.99	3.02	3.06
		SE	0.089	0.086	0.089
		Median	2.97	2.87	3.02
		Min.	1.75	1.20	1.64
		Max.	5.68	4.97	4.89
	Visit 9 (Week 12)	n	72	81	68
		Mean	2.97	3.04	3.07
		SE	0.089	0.087	0.091
		Median	2.91	2.90	2.97
		Min.	1.43	1.22	1.61
		Max.	5.75	5.08	4.90

Table 7.50
 Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042713

Treatment: FSC100/50

			A, A	A, G	G, G
-----			-----		
FEV1 (L)	Visit 10 (Week 16)	n	71	80	68
		Mean	2.97	3.04	3.06
		SE	0.090	0.087	0.091
		Median	2.96	2.94	3.07
		Min.	1.62	1.15	1.62
		Max.	5.33	5.02	4.93
	Endpoint	n	75	83	75
		Mean	2.96	3.05	3.07
		SE	0.086	0.086	0.086
		Median	2.93	2.94	3.07
		Min.	1.62	1.15	1.62
		Max.	5.33	5.02	4.93
	Overall	n	75	83	75
		Mean	2.97	3.03	3.08
		SE	0.086	0.085	0.083
		Median	2.88	2.92	3.06
		Min.	1.61	1.23	1.70
		Max.	5.69	4.98	4.86
	Visit 11 (Wash-out)	n	70	79	68
		Mean	2.80	2.83	2.96
		SE	0.092	0.082	0.082
		Median	2.59	2.80	2.89
		Min.	1.27	1.20	1.52
		Max.	4.78	4.62	4.69

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Table 7.50
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042713

Treatment: FSC100/50

			A, A	A, G	G, G
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FEV1 change	Visit 7 (Week 4)	n	75	83	75
		Mean	0.24	0.21	0.20
		SE	0.031	0.036	0.040
		Median	0.19	0.15	0.18
		Min.	-0.20	-0.80	-0.67
		Max.	1.03	1.62	1.55
	Visit 8 (Week 8)	n	73	83	70
		Mean	0.23	0.21	0.23
		SE	0.033	0.035	0.035
		Median	0.21	0.11	0.21
		Min.	-0.54	-0.19	-0.51
		Max.	1.18	1.50	1.15
	Visit 9 (Week 12)	n	72	81	68
		Mean	0.22	0.22	0.23
		SE	0.033	0.039	0.038
		Median	0.22	0.14	0.17
		Min.	-0.60	-0.64	-0.38
		Max.	1.04	1.54	1.56
	Visit 10 (Week 16)	n	71	80	68
		Mean	0.22	0.23	0.21
		SE	0.038	0.041	0.048
		Median	0.20	0.16	0.18
		Min.	-0.67	-0.32	-0.74
		Max.	1.29	1.61	1.65

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Table 7.50
 Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042713

Treatment: FSC100/50

		A, A		A, G		G, G	
FEV1 change	Endpoint	n	75	83	75		
		Mean	0.21	0.23	0.21		
		SE	0.036	0.039	0.044		
		Median	0.19	0.16	0.19		
		Min.	-0.67	-0.32	-0.74		
		Max.	1.29	1.61	1.65		
	Overall	n	75	83	75		
		Mean	0.23	0.22	0.21		
		SE	0.028	0.035	0.032		
		Median	0.21	0.14	0.17		
		Min.	-0.41	-0.29	-0.35		
		Max.	1.02	1.52	1.44		
	Visit 11 (Wash-out)	n	70	79	68		
		Mean	0.05	0.02	0.12		
		SE	0.031	0.033	0.037		
		Median	0.05	0.04	0.07		
		Min.	-1.03	-0.63	-0.58		
		Max.	0.60	0.84	1.53		

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Table 7.50
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042713

Treatment: Salmeterol

			A, A	A, G	G, G
-----			-----		
Subjects in treatment			72	79	81
FEV1 (L)	Visit 2 (Week -16)	n	72	79	81
		Mean	2.99	2.84	2.79
		SE	0.090	0.077	0.079
		Median	2.95	2.79	2.70
		Min.	1.60	1.44	1.77
		Max.	4.72	4.76	5.09
	Visit 3 (Week -12)	n	72	79	81
		Mean	2.94	2.93	2.82
		SE	0.088	0.083	0.084
		Median	2.86	2.79	2.75
		Min.	1.64	1.39	1.65
		Max.	4.58	4.66	5.46
	Visit 4 (Week -8)	n	72	79	81
		Mean	3.00	2.88	2.84
		SE	0.088	0.083	0.086
		Median	3.00	2.78	2.72
		Min.	1.58	1.44	1.62
		Max.	4.51	4.69	5.46
	Visit 5 (Week -4)	n	72	79	81
		Mean	3.02	2.91	2.83
		SE	0.092	0.079	0.088
		Median	2.94	2.81	2.74
		Min.	1.62	1.51	1.66
		Max.	4.93	4.61	5.66

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Table 7.50
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042713

Treatment: Salmeterol

			A, A	A, G	G, G
FEV1 (L)	Visit 6 (Day 1)	n	72	79	81
		Mean	2.94	2.88	2.86
		SE	0.090	0.086	0.084
		Median	2.91	2.79	2.79
		Min.	1.66	1.32	1.54
		Max.	4.53	4.73	4.93
	Visit 7 (Week 4)	n	69	76	77
		Mean	3.15	3.02	2.99
		SE	0.101	0.083	0.092
		Median	3.05	2.93	2.92
		Min.	1.45	1.22	1.71
		Max.	4.87	4.89	5.35
	Visit 8 (Week 8)	n	65	72	73
		Mean	3.02	3.05	2.91
		SE	0.094	0.086	0.088
		Median	2.97	2.96	2.81
		Min.	1.62	1.24	1.66
		Max.	4.38	5.36	5.11
	Visit 9 (Week 12)	n	61	69	70
		Mean	3.13	2.95	2.91
		SE	0.102	0.080	0.086
		Median	3.07	2.92	2.92
		Min.	1.56	1.20	1.65
		Max.	4.82	4.41	4.99

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Table 7.50
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042713

Treatment: Salmeterol

			A, A	A, G	G, G
-----			-----		
FEV1 (L)	Visit 10 (Week 16)	n	59	68	70
		Mean	3.16	2.93	2.87
		SE	0.112	0.080	0.093
		Median	3.03	2.90	2.80
		Min.	1.52	1.22	1.43
		Max.	5.15	4.47	5.09
	Endpoint	n	69	76	77
		Mean	3.10	3.01	2.92
		SE	0.106	0.088	0.093
		Median	2.97	2.92	2.80
		Min.	1.52	1.22	1.43
		Max.	5.15	5.36	5.16
	Overall	n	69	76	77
		Mean	3.10	3.03	2.96
		SE	0.096	0.082	0.089
		Median	3.05	2.96	2.91
		Min.	1.57	1.22	1.68
		Max.	4.71	4.89	5.16
	Visit 11 (Wash-out)	n	58	67	70
		Mean	2.93	2.85	2.78
		SE	0.101	0.083	0.094
		Median	2.86	2.82	2.75
		Min.	1.18	1.10	1.39
		Max.	4.38	4.55	5.32

Table 7.50
 Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042713

Treatment: Salmeterol

			A, A	A, G	G, G
FEV1 change	Visit 7 (Week 4)	n	69	76	77
		Mean	0.25	0.13	0.12
		SE	0.050	0.038	0.033
		Median	0.14	0.14	0.10
		Min.	-0.26	-1.33	-0.78
		Max.	2.38	0.99	1.47
	Visit 8 (Week 8)	n	65	72	73
		Mean	0.14	0.18	0.08
		SE	0.035	0.040	0.037
		Median	0.13	0.13	0.07
		Min.	-0.90	-0.29	-0.84
		Max.	0.82	1.73	1.27
	Visit 9 (Week 12)	n	61	69	70
		Mean	0.20	0.11	0.07
		SE	0.041	0.036	0.031
		Median	0.14	0.10	0.07
		Min.	-0.43	-0.61	-0.60
		Max.	1.27	1.05	1.17
	Visit 10 (Week 16)	n	59	68	70
		Mean	0.22	0.10	0.04
		SE	0.063	0.035	0.031
		Median	0.08	0.11	0.04
		Min.	-0.38	-0.90	-0.66
		Max.	2.54	1.16	0.71

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Table 7.50
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042713

Treatment: Salmeterol

			A, A	A, G	G, G
FEV1 change	Endpoint	n	69	76	77
		Mean	0.20	0.12	0.05
		SE	0.055	0.035	0.030
		Median	0.08	0.12	0.04
		Min.	-0.38	-0.90	-0.66
		Max.	2.54	1.16	0.71
	Overall	n	69	76	77
		Mean	0.20	0.14	0.08
		SE	0.036	0.031	0.026
		Median	0.10	0.13	0.06
		Min.	-0.24	-0.47	-0.41
		Max.	1.19	1.05	1.16
	Visit 11 (Wash-out)	n	58	67	70
		Mean	-0.01	0.03	-0.05
		SE	0.041	0.038	0.039
		Median	0.00	0.05	-0.05
		Min.	-0.75	-0.75	-1.54
		Max.	0.93	1.03	1.02

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Table 7.51
Analysis of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042713

			A/A vs. A/G	A/A vs. G/G	A/G vs. G/G
FSC100/50	Visit 7 (Week 4)	p-value	0.379	0.365	0.960
		LS Means Diff	0.04	0.05	0.00
		95% CI for Diff	(-0.06, 0.14)	(-0.06, 0.15)	(-0.10, 0.10)
	Visit 8 (Week 8)	p-value	0.302	0.608	0.619
		LS Means Diff	0.05	0.03	-0.02
		95% CI for Diff	(-0.04, 0.14)	(-0.07, 0.12)	(-0.12, 0.07)
	Visit 9 (Week 12)	p-value	0.611	0.684	0.933
		LS Means Diff	0.03	0.02	-0.00
		95% CI for Diff	(-0.07, 0.12)	(-0.08, 0.12)	(-0.10, 0.09)
	Visit 10 (Week 16)	p-value	0.966	0.665	0.685
		LS Means Diff	0.00	0.03	0.02
		95% CI for Diff	(-0.11, 0.11)	(-0.09, 0.14)	(-0.09, 0.14)
	Endpoint	p-value	0.984	0.737	0.713
		LS Means Diff	-0.00	0.02	0.02
		95% CI for Diff	(-0.11, 0.11)	(-0.09, 0.13)	(-0.09, 0.13)
	Overall	p-value	0.507	0.510	0.990
		LS Means Diff	0.03	0.03	0.00
		95% CI for Diff	(-0.06, 0.12)	(-0.06, 0.12)	(-0.09, 0.09)
	Visit 11 (Wash-out)	p-value	0.445	0.198	0.037
		LS Means Diff	0.04	-0.06	-0.10
		95% CI for Diff	(-0.06, 0.13)	(-0.16, 0.03)	(-0.19, -0.01)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS1042713. Least squares mean differences are calculated as A/A-A/G, A/A-G/G and A/G-G/G.

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Table 7.51
Analysis of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042713

			A/A vs. A/G	A/A vs. G/G	A/G vs. G/G
Salmeterol	Visit 7 (Week 4)	p-value	0.082	0.049	0.809
		LS Means Diff	0.10	0.11	0.01
		95% CI for Diff	(-0.01, 0.21)	(0.00, 0.23)	(-0.10, 0.12)
	Visit 8 (Week 8)	p-value	0.518	0.179	0.040
		LS Means Diff	-0.03	0.07	0.11
		95% CI for Diff	(-0.14, 0.07)	(-0.03, 0.18)	(0.01, 0.21)
	Visit 9 (Week 12)	p-value	0.083	0.020	0.520
		LS Means Diff	0.09	0.12	0.03
		95% CI for Diff	(-0.01, 0.18)	(0.02, 0.22)	(-0.06, 0.12)
	Visit 10 (Week 16)	p-value	0.041	0.005	0.403
		LS Means Diff	0.13	0.18	0.05
		95% CI for Diff	(0.01, 0.25)	(0.05, 0.30)	(-0.07, 0.17)
	Endpoint	p-value	0.190	0.018	0.263
		LS Means Diff	0.08	0.14	0.06
		95% CI for Diff	(-0.04, 0.19)	(0.02, 0.25)	(-0.05, 0.17)
	Overall	p-value	0.167	0.015	0.270
		LS Means Diff	0.06	0.11	0.05
		95% CI for Diff	(-0.03, 0.14)	(0.02, 0.19)	(-0.04, 0.13)
	Visit 11 (Wash-out)	p-value	0.338	0.755	0.181
		LS Means Diff	-0.05	0.02	0.07
		95% CI for Diff	(-0.16, 0.06)	(-0.09, 0.13)	(-0.03, 0.17)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS1042713. Least squares mean differences are calculated as A/A-A/G, A/A-G/G and A/G-G/G.

Table 7.52
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042714

Treatment: FSC100/50

			C, C	C, G	G, G
-----			-----		
Subjects in treatment			147	73	23
FEV1 (L)	Visit 2 (Week -16)	n	147	73	23
		Mean	2.73	3.04	2.73
		SE	0.059	0.074	0.111
		Median	2.66	2.95	2.70
		Min.	1.25	1.93	1.87
		Max.	5.03	4.48	4.03
	Visit 3 (Week -12)	n	147	73	23
		Mean	2.75	3.03	2.78
		SE	0.058	0.071	0.107
		Median	2.64	2.97	2.77
		Min.	1.45	1.68	1.72
		Max.	5.02	4.63	3.68
	Visit 4 (Week -8)	n	147	73	23
		Mean	2.75	3.03	2.84
		SE	0.059	0.065	0.101
		Median	2.68	3.04	2.83
		Min.	1.30	2.11	1.86
		Max.	5.08	4.34	3.55
	Visit 5 (Week -4)	n	147	73	23
		Mean	2.76	3.03	2.79
		SE	0.058	0.067	0.102
		Median	2.69	3.00	2.88
		Min.	1.46	2.08	1.66
		Max.	4.74	4.52	3.55

Table 7.52
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042714

Treatment: FSC100/50

			C, C	C, G	G, G
FEV1 (L)	Visit 6 (Day 1)	n	147	73	23
		Mean	2.73	3.03	2.75
		SE	0.060	0.068	0.093
		Median	2.59	2.98	2.68
		Min.	1.32	2.07	1.84
		Max.	4.95	4.34	3.45
	Visit 7 (Week 4)	n	140	72	21
		Mean	2.93	3.24	2.92
		SE	0.068	0.082	0.113
		Median	2.86	3.19	2.96
		Min.	1.36	1.87	1.83
		Max.	5.98	4.73	3.74
	Visit 8 (Week 8)	n	138	69	19
		Mean	2.94	3.22	2.88
		SE	0.067	0.087	0.137
		Median	2.87	3.07	2.95
		Min.	1.20	1.92	1.64
		Max.	5.68	4.89	3.78
	Visit 9 (Week 12)	n	135	67	19
		Mean	2.94	3.25	2.88
		SE	0.068	0.089	0.131
		Median	2.87	3.08	3.09
		Min.	1.22	2.05	1.61
		Max.	5.75	4.90	3.84

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Table 7.52
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042714

Treatment: FSC100/50

			C, C	C, G	G, G
-----			-----		
FEV1 change	Visit 7 (Week 4)	n	140	72	21
		Mean	0.22	0.21	0.22
		SE	0.025	0.044	0.044
		Median	0.18	0.13	0.19
		Min.	-0.80	-0.67	-0.01
		Max.	1.62	1.55	0.80
	Visit 8 (Week 8)	n	138	69	19
		Mean	0.22	0.23	0.20
		SE	0.024	0.040	0.060
		Median	0.19	0.09	0.12
		Min.	-0.54	-0.51	-0.20
		Max.	1.41	1.50	0.85
	Visit 9 (Week 12)	n	135	67	19
		Mean	0.22	0.25	0.20
		SE	0.026	0.044	0.059
		Median	0.22	0.14	0.17
		Min.	-0.64	-0.35	-0.23
		Max.	1.44	1.56	0.61
	Visit 10 (Week 16)	n	133	67	19
		Mean	0.20	0.28	0.20
		SE	0.030	0.049	0.071
		Median	0.17	0.20	0.16
		Min.	-0.68	-0.74	-0.37
		Max.	1.59	1.65	0.88

Table 7.52
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042714

Treatment: FSC100/50

		C, C		C, G	G, G
-----		-----		-----	-----
FEV1 change	Endpoint	n	140	72	21
		Mean	0.19	0.27	0.20
		SE	0.028	0.046	0.064
		Median	0.17	0.20	0.19
		Min.	-0.68	-0.74	-0.37
		Max.	1.59	1.65	0.88
	Overall	n	140	72	21
		Mean	0.21	0.24	0.21
		SE	0.023	0.038	0.048
		Median	0.19	0.12	0.21
		Min.	-0.41	-0.28	-0.14
		Max.	1.52	1.44	0.72
	Visit 11 (Wash-out)	n	132	66	19
		Mean	0.06	0.05	0.13
		SE	0.027	0.032	0.054
		Median	0.06	0.04	0.15
		Min.	-1.03	-0.57	-0.14
		Max.	1.53	0.81	0.88

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Table 7.52
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042714

Treatment: Salmeterol

			C, C	C, G	G, G
-----			-----		
Subjects in treatment			133	71	25
FEV1 (L)	Visit 2 (Week -16)	n	133	71	25
		Mean	2.88	2.84	2.88
		SE	0.065	0.089	0.092
		Median	2.83	2.69	2.93
		Min.	1.44	1.55	1.99
		Max.	4.76	5.09	3.95
	Visit 3 (Week -12)	n	133	71	25
		Mean	2.91	2.86	2.90
		SE	0.066	0.094	0.103
		Median	2.79	2.70	2.87
		Min.	1.39	1.65	1.96
		Max.	4.66	5.46	4.39
	Visit 4 (Week -8)	n	133	71	25
		Mean	2.91	2.91	2.87
		SE	0.064	0.099	0.094
		Median	2.88	2.71	2.87
		Min.	1.44	1.70	2.15
		Max.	4.63	5.46	3.99
	Visit 5 (Week -4)	n	133	71	25
		Mean	2.93	2.92	2.82
		SE	0.066	0.097	0.096
		Median	2.82	2.75	2.76
		Min.	1.51	1.66	1.92
		Max.	4.93	5.66	4.01

Table 7.52
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042714

Treatment: Salmeterol

			C, C	C, G	G, G
FEV1 (L)	Visit 6 (Day 1)	n	133	71	25
		Mean	2.88	2.89	2.93
		SE	0.068	0.093	0.089
		Median	2.76	2.80	2.91
		Min.	1.32	1.65	2.11
		Max.	4.71	4.93	4.00
	Visit 7 (Week 4)	n	127	69	23
		Mean	3.06	3.01	3.09
		SE	0.072	0.098	0.108
		Median	3.00	2.89	2.99
		Min.	1.22	1.80	1.96
		Max.	4.89	5.35	4.28
	Visit 8 (Week 8)	n	121	67	20
		Mean	2.99	2.99	3.12
		SE	0.069	0.096	0.101
		Median	2.82	2.93	3.17
		Min.	1.24	1.72	2.09
		Max.	5.11	5.36	4.29
	Visit 9 (Week 12)	n	114	64	20
		Mean	3.03	2.93	3.05
		SE	0.073	0.087	0.114
		Median	2.94	2.91	3.02
		Min.	1.20	1.70	1.82
		Max.	4.83	4.99	4.36

Table 7.52
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042714

Treatment: Salmeterol

			C, C	C, G	G, G
-----			-----		
FEV1 (L)	Visit 10 (Week 16)	n	111	64	20
		Mean	3.02	2.92	3.01
		SE	0.080	0.090	0.114
		Median	2.90	2.89	3.06
		Min.	1.22	1.43	1.67
		Max.	5.15	5.09	4.10
	Endpoint	n	127	69	23
		Mean	3.01	2.98	3.06
		SE	0.076	0.098	0.116
		Median	2.90	2.89	3.07
		Min.	1.22	1.43	1.67
		Max.	5.15	5.36	4.28
	Overall	n	127	69	23
		Mean	3.03	2.99	3.10
		SE	0.069	0.094	0.108
		Median	2.92	2.95	3.00
		Min.	1.22	1.73	1.89
		Max.	4.89	5.16	4.28
	Visit 11 (Wash-out)	n	110	63	20
		Mean	2.89	2.78	2.88
		SE	0.076	0.091	0.110
		Median	2.82	2.65	2.88
		Min.	1.10	1.46	1.67
		Max.	5.32	4.65	4.17

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Table 7.52
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042714

Treatment: Salmeterol

			C, C	C, G	G, G
FEV1 change	Visit 7 (Week 4)	n	127	69	23
		Mean	0.20	0.11	0.12
		SE	0.036	0.033	0.045
		Median	0.13	0.14	0.09
		Min.	-0.78	-1.33	-0.33
		Max.	2.38	0.73	0.65
	Visit 8 (Week 8)	n	121	67	20
		Mean	0.15	0.10	0.16
		SE	0.032	0.032	0.046
		Median	0.08	0.11	0.14
		Min.	-0.90	-0.78	-0.20
		Max.	1.73	0.82	0.58
	Visit 9 (Week 12)	n	114	64	20
		Mean	0.16	0.08	0.09
		SE	0.031	0.030	0.051
		Median	0.10	0.09	0.07
		Min.	-0.61	-0.61	-0.47
		Max.	1.27	0.86	0.44
	Visit 10 (Week 16)	n	111	64	20
		Mean	0.15	0.07	0.05
		SE	0.041	0.028	0.055
		Median	0.07	0.08	0.09
		Min.	-0.90	-0.41	-0.62
		Max.	2.54	0.60	0.47

Table 7.52
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042714

Treatment: Salmeterol

			C, C	C, G	G, G
FEV1 change	Endpoint	n	127	69	23
		Mean	0.15	0.09	0.09
		SE	0.037	0.027	0.055
		Median	0.07	0.09	0.10
		Min.	-0.90	-0.41	-0.62
		Max.	2.54	0.63	0.65
		Overall			
	Overall	n	127	69	23
		Mean	0.16	0.09	0.13
		SE	0.028	0.022	0.043
		Median	0.10	0.08	0.12
		Min.	-0.47	-0.35	-0.41
		Max.	1.19	0.58	0.65
	Visit 11 (Wash-out)	n	110	63	20
		Mean	0.03	-0.06	-0.08
		SE	0.035	0.030	0.049
		Median	0.02	-0.02	-0.04
		Min.	-1.54	-0.75	-0.62
		Max.	1.03	0.52	0.33

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Table 7.53
Analysis of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042714

			C/C vs. C/G	C/C vs. G/G	C/G vs. G/G
FSC100/50	Visit 7 (Week 4)	p-value	0.611	0.709	0.956
		LS Means Diff	0.02	0.03	0.00
		95% CI for Diff	(-0.07, 0.12)	(-0.12, 0.18)	(-0.15, 0.16)
	Visit 8 (Week 8)	p-value	0.597	0.268	0.447
		LS Means Diff	0.02	0.08	0.06
		95% CI for Diff	(-0.06, 0.11)	(-0.06, 0.23)	(-0.09, 0.21)
	Visit 9 (Week 12)	p-value	0.990	0.289	0.313
		LS Means Diff	0.00	0.08	0.08
		95% CI for Diff	(-0.09, 0.09)	(-0.07, 0.23)	(-0.08, 0.24)
	Visit 10 (Week 16)	p-value	0.203	0.530	0.179
		LS Means Diff	-0.07	0.06	0.12
		95% CI for Diff	(-0.17, 0.04)	(-0.12, 0.23)	(-0.06, 0.30)
	Endpoint	p-value	0.236	0.573	0.213
		LS Means Diff	-0.06	0.05	0.11
		95% CI for Diff	(-0.16, 0.04)	(-0.12, 0.21)	(-0.06, 0.28)
	Overall	p-value	0.991	0.419	0.434
		LS Means Diff	-0.00	0.05	0.05
		95% CI for Diff	(-0.08, 0.08)	(-0.08, 0.19)	(-0.08, 0.19)
	Visit 11 (Wash-out)	p-value	0.874	0.577	0.531
		LS Means Diff	0.01	-0.04	-0.05
		95% CI for Diff	(-0.08, 0.10)	(-0.19, 0.10)	(-0.20, 0.10)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS1042714. Least squares mean differences are calculated as C/C-C/G, C/C-G/G and C/G-G/G.

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Table 7.53
Analysis of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042714

			C/C vs. C/G	C/C vs. G/G	C/G vs. G/G
Salmeterol	Visit 7 (Week 4)	p-value	0.251	0.487	0.944
		LS Means Diff	0.06	0.06	-0.01
		95% CI for Diff	(-0.04, 0.17)	(-0.10, 0.22)	(-0.17, 0.16)
	Visit 8 (Week 8)	p-value	0.192	0.829	0.544
		LS Means Diff	0.07	0.02	-0.05
		95% CI for Diff	(-0.03, 0.16)	(-0.14, 0.17)	(-0.20, 0.11)
	Visit 9 (Week 12)	p-value	0.126	0.344	0.960
		LS Means Diff	0.07	0.07	-0.00
		95% CI for Diff	(-0.02, 0.16)	(-0.07, 0.21)	(-0.15, 0.14)
	Visit 10 (Week 16)	p-value	0.156	0.211	0.749
		LS Means Diff	0.08	0.11	0.03
		95% CI for Diff	(-0.03, 0.20)	(-0.06, 0.29)	(-0.15, 0.21)
	Endpoint	p-value	0.343	0.439	0.890
		LS Means Diff	0.05	0.06	0.01
		95% CI for Diff	(-0.06, 0.16)	(-0.10, 0.22)	(-0.15, 0.18)
	Overall	p-value	0.142	0.599	0.657
		LS Means Diff	0.06	0.03	-0.03
		95% CI for Diff	(-0.02, 0.14)	(-0.09, 0.15)	(-0.15, 0.09)
	Visit 11 (Wash-out)	p-value	0.151	0.214	0.768
		LS Means Diff	0.07	0.10	0.02
		95% CI for Diff	(-0.03, 0.17)	(-0.06, 0.25)	(-0.13, 0.18)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS1042714. Least squares mean differences are calculated as C/C-C/G, C/C-G/G and C/G-G/G.

Table 7.54
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042718

Treatment: FSC100/50

			A, A	A, C	C, C
-----			-----		
Subjects in treatment			17	78	148
FEV1 (L)	Visit 2 (Week -16)	n	17	78	148
		Mean	2.55	2.84	2.84
		SE	0.135	0.084	0.054
		Median	2.64	2.80	2.81
		Min.	1.62	1.25	1.44
		Max.	3.32	4.52	5.03
	Visit 3 (Week -12)	n	17	78	148
		Mean	2.59	2.86	2.85
		SE	0.138	0.081	0.054
		Median	2.67	2.88	2.77
		Min.	1.70	1.45	1.48
		Max.	3.39	4.63	5.02
	Visit 4 (Week -8)	n	17	78	148
		Mean	2.57	2.86	2.86
		SE	0.139	0.079	0.053
		Median	2.63	2.83	2.79
		Min.	1.62	1.30	1.57
		Max.	3.64	4.60	5.08
	Visit 5 (Week -4)	n	17	78	148
		Mean	2.54	2.89	2.86
		SE	0.143	0.081	0.052
		Median	2.54	2.85	2.83
		Min.	1.62	1.46	1.63
		Max.	3.35	4.63	4.74

Table 7.54
 Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042718

Treatment: FSC100/50

			A, A	A, C	C, C
FEV1 (L)	Visit 6 (Day 1)	n	17	78	148
		Mean	2.49	2.89	2.83
		SE	0.135	0.082	0.054
		Median	2.61	2.80	2.77
		Min.	1.45	1.33	1.32
		Max.	3.28	4.51	4.95
	Visit 7 (Week 4)	n	17	77	139
		Mean	2.69	3.09	3.03
		SE	0.146	0.095	0.062
		Median	2.78	2.97	2.97
		Min.	1.75	1.36	1.63
		Max.	3.50	4.86	5.98
	Visit 8 (Week 8)	n	17	74	135
		Mean	2.76	3.05	3.04
		SE	0.142	0.099	0.063
		Median	2.95	2.94	2.98
		Min.	1.76	1.20	1.64
		Max.	3.68	4.97	5.68
	Visit 9 (Week 12)	n	16	72	133
		Mean	2.73	3.09	3.03
		SE	0.137	0.104	0.062
		Median	2.82	2.89	2.96
		Min.	1.79	1.22	1.43
		Max.	3.70	5.08	5.75

Table 7.54
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042718

Treatment: FSC100/50

		A, A		A, C		C, C	
-----		-----		-----		-----	
FEV1 (L)	Visit 10 (Week 16)	n	16	71	132		
		Mean	2.69	3.07	3.04		
		SE	0.155	0.101	0.062		
		Median	2.86	2.94	3.02		
		Min.	1.62	1.15	1.62		
		Max.	3.67	5.02	5.33		
	Endpoint	n	17	77	139		
		Mean	2.64	3.11	3.03		
		SE	0.154	0.096	0.060		
		Median	2.81	3.02	2.99		
		Min.	1.62	1.15	1.62		
		Max.	3.67	5.02	5.33		
	Overall	n	17	77	139		
		Mean	2.69	3.10	3.03		
		SE	0.142	0.095	0.060		
		Median	2.82	2.93	2.98		
		Min.	1.78	1.23	1.61		
		Max.	3.64	4.98	5.69		
	Visit 11 (Wash-out)	n	16	71	130		
		Mean	2.71	2.91	2.86		
		SE	0.169	0.093	0.061		
		Median	2.77	2.83	2.83		
		Min.	1.52	1.20	1.27		
		Max.	4.06	4.69	4.78		

Table 7.54
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042718

Treatment: FSC100/50

			A, A	A, C	C, C

FEV1 change	Visit 7 (Week 4)	n	17	77	139
		Mean	0.20	0.20	0.23
		SE	0.059	0.046	0.023
		Median	0.21	0.15	0.19
		Min.	-0.32	-0.80	-0.35
		Max.	0.69	1.62	1.12
	Visit 8 (Week 8)	n	17	74	135
		Mean	0.27	0.20	0.23
		SE	0.049	0.037	0.025
		Median	0.24	0.14	0.18
		Min.	-0.11	-0.51	-0.54
		Max.	0.69	1.41	1.50
	Visit 9 (Week 12)	n	16	72	133
		Mean	0.19	0.24	0.22
		SE	0.063	0.041	0.027
		Median	0.19	0.18	0.18
		Min.	-0.34	-0.38	-0.64
		Max.	0.60	1.56	1.54
	Visit 10 (Week 16)	n	16	71	132
		Mean	0.15	0.22	0.23
		SE	0.082	0.050	0.029
		Median	0.12	0.16	0.19
		Min.	-0.68	-0.74	-0.67
		Max.	0.77	1.65	1.61

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Table 7.54
 Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042718

Treatment: FSC100/50

		A, A		A, C		C, C	
FEV1 change	Endpoint	n	17	77	139		
		Mean	0.16	0.22	0.22		
		SE	0.077	0.046	0.027		
		Median	0.13	0.16	0.19		
		Min.	-0.68	-0.74	-0.67		
		Max.	0.77	1.65	1.61		
	Overall	n	17	77	139		
		Mean	0.21	0.21	0.23		
		SE	0.054	0.037	0.022		
		Median	0.22	0.16	0.19		
		Min.	-0.21	-0.35	-0.41		
		Max.	0.60	1.52	1.44		
	Visit 11 (Wash-out)	n	16	71	130		
		Mean	0.17	0.06	0.05		
		SE	0.100	0.036	0.023		
		Median	0.07	0.06	0.05		
		Min.	-0.26	-0.58	-1.03		
		Max.	1.53	0.84	0.88		

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Table 7.54
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042718

Treatment: Salmeterol

			A, A	A, C	C, C
-----			-----		
Subjects in treatment			21	68	143
FEV1 (L)	Visit 2 (Week -16)	n	21	68	143
		Mean	2.54	2.82	2.94
		SE	0.121	0.098	0.058
		Median	2.46	2.71	2.84
		Min.	1.80	1.44	1.55
		Max.	4.25	5.09	4.76
	Visit 3 (Week -12)	n	21	68	143
		Mean	2.65	2.89	2.93
		SE	0.146	0.105	0.058
		Median	2.60	2.73	2.82
		Min.	1.71	1.39	1.64
		Max.	4.57	5.46	4.66
	Visit 4 (Week -8)	n	21	68	143
		Mean	2.64	2.87	2.96
		SE	0.149	0.106	0.058
		Median	2.59	2.67	2.90
		Min.	1.62	1.44	1.58
		Max.	4.63	5.46	4.69
	Visit 5 (Week -4)	n	21	68	143
		Mean	2.60	2.92	2.96
		SE	0.150	0.106	0.059
		Median	2.71	2.78	2.85
		Min.	1.75	1.51	1.62
		Max.	4.88	5.66	4.93

Table 7.54
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042718

Treatment: Salmeterol

			A, A	A, C	C, C
FEV1 (L)	Visit 6 (Day 1)	n	21	68	143
		Mean	2.62	2.89	2.93
		SE	0.142	0.110	0.058
		Median	2.51	2.77	2.87
		Min.	1.54	1.32	1.66
		Max.	4.30	4.93	4.73
	Visit 7 (Week 4)	n	20	65	137
		Mean	2.75	3.02	3.11
		SE	0.162	0.112	0.063
		Median	2.57	2.89	3.02
		Min.	1.71	1.22	1.45
		Max.	4.61	5.35	4.89
	Visit 8 (Week 8)	n	20	62	128
		Mean	2.70	2.94	3.06
		SE	0.156	0.107	0.061
		Median	2.67	2.80	3.01
		Min.	1.66	1.24	1.62
		Max.	5.11	5.10	5.36
	Visit 9 (Week 12)	n	18	60	122
		Mean	2.76	2.88	3.08
		SE	0.159	0.106	0.061
		Median	2.70	2.72	3.02
		Min.	1.65	1.20	1.56
		Max.	4.83	4.99	4.82

Table 7.54
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042718

Treatment: Salmeterol

			A, A	A, C	C, C
-----			-----		
FEV1 (L)	Visit 10 (Week 16)	n	18	59	120
		Mean	2.65	2.86	3.08
		SE	0.184	0.110	0.065
		Median	2.49	2.68	3.02
		Min.	1.53	1.22	1.52
		Max.	4.66	5.09	5.15
	Endpoint	n	20	65	137
		Mean	2.63	2.97	3.08
		SE	0.169	0.111	0.067
		Median	2.49	2.80	3.00
		Min.	1.53	1.22	1.52
		Max.	4.66	5.16	5.36
	Overall	n	20	65	137
		Mean	2.70	2.99	3.09
		SE	0.151	0.108	0.061
		Median	2.65	2.84	3.04
		Min.	1.68	1.22	1.57
		Max.	4.80	5.16	4.89
	Visit 11 (Wash-out)	n	18	59	118
		Mean	2.62	2.83	2.89
		SE	0.206	0.110	0.061
		Median	2.46	2.63	2.85
		Min.	1.39	1.10	1.18
		Max.	5.32	4.65	4.38

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Table 7.54
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042718

Treatment: Salmeterol

			A, A	A, C	C, C
FEV1 change	Visit 7 (Week 4)	n	20	65	137
		Mean	0.13	0.12	0.19
		SE	0.100	0.035	0.031
		Median	0.05	0.14	0.13
		Min.	-0.78	-0.63	-1.33
		Max.	1.47	0.92	2.38
	Visit 8 (Week 8)	n	20	62	128
		Mean	0.08	0.10	0.16
		SE	0.098	0.047	0.023
		Median	0.01	0.05	0.14
		Min.	-0.84	-0.78	-0.90
		Max.	1.27	1.73	0.99
	Visit 9 (Week 12)	n	18	60	122
		Mean	0.12	0.06	0.16
		SE	0.087	0.035	0.027
		Median	0.05	0.07	0.13
		Min.	-0.45	-0.61	-0.61
		Max.	1.17	0.79	1.27
	Visit 10 (Week 16)	n	18	59	120
		Mean	0.01	0.05	0.16
		SE	0.071	0.037	0.035
		Median	-0.04	0.04	0.09
		Min.	-0.66	-0.90	-0.62
		Max.	0.71	0.73	2.54

Table 7.54
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042718

Treatment: Salmeterol

			A, A	A, C	C, C
-----			-----		
FEV1 change	Endpoint	n	20	65	137
		Mean	0.01	0.07	0.16
		SE	0.065	0.037	0.032
		Median	-0.04	0.07	0.10
		Min.	-0.66	-0.90	-0.62
		Max.	0.71	1.02	2.54
	Overall	n	20	65	137
		Mean	0.08	0.09	0.17
		SE	0.071	0.032	0.022
		Median	-0.03	0.09	0.12
		Min.	-0.36	-0.47	-0.41
		Max.	1.16	0.97	1.19
	Visit 11 (Wash-out)	n	18	59	118
		Mean	-0.01	0.02	-0.03
		SE	0.129	0.036	0.027
		Median	-0.12	0.00	-0.01
		Min.	-1.54	-0.43	-0.75
		Max.	1.02	1.03	0.93

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Table 7.55
Analysis of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042718

			A/A vs. A/C	A/A vs. C/C	A/C vs. C/C
FSC100/50	Visit 7 (Week 4)	p-value	0.694	0.934	0.552
		LS Means Diff	0.03	0.01	-0.03
		95% CI for Diff	(-0.14, 0.20)	(-0.16, 0.17)	(-0.12, 0.06)
	Visit 8 (Week 8)	p-value	0.099	0.185	0.480
		LS Means Diff	0.13	0.10	-0.03
		95% CI for Diff	(-0.03, 0.29)	(-0.05, 0.25)	(-0.11, 0.05)
	Visit 9 (Week 12)	p-value	0.948	0.753	0.651
		LS Means Diff	0.01	0.03	0.02
		95% CI for Diff	(-0.16, 0.17)	(-0.14, 0.19)	(-0.07, 0.11)
	Visit 10 (Week 16)	p-value	0.681	0.714	0.912
		LS Means Diff	-0.04	-0.03	0.01
		95% CI for Diff	(-0.23, 0.15)	(-0.22, 0.15)	(-0.10, 0.11)
	Endpoint	p-value	0.767	0.817	0.890
		LS Means Diff	-0.03	-0.02	0.01
		95% CI for Diff	(-0.21, 0.16)	(-0.20, 0.16)	(-0.09, 0.10)
	Overall	p-value	0.585	0.693	0.752
		LS Means Diff	0.04	0.03	-0.01
		95% CI for Diff	(-0.11, 0.19)	(-0.11, 0.17)	(-0.09, 0.07)
	Visit 11 (Wash-out)	p-value	0.149	0.064	0.517
		LS Means Diff	0.12	0.15	0.03
		95% CI for Diff	(-0.04, 0.28)	(-0.01, 0.30)	(-0.06, 0.11)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS1042718. Least squares mean differences are calculated as A/A-A/C, A/A-C/C and A/C-C/C.

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Table 7.55
Analysis of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042718

			A/A vs. A/C	A/A vs. C/C	A/C vs. C/C
Salmeterol	Visit 7 (Week 4)	p-value	0.496	0.175	0.288
		LS Means Diff	-0.06	-0.12	-0.06
		95% CI for Diff	(-0.24, 0.12)	(-0.29, 0.05)	(-0.16, 0.05)
	Visit 8 (Week 8)	p-value	0.770	0.378	0.353
		LS Means Diff	-0.02	-0.07	-0.05
		95% CI for Diff	(-0.19, 0.14)	(-0.22, 0.09)	(-0.14, 0.05)
	Visit 9 (Week 12)	p-value	0.778	0.322	0.035
		LS Means Diff	0.02	-0.07	-0.09
		95% CI for Diff	(-0.13, 0.17)	(-0.22, 0.07)	(-0.18, -0.01)
	Visit 10 (Week 16)	p-value	0.456	0.071	0.088
		LS Means Diff	-0.07	-0.17	-0.10
		95% CI for Diff	(-0.26, 0.12)	(-0.35, 0.01)	(-0.20, 0.01)
	Endpoint	p-value	0.240	0.037	0.159
		LS Means Diff	-0.11	-0.18	-0.07
		95% CI for Diff	(-0.28, 0.07)	(-0.35, -0.01)	(-0.18, 0.03)
	Overall	p-value	0.356	0.049	0.097
		LS Means Diff	-0.06	-0.13	-0.06
		95% CI for Diff	(-0.19, 0.07)	(-0.25, -0.00)	(-0.14, 0.01)
	Visit 11 (Wash-out)	p-value	0.402	0.956	0.182
		LS Means Diff	-0.07	-0.00	0.07
		95% CI for Diff	(-0.24, 0.09)	(-0.16, 0.15)	(-0.03, 0.16)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS1042718. Least squares mean differences are calculated as A/A-A/C, A/A-C/C and A/C-C/C.

Table 7.56
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042719

Treatment: FSC100/50

			C, C	C, G	G, G
-----			-----		
Subjects in treatment			28	99	116
FEV1 (L)	Visit 2 (Week -16)	n	28	99	116
		Mean	2.76	2.83	2.83
		SE	0.125	0.075	0.060
		Median	2.78	2.80	2.77
		Min.	1.62	1.25	1.44
		Max.	4.03	5.03	4.70
	Visit 3 (Week -12)	n	28	99	116
		Mean	2.78	2.85	2.84
		SE	0.129	0.072	0.059
		Median	2.73	2.79	2.77
		Min.	1.70	1.45	1.48
		Max.	4.06	5.02	4.61
	Visit 4 (Week -8)	n	28	99	116
		Mean	2.74	2.87	2.83
		SE	0.123	0.070	0.060
		Median	2.69	2.88	2.75
		Min.	1.62	1.30	1.57
		Max.	4.05	5.08	4.59
	Visit 5 (Week -4)	n	28	99	116
		Mean	2.77	2.87	2.84
		SE	0.132	0.069	0.058
		Median	2.78	2.85	2.80
		Min.	1.62	1.46	1.63
		Max.	4.13	4.74	4.63

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Table 7.56
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042719

Treatment: FSC100/50

			C, C	C, G	G, G
FEV1 (L)	Visit 6 (Day 1)	n	28	99	116
		Mean	2.72	2.88	2.80
		SE	0.116	0.074	0.059
		Median	2.81	2.79	2.76
		Min.	1.45	1.33	1.32
		Max.	3.88	4.95	4.51
	Visit 7 (Week 4)	n	27	98	108
		Mean	2.83	3.09	3.02
		SE	0.117	0.086	0.068
		Median	2.98	2.97	2.97
		Min.	1.75	1.36	1.63
		Max.	3.79	5.98	4.86
	Visit 8 (Week 8)	n	27	94	105
		Mean	2.93	3.05	3.02
		SE	0.123	0.087	0.070
		Median	3.02	2.92	2.95
		Min.	1.75	1.20	1.64
		Max.	4.26	5.68	4.97
	Visit 9 (Week 12)	n	27	91	103
		Mean	2.88	3.08	3.02
		SE	0.125	0.089	0.071
		Median	2.96	2.91	2.94
		Min.	1.77	1.22	1.43
		Max.	3.96	5.75	5.08

Table 7.56
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042719

Treatment: FSC100/50

			C, C	C, G	G, G
-----			-----		
FEV1 (L)	Visit 10 (Week 16)	n	27	89	103
		Mean	2.86	3.07	3.03
		SE	0.146	0.085	0.071
		Median	2.95	2.97	2.99
		Min.	1.62	1.15	1.62
		Max.	4.64	5.33	5.02
	Endpoint	n	27	98	108
		Mean	2.86	3.08	3.02
		SE	0.146	0.081	0.069
		Median	2.95	2.99	2.98
		Min.	1.62	1.15	1.62
		Max.	4.64	5.33	5.02
	Overall	n	27	98	108
		Mean	2.88	3.08	3.02
		SE	0.124	0.083	0.067
		Median	2.96	2.92	2.95
		Min.	1.78	1.23	1.61
		Max.	3.93	5.69	4.98
	Visit 11 (Wash-out)	n	27	88	102
		Mean	2.84	2.90	2.84
		SE	0.143	0.080	0.069
		Median	2.85	2.82	2.82
		Min.	1.52	1.20	1.27
		Max.	4.26	4.78	4.64

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Table 7.56
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042719

Treatment: FSC100/50

			C, C	C, G	G, G
FEV1 change	Visit 7 (Week 4)	n	27	98	108
		Mean	0.16	0.21	0.24
		SE	0.055	0.036	0.027
		Median	0.18	0.16	0.19
		Min.	-0.67	-0.80	-0.35
		Max.	0.69	1.62	1.12
	Visit 8 (Week 8)	n	27	94	105
		Mean	0.26	0.19	0.24
		SE	0.041	0.031	0.030
		Median	0.22	0.14	0.21
		Min.	-0.13	-0.51	-0.54
		Max.	0.69	1.41	1.50
	Visit 9 (Week 12)	n	27	91	103
		Mean	0.21	0.22	0.24
		SE	0.049	0.035	0.032
		Median	0.22	0.15	0.18
		Min.	-0.38	-0.64	-0.60
		Max.	0.61	1.56	1.54
	Visit 10 (Week 16)	n	27	89	103
		Mean	0.18	0.21	0.25
		SE	0.068	0.039	0.035
		Median	0.13	0.16	0.19
		Min.	-0.68	-0.74	-0.67
		Max.	0.99	1.65	1.61

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Table 7.56
 Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042719

Treatment: FSC100/50

		C, C		C, G	G, G
-----		-----		-----	-----
FEV1 change	Endpoint	n	27	98	108
		Mean	0.18	0.21	0.24
		SE	0.068	0.036	0.034
		Median	0.13	0.16	0.19
		Min.	-0.68	-0.74	-0.67
		Max.	0.99	1.65	1.61
	Overall	n	27	98	108
		Mean	0.20	0.20	0.24
		SE	0.044	0.030	0.027
		Median	0.18	0.17	0.20
		Min.	-0.35	-0.29	-0.41
		Max.	0.60	1.52	1.44
	Visit 11 (Wash-out)	n	27	88	102
		Mean	0.16	0.04	0.05
		SE	0.071	0.028	0.028
		Median	0.10	0.06	0.04
		Min.	-0.58	-0.63	-1.03
		Max.	1.53	0.84	0.88

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Table 7.56
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042719

Treatment: Salmeterol

			C, C	C, G	G, G
-----			-----		
Subjects in treatment			25	90	117
FEV1 (L)	Visit 2 (Week -16)	n	25	90	117
		Mean	2.88	2.82	2.90
		SE	0.157	0.079	0.064
		Median	2.74	2.74	2.84
		Min.	1.80	1.44	1.55
		Max.	4.28	5.09	4.72
	Visit 3 (Week -12)	n	25	90	117
		Mean	2.93	2.88	2.90
		SE	0.163	0.084	0.065
		Median	2.89	2.73	2.80
		Min.	1.71	1.39	1.64
		Max.	4.57	5.46	4.63
	Visit 4 (Week -8)	n	25	90	117
		Mean	2.92	2.86	2.93
		SE	0.166	0.085	0.065
		Median	2.72	2.69	2.89
		Min.	1.62	1.44	1.58
		Max.	4.63	5.46	4.69
	Visit 5 (Week -4)	n	25	90	117
		Mean	2.92	2.90	2.93
		SE	0.173	0.083	0.067
		Median	2.74	2.79	2.84
		Min.	1.75	1.51	1.62
		Max.	4.88	5.66	4.93

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Table 7.56
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042719

Treatment: Salmeterol

			C, C	C, G	G, G
FEV1 (L)	Visit 6 (Day 1)	n	25	90	117
		Mean	2.88	2.86	2.92
		SE	0.168	0.086	0.065
		Median	2.66	2.78	2.86
		Min.	1.54	1.32	1.66
		Max.	4.50	4.93	4.73
	Visit 7 (Week 4)	n	24	86	112
		Mean	3.06	3.00	3.09
		SE	0.178	0.088	0.071
		Median	2.85	2.90	3.00
		Min.	1.71	1.22	1.45
		Max.	4.61	5.35	4.87
	Visit 8 (Week 8)	n	24	82	104
		Mean	2.99	2.92	3.05
		SE	0.175	0.082	0.070
		Median	2.77	2.80	3.01
		Min.	1.66	1.24	1.62
		Max.	5.11	5.10	5.36
	Visit 9 (Week 12)	n	21	81	98
		Mean	3.01	2.89	3.07
		SE	0.180	0.082	0.070
		Median	2.74	2.85	3.02
		Min.	1.65	1.20	1.56
		Max.	4.83	4.99	4.82

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Table 7.56
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042719

Treatment: Salmeterol

			C, C	C, G	G, G
FEV1 (L)	Visit 10 (Week 16)	n	21	80	96
		Mean	3.00	2.84	3.09
		SE	0.197	0.085	0.075
		Median	2.75	2.80	3.03
		Min.	1.71	1.22	1.52
		Max.	4.66	5.09	5.15
	Endpoint	n	24	86	112
		Mean	3.00	2.93	3.07
		SE	0.184	0.090	0.075
		Median	2.78	2.84	2.99
		Min.	1.71	1.22	1.52
		Max.	4.66	5.16	5.36
	Overall	n	24	86	112
		Mean	3.01	2.97	3.07
		SE	0.172	0.086	0.068
		Median	2.77	2.89	3.04
		Min.	1.68	1.22	1.57
		Max.	4.80	5.16	4.71
	Visit 11 (Wash-out)	n	21	79	95
		Mean	2.94	2.79	2.87
		SE	0.222	0.084	0.069
		Median	2.67	2.67	2.85
		Min.	1.39	1.10	1.18
		Max.	5.32	4.65	4.38

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Table 7.56
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042719

Treatment: Salmeterol

			C, C	C, G	G, G
FEV1 change	Visit 7 (Week 4)	n	24	86	112
		Mean	0.16	0.14	0.18
		SE	0.090	0.029	0.036
		Median	0.10	0.14	0.11
		Min.	-0.78	-0.63	-1.33
		Max.	1.47	0.99	2.38
	Visit 8 (Week 8)	n	24	82	104
		Mean	0.09	0.13	0.14
		SE	0.097	0.037	0.024
		Median	0.01	0.07	0.14
		Min.	-0.84	-0.78	-0.90
		Max.	1.27	1.73	0.82
	Visit 9 (Week 12)	n	21	81	98
		Mean	0.08	0.11	0.15
		SE	0.079	0.032	0.030
		Median	-0.01	0.09	0.12
		Min.	-0.45	-0.61	-0.61
		Max.	1.17	1.05	1.27
	Visit 10 (Week 16)	n	21	80	96
		Mean	0.07	0.08	0.16
		SE	0.066	0.036	0.040
		Median	-0.03	0.06	0.09
		Min.	-0.41	-0.90	-0.40
		Max.	0.74	1.16	2.54

Table 7.56
 Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042719

Treatment: Salmeterol

		C, C		C, G	G, G
-----		-----		-----	
FEV1 change	Endpoint	n	24	86	112
		Mean	0.10	0.08	0.16
		SE	0.071	0.034	0.035
		Median	-0.03	0.08	0.09
		Min.	-0.41	-0.90	-0.40
		Max.	1.02	1.16	2.54
	Overall	n	24	86	112
		Mean	0.11	0.12	0.16
		SE	0.075	0.027	0.024
		Median	-0.03	0.09	0.10
		Min.	-0.36	-0.47	-0.35
		Max.	1.16	1.05	1.19
	Visit 11 (Wash-out)	n	21	79	95
		Mean	0.01	0.04	-0.05
		SE	0.111	0.033	0.028
		Median	-0.04	0.01	-0.02
		Min.	-1.54	-0.62	-0.75
		Max.	1.02	1.03	0.65

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Table 7.57
Analysis of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042719

			C/C vs. C/G	C/C vs. G/G	C/G vs. G/G
FSC100/50	Visit 7 (Week 4)	p-value	0.570	0.334	0.546
		LS Means Diff	-0.04	-0.07	-0.03
		95% CI for Diff	(-0.18,0.10)	(-0.20,0.07)	(-0.11,0.06)
	Visit 8 (Week 8)	p-value	0.158	0.513	0.237
		LS Means Diff	0.09	0.04	-0.05
		95% CI for Diff	(-0.04,0.21)	(-0.08,0.16)	(-0.13,0.03)
	Visit 9 (Week 12)	p-value	0.777	0.967	0.621
		LS Means Diff	0.02	-0.00	-0.02
		95% CI for Diff	(-0.11,0.15)	(-0.13,0.13)	(-0.11,0.06)
	Visit 10 (Week 16)	p-value	0.928	0.608	0.528
		LS Means Diff	-0.01	-0.04	-0.03
		95% CI for Diff	(-0.16,0.14)	(-0.19,0.11)	(-0.13,0.07)
	Endpoint	p-value	0.926	0.664	0.600
		LS Means Diff	-0.01	-0.03	-0.03
		95% CI for Diff	(-0.15,0.14)	(-0.18,0.11)	(-0.12,0.07)
	Overall	p-value	0.771	0.809	0.409
		LS Means Diff	0.02	-0.01	-0.03
		95% CI for Diff	(-0.10,0.14)	(-0.13,0.10)	(-0.11,0.04)
	Visit 11 (Wash-out)	p-value	0.040	0.058	0.775
		LS Means Diff	0.13	0.12	-0.01
		95% CI for Diff	(0.01,0.26)	(-0.00,0.24)	(-0.09,0.07)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS1042719. Least squares mean differences are calculated as C/C-C/G, C/C-G/G and C/G-G/G.

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Table 7.57
Analysis of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1042719

			C/C vs. C/G	C/C vs. G/G	C/G vs. G/G
Salmeterol	Visit 7 (Week 4)	p-value	0.787	0.614	0.718
		LS Means Diff	-0.02	-0.04	-0.02
		95% CI for Diff	(-0.18, 0.14)	(-0.20, 0.12)	(-0.12, 0.08)
	Visit 8 (Week 8)	p-value	0.762	0.663	0.845
		LS Means Diff	-0.02	-0.03	-0.01
		95% CI for Diff	(-0.17, 0.12)	(-0.17, 0.11)	(-0.10, 0.08)
	Visit 9 (Week 12)	p-value	0.526	0.294	0.516
		LS Means Diff	-0.04	-0.07	-0.03
		95% CI for Diff	(-0.18, 0.09)	(-0.21, 0.06)	(-0.11, 0.06)
	Visit 10 (Week 16)	p-value	0.876	0.367	0.236
		LS Means Diff	-0.01	-0.08	-0.06
		95% CI for Diff	(-0.18, 0.16)	(-0.25, 0.09)	(-0.17, 0.04)
	Endpoint	p-value	0.964	0.455	0.269
		LS Means Diff	-0.00	-0.06	-0.06
		95% CI for Diff	(-0.16, 0.16)	(-0.22, 0.10)	(-0.15, 0.04)
	Overall	p-value	0.641	0.354	0.478
		LS Means Diff	-0.03	-0.06	-0.03
		95% CI for Diff	(-0.15, 0.09)	(-0.17, 0.06)	(-0.10, 0.05)
	Visit 11 (Wash-out)	p-value	0.590	0.379	0.025
		LS Means Diff	-0.04	0.07	0.11
		95% CI for Diff	(-0.19, 0.11)	(-0.08, 0.21)	(0.01, 0.20)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS1042719. Least squares mean differences are calculated as C/C-C/G, C/C-G/G and C/G-G/G.

Table 7.58
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS17778257

Treatment: FSC100/50

			A, A	A, T	T, T
-----			-----		
Subjects in treatment			100	88	55
FEV1 (L)	Visit 2 (Week -16)	n	100	88	55
		Mean	2.75	2.92	2.79
		SE	0.065	0.077	0.091
		Median	2.67	2.93	2.79
		Min.	1.44	1.25	1.47
		Max.	4.48	4.70	5.03
	Visit 3 (Week -12)	n	100	88	55
		Mean	2.78	2.92	2.80
		SE	0.062	0.075	0.095
		Median	2.74	2.88	2.71
		Min.	1.48	1.45	1.51
		Max.	4.63	4.61	5.02
	Visit 4 (Week -8)	n	100	88	55
		Mean	2.79	2.92	2.81
		SE	0.059	0.075	0.097
		Median	2.75	2.88	2.70
		Min.	1.57	1.30	1.69
		Max.	4.34	4.60	5.08
	Visit 5 (Week -4)	n	100	88	55
		Mean	2.78	2.93	2.83
		SE	0.061	0.073	0.094
		Median	2.77	2.92	2.69
		Min.	1.62	1.46	1.70
		Max.	4.52	4.63	4.74

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Table 7.58
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS17778257

Treatment: FSC100/50

			A, A	A, T	T, T
FEV1 (L)	Visit 6 (Day 1)	n	100	88	55
		Mean	2.76	2.92	2.79
		SE	0.063	0.075	0.097
		Median	2.71	2.87	2.79
		Min.	1.32	1.33	1.57
		Max.	4.34	4.77	4.95
	Visit 7 (Week 4)	n	96	86	51
		Mean	2.94	3.13	3.01
		SE	0.073	0.085	0.112
		Median	2.89	3.07	3.01
		Min.	1.63	1.36	1.93
		Max.	4.73	4.86	5.98
	Visit 8 (Week 8)	n	91	86	49
		Mean	2.93	3.13	3.01
		SE	0.075	0.086	0.111
		Median	2.86	3.03	2.96
		Min.	1.64	1.20	1.77
		Max.	4.89	4.97	5.68
	Visit 9 (Week 12)	n	88	84	49
		Mean	2.94	3.14	3.00
		SE	0.078	0.086	0.109
		Median	2.85	3.05	2.92
		Min.	1.43	1.22	1.87
		Max.	4.90	5.08	5.75

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Table 7.58
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS17778257

Treatment: FSC100/50

			A, A	A, T	T, T
-----			-----		
FEV1 (L)	Visit 10 (Week 16)	n	88	82	49
		Mean	2.94	3.12	3.01
		SE	0.077	0.088	0.109
		Median	2.93	3.02	2.99
		Min.	1.62	1.15	1.73
		Max.	4.93	5.02	5.33
	Endpoint	n	96	86	51
		Mean	2.96	3.13	2.99
		SE	0.074	0.085	0.106
		Median	2.95	3.02	2.96
		Min.	1.62	1.15	1.73
		Max.	4.93	5.02	5.33
	Overall	n	96	86	51
		Mean	2.95	3.13	2.99
		SE	0.072	0.084	0.107
		Median	2.89	3.03	2.88
		Min.	1.61	1.23	1.84
		Max.	4.86	4.98	5.69
	Visit 11 (Wash-out)	n	88	81	48
		Mean	2.83	2.93	2.80
		SE	0.073	0.083	0.110
		Median	2.81	2.89	2.70
		Min.	1.37	1.20	1.27
		Max.	4.69	4.64	4.78

Table 7.58
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS17778257

Treatment: FSC100/50

		A, A	A, T	T, T
FEV1 change	Visit 7 (Week 4)	n	96	86
		Mean	0.20	0.21
		SE	0.034	0.035
		Median	0.18	0.16
		Min.	-0.67	-0.80
		Max.	1.55	1.62
	Visit 8 (Week 8)	n	91	86
		Mean	0.22	0.22
		SE	0.029	0.035
		Median	0.20	0.12
		Min.	-0.51	-0.19
		Max.	1.15	1.50
	Visit 9 (Week 12)	n	88	84
		Mean	0.21	0.24
		SE	0.032	0.039
		Median	0.16	0.20
		Min.	-0.38	-0.64
		Max.	1.56	1.54
	Visit 10 (Week 16)	n	88	82
		Mean	0.21	0.22
		SE	0.039	0.041
		Median	0.19	0.16
		Min.	-0.74	-0.67
		Max.	1.65	1.61

Table 7.58
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS17778257

Treatment: FSC100/50

		A, A		A, T		T, T	
FEV1 change	Endpoint	n					
		96		86		51	
		Mean	0.21	0.22		0.24	
		SE	0.036	0.040		0.045	
		Median	0.19	0.16		0.20	
		Min.	-0.74	-0.67		-0.42	
		Max.	1.65	1.61		1.29	
	Overall	n	96	86		51	
		Mean	0.20	0.22		0.24	
		SE	0.027	0.034		0.037	
		Median	0.17	0.16		0.21	
		Min.	-0.35	-0.29		-0.41	
		Max.	1.44	1.52		1.02	
	Visit 11 (Wash-out)	n	88	81		48	
		Mean	0.10	0.03		0.04	
		SE	0.032	0.030		0.040	
		Median	0.07	0.04		0.03	
		Min.	-0.58	-0.63		-1.03	
		Max.	1.53	0.84		0.60	

Table 7.58
 Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS17778257

Treatment: Salmeterol

			A, A	A, T	T, T
-----			-----		
Subjects in treatment			100	86	46
FEV1 (L)	Visit 2 (Week -16)	n	100	86	46
		Mean	2.75	2.86	3.14
		SE	0.068	0.078	0.111
		Median	2.71	2.74	3.12
		Min.	1.68	1.44	1.61
		Max.	5.09	4.76	4.72
	Visit 3 (Week -12)	n	100	86	46
		Mean	2.79	2.90	3.12
		SE	0.073	0.082	0.105
		Median	2.72	2.76	3.07
		Min.	1.65	1.39	1.65
		Max.	5.46	4.66	4.58
	Visit 4 (Week -8)	n	100	86	46
		Mean	2.80	2.88	3.17
		SE	0.075	0.081	0.105
		Median	2.67	2.80	3.13
		Min.	1.62	1.44	1.58
		Max.	5.46	4.69	4.51
	Visit 5 (Week -4)	n	100	86	46
		Mean	2.80	2.91	3.18
		SE	0.075	0.081	0.111
		Median	2.75	2.81	3.08
		Min.	1.66	1.51	1.62
		Max.	5.66	4.61	4.93

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Table 7.58
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS17778257

Treatment: Salmeterol

			A, A	A, T	T, T
FEV1 (L)	Visit 6 (Day 1)	n	100	86	46
		Mean	2.80	2.87	3.12
		SE	0.075	0.085	0.102
		Median	2.76	2.76	2.99
		Min.	1.54	1.32	1.66
		Max.	4.93	4.73	4.53
	Visit 7 (Week 4)	n	96	83	43
		Mean	2.97	3.04	3.27
		SE	0.082	0.083	0.122
		Median	2.90	3.02	3.18
		Min.	1.71	1.22	1.45
		Max.	5.35	4.89	4.63
	Visit 8 (Week 8)	n	92	77	41
		Mean	2.87	3.04	3.19
		SE	0.075	0.088	0.111
		Median	2.78	2.93	3.07
		Min.	1.62	1.24	1.73
		Max.	5.11	5.36	4.38
	Visit 9 (Week 12)	n	88	72	40
		Mean	2.86	3.02	3.22
		SE	0.075	0.084	0.120
		Median	2.84	2.97	3.10
		Min.	1.65	1.20	1.56
		Max.	4.99	4.82	4.79

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Table 7.58
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS17778257

Treatment: Salmeterol

			A, A	A, T	T, T
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FEV1 (L)	Visit 10 (Week 16)	n	87	70	40
		Mean	2.84	3.01	3.23
		SE	0.081	0.089	0.127
		Median	2.79	2.91	3.04
		Min.	1.43	1.22	1.52
		Max.	5.09	5.13	5.15
	Endpoint	n	96	83	43
		Mean	2.87	3.04	3.26
		SE	0.081	0.091	0.125
		Median	2.80	2.91	3.04
		Min.	1.43	1.22	1.52
		Max.	5.16	5.36	5.15
	Overall	n	96	83	43
		Mean	2.91	3.03	3.26
		SE	0.077	0.082	0.117
		Median	2.91	3.03	3.06
		Min.	1.68	1.22	1.57
		Max.	5.16	4.89	4.71
	Visit 11 (Wash-out)	n	87	69	39
		Mean	2.75	2.87	3.04
		SE	0.082	0.086	0.117
		Median	2.74	2.80	2.95
		Min.	1.39	1.10	1.18
		Max.	5.32	4.55	4.38

Table 7.58
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS17778257

Treatment: Salmeterol

		A, A	A, T	T, T
FEV1 change	Visit 7 (Week 4)	n	96	83
		Mean	0.15	0.15
		SE	0.039	0.037
		Median	0.11	0.13
		Min.	-0.78	-1.33
		Max.	2.38	1.30
	Visit 8 (Week 8)	n	92	77
		Mean	0.09	0.16
		SE	0.033	0.039
		Median	0.07	0.12
		Min.	-0.84	-0.90
		Max.	1.27	1.73
	Visit 9 (Week 12)	n	88	72
		Mean	0.08	0.14
		SE	0.029	0.035
		Median	0.06	0.14
		Min.	-0.60	-0.61
		Max.	1.17	1.25
	Visit 10 (Week 16)	n	87	70
		Mean	0.04	0.15
		SE	0.029	0.049
		Median	0.03	0.11
		Min.	-0.66	-0.90
		Max.	1.16	2.54

Table 7.58
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS17778257

Treatment: Salmeterol

		A, A		A, T		T, T	
FEV1 change	Endpoint	n	96	83	43		
		Mean	0.05	0.16	0.20		
		SE	0.027	0.044	0.058		
		Median	0.04	0.12	0.08		
		Min.	-0.66	-0.90	-0.30		
		Max.	1.16	2.54	1.63		
	Overall	n	96	83	43		
		Mean	0.10	0.15	0.19		
		SE	0.025	0.030	0.044		
		Median	0.06	0.14	0.09		
		Min.	-0.41	-0.47	-0.23		
		Max.	1.16	1.08	1.19		
	Visit 11 (Wash-out)	n	87	69	39		
		Mean	-0.04	0.02	0.02		
		SE	0.036	0.033	0.056		
		Median	-0.05	0.04	0.04		
		Min.	-1.54	-0.49	-0.75		
		Max.	1.02	1.03	0.93		

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Table 7.59
Analysis of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS17778257

			A/A vs. A/T	A/A vs. T/T	A/T vs. T/T
FSC100/50	Visit 7 (Week 4)	p-value	0.716	0.220	0.367
		LS Means Diff	-0.02	-0.07	-0.05
		95% CI for Diff	(-0.11,0.08)	(-0.18,0.04)	(-0.16,0.06)
	Visit 8 (Week 8)	p-value	0.763	0.670	0.498
		LS Means Diff	0.01	-0.02	-0.04
		95% CI for Diff	(-0.07,0.10)	(-0.13,0.08)	(-0.14,0.07)
	Visit 9 (Week 12)	p-value	0.578	0.535	0.882
		LS Means Diff	-0.03	-0.03	-0.01
		95% CI for Diff	(-0.12,0.07)	(-0.14,0.07)	(-0.12,0.10)
	Visit 10 (Week 16)	p-value	0.786	0.412	0.558
		LS Means Diff	-0.01	-0.05	-0.04
		95% CI for Diff	(-0.12,0.09)	(-0.18,0.07)	(-0.16,0.09)
	Endpoint	p-value	0.801	0.410	0.549
		LS Means Diff	-0.01	-0.05	-0.04
		95% CI for Diff	(-0.11,0.09)	(-0.17,0.07)	(-0.16,0.08)
	Overall	p-value	0.749	0.357	0.523
		LS Means Diff	-0.01	-0.04	-0.03
		95% CI for Diff	(-0.09,0.07)	(-0.14,0.05)	(-0.13,0.07)
	Visit 11 (Wash-out)	p-value	0.112	0.218	0.901
		LS Means Diff	0.07	0.06	-0.01
		95% CI for Diff	(-0.02,0.16)	(-0.04,0.17)	(-0.11,0.10)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS17778257. Least squares mean differences are calculated as A/A-A/T, A/A-T/T and A/T-T/T.

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Table 7.59
Analysis of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS17778257

			A/A vs. A/T	A/A vs. T/T	A/T vs. T/T
Salmeterol	Visit 7 (Week 4)	p-value	0.966	0.208	0.221
		LS Means Diff	-0.00	-0.08	-0.08
		95% CI for Diff	(-0.11, 0.10)	(-0.21, 0.05)	(-0.21, 0.05)
	Visit 8 (Week 8)	p-value	0.118	0.048	0.481
		LS Means Diff	-0.08	-0.12	-0.04
		95% CI for Diff	(-0.17, 0.02)	(-0.24, -0.00)	(-0.16, 0.08)
	Visit 9 (Week 12)	p-value	0.291	0.014	0.115
		LS Means Diff	-0.05	-0.13	-0.09
		95% CI for Diff	(-0.14, 0.04)	(-0.24, -0.03)	(-0.19, 0.02)
	Visit 10 (Week 16)	p-value	0.103	0.009	0.212
		LS Means Diff	-0.09	-0.18	-0.09
		95% CI for Diff	(-0.20, 0.02)	(-0.31, -0.04)	(-0.22, 0.05)
	Endpoint	p-value	0.068	0.017	0.352
		LS Means Diff	-0.09	-0.15	-0.06
		95% CI for Diff	(-0.20, 0.01)	(-0.28, -0.03)	(-0.19, 0.07)
	Overall	p-value	0.229	0.020	0.173
		LS Means Diff	-0.05	-0.11	-0.07
		95% CI for Diff	(-0.12, 0.03)	(-0.21, -0.02)	(-0.16, 0.03)
	Visit 11 (Wash-out)	p-value	0.398	0.234	0.631
		LS Means Diff	-0.04	-0.07	-0.03
		95% CI for Diff	(-0.14, 0.06)	(-0.19, 0.05)	(-0.15, 0.09)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS17778257. Least squares mean differences are calculated as A/A-A/T, A/A-T/T and A/T-T/T.

Table 7.60
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS11168070

Treatment: FSC100/50

			C, C	C, G	G, G
-----			-----		
Subjects in treatment			147	73	23
FEV1 (L)	Visit 2 (Week -16)	n	147	73	23
		Mean	2.73	3.04	2.73
		SE	0.059	0.074	0.111
		Median	2.66	2.95	2.70
		Min.	1.25	1.93	1.87
		Max.	5.03	4.48	4.03
	Visit 3 (Week -12)	n	147	73	23
		Mean	2.75	3.03	2.78
		SE	0.058	0.071	0.107
		Median	2.64	2.97	2.77
		Min.	1.45	1.68	1.72
		Max.	5.02	4.63	3.68
	Visit 4 (Week -8)	n	147	73	23
		Mean	2.75	3.03	2.84
		SE	0.059	0.065	0.101
		Median	2.68	3.04	2.83
		Min.	1.30	2.11	1.86
		Max.	5.08	4.34	3.55
	Visit 5 (Week -4)	n	147	73	23
		Mean	2.76	3.03	2.79
		SE	0.058	0.067	0.102
		Median	2.69	3.00	2.88
		Min.	1.46	2.08	1.66
		Max.	4.74	4.52	3.55

Table 7.60
 Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS11168070

Treatment: FSC100/50

		C, C	C, G	G, G
FEV1 (L)	Visit 6 (Day 1)	n	147	73
		Mean	2.73	3.03
		SE	0.060	0.068
		Median	2.59	2.98
		Min.	1.32	2.07
		Max.	4.95	4.34
	Visit 7 (Week 4)	n	140	72
		Mean	2.93	3.24
		SE	0.068	0.082
		Median	2.86	3.19
		Min.	1.36	1.87
		Max.	5.98	4.73
	Visit 8 (Week 8)	n	138	69
		Mean	2.94	3.22
		SE	0.067	0.087
		Median	2.87	3.07
		Min.	1.20	1.92
		Max.	5.68	4.89
	Visit 9 (Week 12)	n	135	67
		Mean	2.94	3.25
		SE	0.068	0.089
		Median	2.87	3.08
		Min.	1.22	2.05
		Max.	5.75	4.90

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Table 7.60
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS11168070

Treatment: FSC100/50

			C, C	C, G	G, G
-----			-----		
FEV1 (L)	Visit 10 (Week 16)	n	133	67	19
		Mean	2.91	3.29	2.88
		SE	0.068	0.085	0.121
		Median	2.84	3.14	2.99
		Min.	1.15	2.13	1.71
		Max.	5.33	4.93	3.56
	Endpoint	n	140	72	21
		Mean	2.91	3.29	2.90
		SE	0.067	0.082	0.112
		Median	2.84	3.18	2.99
		Min.	1.15	2.13	1.71
		Max.	5.33	4.93	3.56
	Overall	n	140	72	21
		Mean	2.93	3.26	2.91
		SE	0.066	0.081	0.115
		Median	2.87	3.16	2.98
		Min.	1.23	2.10	1.70
		Max.	5.69	4.86	3.68
	Visit 11 (Wash-out)	n	132	66	19
		Mean	2.77	3.06	2.80
		SE	0.067	0.077	0.125
		Median	2.65	2.94	2.85
		Min.	1.20	1.99	1.76
		Max.	4.78	4.69	3.99

Table 7.60
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS11168070

Treatment: FSC100/50

			C, C	C, G	G, G
-----			-----		
FEV1 change	Visit 7 (Week 4)	n	140	72	21
		Mean	0.22	0.21	0.22
		SE	0.025	0.044	0.044
		Median	0.18	0.13	0.19
		Min.	-0.80	-0.67	-0.01
		Max.	1.62	1.55	0.80
	Visit 8 (Week 8)	n	138	69	19
		Mean	0.22	0.23	0.20
		SE	0.024	0.040	0.060
		Median	0.19	0.09	0.12
		Min.	-0.54	-0.51	-0.20
		Max.	1.41	1.50	0.85
	Visit 9 (Week 12)	n	135	67	19
		Mean	0.22	0.25	0.20
		SE	0.026	0.044	0.059
		Median	0.22	0.14	0.17
		Min.	-0.64	-0.35	-0.23
		Max.	1.44	1.56	0.61
	Visit 10 (Week 16)	n	133	67	19
		Mean	0.20	0.28	0.20
		SE	0.030	0.049	0.071
		Median	0.17	0.20	0.16
		Min.	-0.68	-0.74	-0.37
		Max.	1.59	1.65	0.88

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Table 7.60
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS11168070

Treatment: FSC100/50

		C, C		C, G	G, G
-----		-----		-----	-----
FEV1 change	Endpoint	n	140	72	21
		Mean	0.19	0.27	0.20
		SE	0.028	0.046	0.064
		Median	0.17	0.20	0.19
		Min.	-0.68	-0.74	-0.37
		Max.	1.59	1.65	0.88
	Overall	n	140	72	21
		Mean	0.21	0.24	0.21
		SE	0.023	0.038	0.048
		Median	0.19	0.12	0.21
		Min.	-0.41	-0.28	-0.14
		Max.	1.52	1.44	0.72
	Visit 11 (Wash-out)	n	132	66	19
		Mean	0.06	0.05	0.13
		SE	0.027	0.032	0.054
		Median	0.06	0.04	0.15
		Min.	-1.03	-0.57	-0.14
		Max.	1.53	0.81	0.88

Table 7.60
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS11168070

Treatment: Salmeterol

			C, C	C, G	G, G
-----			-----		
Subjects in treatment			136	71	25
FEV1 (L)	Visit 2 (Week -16)	n	136	71	25
		Mean	2.88	2.84	2.88
		SE	0.064	0.089	0.092
		Median	2.84	2.69	2.93
		Min.	1.44	1.55	1.99
		Max.	4.76	5.09	3.95
	Visit 3 (Week -12)	n	136	71	25
		Mean	2.92	2.86	2.90
		SE	0.065	0.094	0.103
		Median	2.81	2.70	2.87
		Min.	1.39	1.65	1.96
		Max.	4.66	5.46	4.39
	Visit 4 (Week -8)	n	136	71	25
		Mean	2.91	2.91	2.87
		SE	0.065	0.099	0.094
		Median	2.88	2.71	2.87
		Min.	1.44	1.70	2.15
		Max.	4.63	5.46	3.99
	Visit 5 (Week -4)	n	136	71	25
		Mean	2.93	2.92	2.82
		SE	0.066	0.097	0.096
		Median	2.82	2.75	2.76
		Min.	1.51	1.66	1.92
		Max.	4.93	5.66	4.01

Table 7.60
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS11168070

Treatment: Salmeterol

			C, C	C, G	G, G
FEV1 (L)	Visit 6 (Day 1)	n	136	71	25
		Mean	2.88	2.89	2.93
		SE	0.068	0.093	0.089
		Median	2.76	2.80	2.91
		Min.	1.32	1.65	2.11
		Max.	4.71	4.93	4.00
	Visit 7 (Week 4)	n	130	69	23
		Mean	3.07	3.01	3.09
		SE	0.072	0.098	0.108
		Median	2.98	2.89	2.99
		Min.	1.22	1.80	1.96
		Max.	4.89	5.35	4.28
	Visit 8 (Week 8)	n	123	67	20
		Mean	2.98	2.99	3.12
		SE	0.068	0.096	0.101
		Median	2.81	2.93	3.17
		Min.	1.24	1.72	2.09
		Max.	5.11	5.36	4.29
	Visit 9 (Week 12)	n	116	64	20
		Mean	3.01	2.93	3.05
		SE	0.072	0.087	0.114
		Median	2.92	2.91	3.02
		Min.	1.20	1.70	1.82
		Max.	4.83	4.99	4.36

Table 7.60
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS11168070

Treatment: Salmeterol

			C, C	C, G	G, G
FEV1 (L)	Visit 10 (Week 16)	n	113	64	20
		Mean	3.00	2.92	3.01
		SE	0.079	0.090	0.114
		Median	2.90	2.89	3.06
		Min.	1.22	1.43	1.67
		Max.	5.15	5.09	4.10
	Endpoint	n	130	69	23
		Mean	3.01	2.98	3.06
		SE	0.076	0.098	0.116
		Median	2.89	2.89	3.07
		Min.	1.22	1.43	1.67
		Max.	5.15	5.36	4.28
	Overall	n	130	69	23
		Mean	3.03	2.99	3.10
		SE	0.069	0.094	0.108
		Median	2.92	2.95	3.00
		Min.	1.22	1.73	1.89
		Max.	4.89	5.16	4.28
	Visit 11 (Wash-out)	n	112	63	20
		Mean	2.88	2.78	2.88
		SE	0.075	0.091	0.110
Median		2.79	2.65	2.88	
Min.		1.10	1.46	1.67	
Max.		5.32	4.65	4.17	

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Table 7.60
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS11168070

Treatment: Salmeterol

			C, C	C, G	G, G
FEV1 change	Visit 7 (Week 4)	n	130	69	23
		Mean	0.20	0.11	0.12
		SE	0.035	0.033	0.045
		Median	0.13	0.14	0.09
		Min.	-0.78	-1.33	-0.33
		Max.	2.38	0.73	0.65
	Visit 8 (Week 8)	n	123	67	20
		Mean	0.14	0.10	0.16
		SE	0.032	0.032	0.046
		Median	0.07	0.11	0.14
		Min.	-0.90	-0.78	-0.20
		Max.	1.73	0.82	0.58
	Visit 9 (Week 12)	n	116	64	20
		Mean	0.16	0.08	0.09
		SE	0.031	0.030	0.051
		Median	0.10	0.09	0.07
		Min.	-0.61	-0.61	-0.47
		Max.	1.27	0.86	0.44
	Visit 10 (Week 16)	n	113	64	20
		Mean	0.15	0.07	0.05
		SE	0.040	0.028	0.055
		Median	0.07	0.08	0.09
		Min.	-0.90	-0.41	-0.62
		Max.	2.54	0.60	0.47

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Table 7.60
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS11168070

Treatment: Salmeterol

			C, C	C, G	G, G
FEV1 change	Endpoint	n	130	69	23
		Mean	0.15	0.09	0.09
		SE	0.036	0.027	0.055
		Median	0.08	0.09	0.10
		Min.	-0.90	-0.41	-0.62
		Max.	2.54	0.63	0.65
	Overall	n	130	69	23
		Mean	0.16	0.09	0.13
		SE	0.027	0.022	0.043
		Median	0.10	0.08	0.12
		Min.	-0.47	-0.35	-0.41
		Max.	1.19	0.58	0.65
	Visit 11 (Wash-out)	n	112	63	20
		Mean	0.03	-0.06	-0.08
		SE	0.034	0.030	0.049
		Median	0.02	-0.02	-0.04
		Min.	-1.54	-0.75	-0.62
		Max.	1.03	0.52	0.33

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Table 7.61
Analysis of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS11168070

			C/C vs. C/G	C/C vs. G/G	C/G vs. G/G
FSC100/50	Visit 7 (Week 4)	p-value	0.611	0.709	0.956
		LS Means Diff	0.02	0.03	0.00
		95% CI for Diff	(-0.07, 0.12)	(-0.12, 0.18)	(-0.15, 0.16)
	Visit 8 (Week 8)	p-value	0.597	0.268	0.447
		LS Means Diff	0.02	0.08	0.06
		95% CI for Diff	(-0.06, 0.11)	(-0.06, 0.23)	(-0.09, 0.21)
	Visit 9 (Week 12)	p-value	0.990	0.289	0.313
		LS Means Diff	0.00	0.08	0.08
		95% CI for Diff	(-0.09, 0.09)	(-0.07, 0.23)	(-0.08, 0.24)
	Visit 10 (Week 16)	p-value	0.203	0.530	0.179
		LS Means Diff	-0.07	0.06	0.12
		95% CI for Diff	(-0.17, 0.04)	(-0.12, 0.23)	(-0.06, 0.30)
	Endpoint	p-value	0.236	0.573	0.213
		LS Means Diff	-0.06	0.05	0.11
		95% CI for Diff	(-0.16, 0.04)	(-0.12, 0.21)	(-0.06, 0.28)
	Overall	p-value	0.991	0.419	0.434
		LS Means Diff	-0.00	0.05	0.05
		95% CI for Diff	(-0.08, 0.08)	(-0.08, 0.19)	(-0.08, 0.19)
	Visit 11 (Wash-out)	p-value	0.874	0.577	0.531
		LS Means Diff	0.01	-0.04	-0.05
		95% CI for Diff	(-0.08, 0.10)	(-0.19, 0.10)	(-0.20, 0.10)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS11168070. Least squares mean differences are calculated as C/C-C/G, C/C-G/G and C/G-G/G.

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Table 7.61
Analysis of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS11168070

			C/C vs. C/G	C/C vs. G/G	C/G vs. G/G
Salmeterol	Visit 7 (Week 4)	p-value	0.245	0.485	0.940
		LS Means Diff	0.06	0.06	-0.01
		95% CI for Diff	(-0.04, 0.17)	(-0.10, 0.21)	(-0.17, 0.16)
	Visit 8 (Week 8)	p-value	0.214	0.855	0.548
		LS Means Diff	0.06	0.01	-0.05
		95% CI for Diff	(-0.04, 0.16)	(-0.14, 0.17)	(-0.20, 0.11)
	Visit 9 (Week 12)	p-value	0.127	0.346	0.959
		LS Means Diff	0.07	0.07	-0.00
		95% CI for Diff	(-0.02, 0.16)	(-0.07, 0.21)	(-0.15, 0.14)
	Visit 10 (Week 16)	p-value	0.161	0.216	0.750
		LS Means Diff	0.08	0.11	0.03
		95% CI for Diff	(-0.03, 0.19)	(-0.06, 0.28)	(-0.15, 0.20)
	Endpoint	p-value	0.348	0.444	0.891
		LS Means Diff	0.05	0.06	0.01
		95% CI for Diff	(-0.06, 0.16)	(-0.10, 0.22)	(-0.15, 0.17)
	Overall	p-value	0.145	0.607	0.655
		LS Means Diff	0.06	0.03	-0.03
		95% CI for Diff	(-0.02, 0.14)	(-0.09, 0.15)	(-0.15, 0.09)
	Visit 11 (Wash-out)	p-value	0.148	0.215	0.774
		LS Means Diff	0.07	0.10	0.02
		95% CI for Diff	(-0.03, 0.17)	(-0.06, 0.25)	(-0.13, 0.18)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS11168070. Least squares mean differences are calculated as C/C-C/G, C/C-G/G and C/G-G/G.

Table 7.62
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS9325122

Treatment: FSC100/50

			C, C	C, T	T, T
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Subjects in treatment			23	65	145
FEV1 (L)	Visit 2 (Week -16)	n	23	65	145
		Mean	2.75	3.05	2.73
		SE	0.114	0.078	0.059
		Median	2.70	2.91	2.66
		Min.	1.87	1.93	1.25
		Max.	4.03	4.48	5.03
	Visit 3 (Week -12)	n	23	65	145
		Mean	2.79	3.05	2.76
		SE	0.110	0.075	0.059
		Median	2.77	2.99	2.67
		Min.	1.72	1.68	1.45
		Max.	3.68	4.63	5.02
	Visit 4 (Week -8)	n	23	65	145
		Mean	2.82	3.05	2.75
		SE	0.098	0.067	0.060
		Median	2.73	3.04	2.68
		Min.	1.86	2.11	1.30
		Max.	3.52	4.34	5.08
	Visit 5 (Week -4)	n	23	65	145
		Mean	2.78	3.05	2.76
		SE	0.103	0.071	0.059
		Median	2.79	3.00	2.69
		Min.	1.66	2.08	1.46
		Max.	3.55	4.52	4.74

Table 7.62
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS9325122

Treatment: FSC100/50

		C, C	C, T	T, T
FEV1 (L)	Visit 6 (Day 1)	n	23	65
		Mean	2.74	3.08
		SE	0.092	0.072
		Median	2.68	3.01
		Min.	1.84	2.07
		Max.	3.45	4.34
	Visit 7 (Week 4)	n	21	64
		Mean	2.94	3.24
		SE	0.117	0.085
		Median	2.88	3.13
		Min.	1.83	1.87
		Max.	3.74	4.73
	Visit 8 (Week 8)	n	19	61
		Mean	2.87	3.25
		SE	0.141	0.089
		Median	2.92	3.07
		Min.	1.64	2.13
		Max.	3.78	4.89
	Visit 9 (Week 12)	n	19	60
		Mean	2.88	3.26
		SE	0.134	0.093
		Median	3.09	3.08
		Min.	1.61	2.05
		Max.	3.84	4.90

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Table 7.62
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS9325122

Treatment: FSC100/50

			C, C	C, T	T, T
-----			-----		
FEV1 (L)	Visit 10 (Week 16)	n	19	60	131
		Mean	2.89	3.27	2.92
		SE	0.120	0.090	0.069
		Median	2.99	3.13	2.84
		Min.	1.71	2.13	1.15
		Max.	3.56	4.93	5.33
	Endpoint	n	21	64	138
		Mean	2.91	3.29	2.91
		SE	0.111	0.086	0.068
		Median	2.99	3.18	2.84
		Min.	1.71	2.13	1.15
		Max.	3.56	4.93	5.33
	Overall	n	21	64	138
		Mean	2.91	3.27	2.93
		SE	0.118	0.084	0.067
		Median	2.98	3.16	2.87
		Min.	1.70	2.10	1.23
		Max.	3.68	4.86	5.69
	Visit 11 (Wash-out)	n	19	60	130
		Mean	2.82	3.08	2.77
		SE	0.131	0.080	0.068
		Median	2.88	2.94	2.66
		Min.	1.76	1.99	1.20
		Max.	3.99	4.69	4.78

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Table 7.62
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS9325122

Treatment: FSC100/50

			C, C	C, T	T, T

FEV1 change	Visit 7 (Week 4)	n	21	64	138
		Mean	0.25	0.17	0.21
		SE	0.051	0.041	0.025
		Median	0.19	0.12	0.18
		Min.	-0.01	-0.67	-0.80
		Max.	0.85	1.40	1.62
	Visit 8 (Week 8)	n	19	61	136
		Mean	0.21	0.21	0.22
		SE	0.066	0.037	0.024
		Median	0.12	0.09	0.19
		Min.	-0.20	-0.51	-0.54
		Max.	0.85	1.15	1.41
	Visit 9 (Week 12)	n	19	60	133
		Mean	0.21	0.22	0.21
		SE	0.061	0.042	0.026
		Median	0.17	0.13	0.22
		Min.	-0.23	-0.35	-0.64
		Max.	0.65	1.56	1.44
	Visit 10 (Week 16)	n	19	60	131
		Mean	0.22	0.24	0.19
		SE	0.063	0.049	0.030
		Median	0.16	0.19	0.17
		Min.	-0.21	-0.74	-0.68
		Max.	0.82	1.65	1.59

Table 7.62
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS9325122

Treatment: FSC100/50

		C, C		C, T	T, T
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FEV1 change	Endpoint	n	21	64	138
		Mean	0.22	0.23	0.19
		SE	0.057	0.047	0.029
		Median	0.19	0.19	0.17
		Min.	-0.21	-0.74	-0.68
		Max.	0.82	1.65	1.59
	Overall	n	21	64	138
		Mean	0.22	0.20	0.21
		SE	0.050	0.035	0.023
		Median	0.21	0.11	0.19
		Min.	-0.14	-0.28	-0.41
		Max.	0.79	1.44	1.52
	Visit 11 (Wash-out)	n	19	60	130
		Mean	0.16	0.05	0.05
		SE	0.066	0.030	0.027
		Median	0.15	0.04	0.06
		Min.	-0.14	-0.39	-1.03
		Max.	0.88	0.61	1.53

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Table 7.62
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS9325122

Treatment: Salmeterol

			C, C	C, T	T, T
-----			-----		
Subjects in treatment			27	63	129
FEV1 (L)	Visit 2 (Week -16)	n	27	63	129
		Mean	2.94	2.80	2.91
		SE	0.103	0.094	0.066
		Median	2.93	2.68	2.84
		Min.	1.99	1.55	1.44
		Max.	4.27	5.09	4.76
	Visit 3 (Week -12)	n	27	63	129
		Mean	2.95	2.85	2.93
		SE	0.115	0.100	0.066
		Median	2.87	2.70	2.83
		Min.	1.96	1.65	1.39
		Max.	4.48	5.46	4.66
	Visit 4 (Week -8)	n	27	63	129
		Mean	2.92	2.88	2.94
		SE	0.107	0.105	0.066
		Median	2.87	2.71	2.89
		Min.	2.15	1.70	1.44
		Max.	4.54	5.46	4.63
	Visit 5 (Week -4)	n	27	63	129
		Mean	2.87	2.90	2.96
		SE	0.100	0.104	0.068
		Median	2.76	2.75	2.84
		Min.	1.92	1.66	1.51
		Max.	4.09	5.66	4.93

Table 7.62
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS9325122

Treatment: Salmeterol

			C, C	C, T	T, T
FEV1 (L)	Visit 6 (Day 1)	n	27	63	129
		Mean	2.97	2.87	2.91
		SE	0.093	0.099	0.069
		Median	2.91	2.77	2.80
		Min.	2.11	1.65	1.32
		Max.	4.02	4.93	4.71
	Visit 7 (Week 4)	n	25	62	123
		Mean	3.14	2.98	3.09
		SE	0.114	0.103	0.075
		Median	2.99	2.85	3.01
		Min.	1.96	1.80	1.22
		Max.	4.46	5.35	4.89
	Visit 8 (Week 8)	n	23	59	116
		Mean	3.21	2.95	2.99
		SE	0.110	0.102	0.070
		Median	3.19	2.82	2.82
		Min.	2.09	1.72	1.24
		Max.	4.29	5.36	5.11
	Visit 9 (Week 12)	n	23	57	110
		Mean	3.14	2.89	3.02
		SE	0.116	0.091	0.075
		Median	3.02	2.79	2.92
		Min.	1.82	1.70	1.20
		Max.	4.36	4.99	4.83

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Table 7.62
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS9325122

Treatment: Salmeterol

			C, C	C, T	T, T
-----			-----		
FEV1 (L)	Visit 10 (Week 16)	n	23	57	107
		Mean	3.12	2.87	3.01
		SE	0.121	0.092	0.081
		Median	3.09	2.79	2.90
		Min.	1.67	1.68	1.22
		Max.	4.25	5.09	5.15
	Endpoint	n	25	62	123
		Mean	3.10	2.97	3.03
		SE	0.114	0.105	0.078
		Median	3.09	2.88	2.90
		Min.	1.67	1.68	1.22
		Max.	4.25	5.36	5.15
	Overall	n	25	62	123
		Mean	3.14	2.98	3.05
		SE	0.108	0.100	0.071
		Median	3.03	2.84	2.97
		Min.	1.89	1.75	1.22
		Max.	4.27	5.16	4.89
	Visit 11 (Wash-out)	n	23	56	106
		Mean	2.96	2.73	2.88
		SE	0.113	0.094	0.078
		Median	2.92	2.60	2.82
		Min.	1.67	1.46	1.10
		Max.	4.17	4.65	5.32

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Table 7.62
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS9325122

Treatment: Salmeterol

			C, C	C, T	T, T
FEV1 change	Visit 7 (Week 4)	n	25	62	123
		Mean	0.13	0.11	0.20
		SE	0.044	0.036	0.036
		Median	0.09	0.15	0.13
		Min.	-0.33	-1.33	-0.78
		Max.	0.65	0.73	2.38
	Visit 8 (Week 8)	n	23	59	116
		Mean	0.17	0.10	0.14
		SE	0.040	0.034	0.033
		Median	0.19	0.10	0.07
		Min.	-0.20	-0.78	-0.90
		Max.	0.58	0.82	1.73
	Visit 9 (Week 12)	n	23	57	110
		Mean	0.09	0.10	0.14
		SE	0.046	0.029	0.031
		Median	0.07	0.09	0.09
		Min.	-0.47	-0.60	-0.61
		Max.	0.44	0.86	1.27
	Visit 10 (Week 16)	n	23	57	107
		Mean	0.07	0.08	0.14
		SE	0.049	0.028	0.041
		Median	0.10	0.08	0.07
		Min.	-0.62	-0.40	-0.90
		Max.	0.47	0.60	2.54

Table 7.62
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS9325122

Treatment: Salmeterol

			C, C	C, T	T, T
FEV1 change	Endpoint	n	25	62	123
		Mean	0.09	0.10	0.14
		SE	0.050	0.028	0.037
		Median	0.10	0.10	0.07
		Min.	-0.62	-0.40	-0.90
		Max.	0.65	0.63	2.54
	Overall	n	25	62	123
		Mean	0.13	0.10	0.16
		SE	0.039	0.023	0.027
		Median	0.12	0.09	0.09
		Min.	-0.41	-0.35	-0.47
		Max.	0.65	0.58	1.19
	Visit 11 (Wash-out)	n	23	56	106
		Mean	-0.09	-0.05	0.02
		SE	0.047	0.030	0.035
		Median	-0.04	0.01	0.00
		Min.	-0.62	-0.75	-1.54
		Max.	0.33	0.50	1.03

Table 7.63
Analysis of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS9325122

			C/C vs. C/T	C/C vs. T/T	C/T vs. T/T
FSC100/50	Visit 7 (Week 4)	p-value	0.452	0.923	0.169
		LS Means Diff	0.06	-0.01	-0.07
		95% CI for Diff	(-0.09, 0.21)	(-0.15, 0.14)	(-0.16, 0.03)
	Visit 8 (Week 8)	p-value	0.637	0.336	0.461
		LS Means Diff	-0.04	-0.07	-0.03
		95% CI for Diff	(-0.18, 0.11)	(-0.21, 0.07)	(-0.12, 0.06)
	Visit 9 (Week 12)	p-value	0.539	0.378	0.711
		LS Means Diff	-0.05	-0.07	-0.02
		95% CI for Diff	(-0.21, 0.11)	(-0.22, 0.08)	(-0.11, 0.08)
	Visit 10 (Week 16)	p-value	0.475	0.702	0.560
		LS Means Diff	-0.07	-0.03	0.03
		95% CI for Diff	(-0.25, 0.11)	(-0.20, 0.14)	(-0.08, 0.14)
	Endpoint	p-value	0.502	0.725	0.581
		LS Means Diff	-0.06	-0.03	0.03
		95% CI for Diff	(-0.23, 0.11)	(-0.19, 0.13)	(-0.07, 0.13)
	Overall	p-value	0.845	0.563	0.565
		LS Means Diff	-0.01	-0.04	-0.02
		95% CI for Diff	(-0.15, 0.12)	(-0.17, 0.09)	(-0.11, 0.06)
	Visit 11 (Wash-out)	p-value	0.278	0.333	0.786
		LS Means Diff	0.09	0.07	-0.01
		95% CI for Diff	(-0.07, 0.24)	(-0.07, 0.22)	(-0.11, 0.08)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS9325122. Least squares mean differences are calculated as C/C-C/T, C/C-T/T and C/T-T/T.

Table 7.63
Analysis of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS9325122

			C/C vs. C/T	C/C vs. T/T	C/T vs. T/T
Salmeterol	Visit 7 (Week 4)	p-value	0.681	0.668	0.233
		LS Means Diff	0.03	-0.03	-0.07
		95% CI for Diff	(-0.13, 0.19)	(-0.19, 0.12)	(-0.18, 0.04)
	Visit 8 (Week 8)	p-value	0.373	0.856	0.302
		LS Means Diff	0.07	0.01	-0.05
		95% CI for Diff	(-0.08, 0.22)	(-0.13, 0.16)	(-0.16, 0.05)
	Visit 9 (Week 12)	p-value	0.989	0.524	0.387
		LS Means Diff	-0.00	-0.04	-0.04
		95% CI for Diff	(-0.13, 0.13)	(-0.17, 0.09)	(-0.13, 0.05)
	Visit 10 (Week 16)	p-value	0.959	0.451	0.331
		LS Means Diff	-0.00	-0.06	-0.06
		95% CI for Diff	(-0.17, 0.17)	(-0.23, 0.10)	(-0.18, 0.06)
	Endpoint	p-value	0.919	0.659	0.638
		LS Means Diff	-0.01	-0.03	-0.03
		95% CI for Diff	(-0.17, 0.15)	(-0.19, 0.12)	(-0.14, 0.08)
	Overall	p-value	0.597	0.844	0.298
		LS Means Diff	0.03	-0.01	-0.04
		95% CI for Diff	(-0.09, 0.15)	(-0.12, 0.10)	(-0.12, 0.04)
	Visit 11 (Wash-out)	p-value	0.694	0.230	0.272
		LS Means Diff	-0.03	-0.09	-0.06
		95% CI for Diff	(-0.18, 0.12)	(-0.23, 0.06)	(-0.16, 0.05)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS9325122. Least squares mean differences are calculated as C/C-C/T, C/C-T/T and C/T-T/T.

Table 7.64
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1800888

Treatment: FSC100/50

			C, C	C, T

Subjects in treatment			240	3
FEV1 (L)	Visit 2 (Week -16)	n	240	3
		Mean	2.82	2.61
		SE	0.044	0.388
		Median	2.79	2.87
		Min.	1.25	1.85
		Max.	5.03	3.12
	Visit 3 (Week -12)	n	240	3
		Mean	2.84	2.79
		SE	0.043	0.524
		Median	2.77	3.12
		Min.	1.45	1.76
		Max.	5.02	3.48
	Visit 4 (Week -8)	n	240	3
		Mean	2.84	2.61
		SE	0.043	0.411
		Median	2.79	2.79
		Min.	1.30	1.83
		Max.	5.08	3.22
	Visit 5 (Week -4)	n	240	3
		Mean	2.84	2.77
		SE	0.043	0.430
		Median	2.83	3.03
		Min.	1.46	1.93
		Max.	4.74	3.35

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Population: ITT Excluding Investigator

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Table 7.64
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1800888

Treatment: FSC100/50

			C, C	C, T
FEV1 (L)	Visit 6 (Day 1)	n	240	3
		Mean	2.83	2.65
		SE	0.044	0.504
		Median	2.78	3.01
		Min.	1.32	1.65
		Max.	4.95	3.28
	Visit 7 (Week 4)	n	230	3
		Mean	3.03	2.97
		SE	0.050	0.540
		Median	2.97	3.49
		Min.	1.36	1.89
		Max.	5.98	3.53
	Visit 8 (Week 8)	n	223	3
		Mean	3.02	3.00
		SE	0.051	0.578
		Median	2.97	3.47
		Min.	1.20	1.85
		Max.	5.68	3.68
	Visit 9 (Week 12)	n	219	2
		Mean	3.02	3.62
		SE	0.052	0.080
		Median	2.94	3.62
		Min.	1.22	3.54
		Max.	5.75	3.70

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Table 7.64
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1800888

Treatment: FSC100/50

			C, C	C, T
FEV1 (L)	Visit 10 (Week 16)	n	217	2
		Mean	3.02	3.56
		SE	0.052	0.110
		Median	2.96	3.56
		Min.	1.15	3.45
		Max.	5.33	3.67
	Endpoint	n	230	3
		Mean	3.03	2.99
		SE	0.050	0.574
		Median	2.98	3.45
		Min.	1.15	1.85
		Max.	5.33	3.67
	Overall	n	230	3
		Mean	3.03	3.00
		SE	0.049	0.567
		Median	2.93	3.50
		Min.	1.23	1.87
		Max.	5.69	3.64
	Visit 11 (Wash-out)	n	215	2
		Mean	2.86	3.26
		SE	0.049	0.305
		Median	2.81	3.26
		Min.	1.20	2.95
		Max.	4.78	3.56

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Population: ITT Excluding Investigator [REDACTED]

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Table 7.64
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1800888

Treatment: FSC100/50

			C, C	C, T
FEV1 change	Visit 7 (Week 4)	n	230	3
		Mean	0.22	0.32
		SE	0.021	0.099
		Median	0.18	0.24
		Min.	-0.80	0.21
		Max.	1.62	0.52
	Visit 8 (Week 8)	n	223	3
		Mean	0.22	0.35
		SE	0.020	0.079
		Median	0.18	0.40
		Min.	-0.54	0.20
		Max.	1.50	0.46
	Visit 9 (Week 12)	n	219	2
		Mean	0.22	0.47
		SE	0.021	0.055
		Median	0.18	0.47
		Min.	-0.64	0.42
		Max.	1.56	0.53
	Visit 10 (Week 16)	n	217	2
		Mean	0.22	0.41
		SE	0.024	0.025
		Median	0.18	0.41
		Min.	-0.74	0.39
		Max.	1.65	0.44

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Table 7.64
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1800888

Treatment: FSC100/50

		C, C		C, T
FEV1 change	Endpoint	n	230	3
		Mean	0.22	0.34
		SE	0.023	0.073
		Median	0.18	0.39
		Min.	-0.74	0.20
		Max.	1.65	0.44
	Overall	n	230	3
		Mean	0.22	0.35
		SE	0.019	0.077
		Median	0.18	0.36
	Visit 11 (Wash-out)	n	215	2
		Mean	0.06	0.11
		SE	0.020	0.170
		Median	0.06	0.11
		Min.	-1.03	-0.06
		Max.	1.53	0.28

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Protocol: SFA100062

Population: ITT Excluding Investigator

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Table 7.64
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1800888

Treatment: Salmeterol

			C, C	C, T

Subjects in treatment			226	6
FEV1 (L)	Visit 2 (Week -16)	n	226	6
		Mean	2.87	2.96
		SE	0.048	0.402
		Median	2.80	2.71
		Min.	1.44	1.77
		Max.	5.09	4.25
	Visit 3 (Week -12)	n	226	6
		Mean	2.89	3.13
		SE	0.049	0.420
		Median	2.78	2.90
		Min.	1.39	1.71
		Max.	5.46	4.56
	Visit 4 (Week -8)	n	226	6
		Mean	2.90	3.02
		SE	0.050	0.394
		Median	2.83	2.84
		Min.	1.44	1.70
		Max.	5.46	4.39
	Visit 5 (Week -4)	n	226	6
		Mean	2.91	3.04
		SE	0.050	0.422
		Median	2.81	2.77
		Min.	1.51	1.66
		Max.	5.66	4.41

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Population: ITT Excluding Investigator

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Table 7.64
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1800888

Treatment: Salmeterol

			C, C	C, T
FEV1 (L)	Visit 6 (Day 1)	n	226	6
		Mean	2.89	3.01
		SE	0.050	0.414
		Median	2.80	2.73
		Min.	1.32	1.65
		Max.	4.93	4.34
	Visit 7 (Week 4)	n	217	5
		Mean	3.05	3.11
		SE	0.053	0.483
		Median	2.95	2.77
		Min.	1.22	1.80
		Max.	5.35	4.51
	Visit 8 (Week 8)	n	205	5
		Mean	2.99	3.13
		SE	0.051	0.548
		Median	2.88	2.69
		Min.	1.24	1.73
		Max.	5.36	4.66
	Visit 9 (Week 12)	n	195	5
		Mean	2.99	3.05
		SE	0.052	0.488
		Median	2.95	2.74
		Min.	1.20	1.76
		Max.	4.99	4.41

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Table 7.64
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1800888

Treatment: Salmeterol

			C, C	C, T
FEV1 (L)	Visit 10 (Week 16)	n	192	5
		Mean	2.98	3.03
		SE	0.055	0.508
		Median	2.91	2.51
		Min.	1.22	1.84
		Max.	5.15	4.65
	Endpoint	n	217	5
		Mean	3.01	3.03
		SE	0.055	0.508
		Median	2.91	2.51
		Min.	1.22	1.84
		Max.	5.36	4.65
	Overall	n	217	5
		Mean	3.02	3.08
		SE	0.051	0.505
		Median	2.97	2.68
		Min.	1.22	1.78
		Max.	5.16	4.56
	Visit 11 (Wash-out)	n	190	5
		Mean	2.84	3.03
		SE	0.053	0.516
		Median	2.80	2.67
		Min.	1.10	1.62
		Max.	5.32	4.42

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Table 7.64
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1800888

Treatment: Salmeterol

			C, C	C, T
FEV1 change	Visit 7 (Week 4)	n	217	5
		Mean	0.17	0.00
		SE	0.024	0.072
		Median	0.13	0.02
		Min.	-1.33	-0.19
		Max.	2.38	0.17
	Visit 8 (Week 8)	n	205	5
		Mean	0.14	0.03
		SE	0.022	0.097
		Median	0.10	0.08
		Min.	-0.90	-0.27
		Max.	1.73	0.32
	Visit 9 (Week 12)	n	195	5
		Mean	0.13	-0.06
		SE	0.021	0.076
		Median	0.09	-0.01
		Min.	-0.61	-0.30
		Max.	1.27	0.11
	Visit 10 (Week 16)	n	192	5
		Mean	0.12	-0.07
		SE	0.026	0.134
		Median	0.08	-0.24
		Min.	-0.90	-0.34
		Max.	2.54	0.31

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Table 7.64
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS1800888

Treatment: Salmeterol

		C, C		C, T
FEV1 change	Endpoint	n	217	5
		Mean	0.13	-0.07
		SE	0.024	0.134
		Median	0.09	-0.24
		Min.	-0.90	-0.34
		Max.	2.54	0.31
	Overall	n	217	5
		Mean	0.14	-0.02
		SE	0.018	0.087
		Median	0.09	-0.07
		Min.	-0.47	-0.25
		Max.	1.19	0.22
	Visit 11 (Wash-out)	n	190	5
		Mean	-0.01	-0.07
		SE	0.023	0.055
		Median	-0.01	-0.07
		Min.	-1.54	-0.26
		Max.	1.03	0.08

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Protocol: SFA100062

Population: ITT Excluding Investigator

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Table 7.65
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS3729943

Treatment: FSC100/50

			C, C	C, G

Subjects in treatment			241	2
FEV1 (L)	Visit 2 (Week -16)	n	241	2
		Mean	2.82	2.52
		SE	0.044	0.120
		Median	2.79	2.52
		Min.	1.25	2.40
		Max.	5.03	2.64
	Visit 3 (Week -12)	n	241	2
		Mean	2.84	2.67
		SE	0.043	0.035
		Median	2.77	2.67
		Min.	1.45	2.63
		Max.	5.02	2.70
	Visit 4 (Week -8)	n	241	2
		Mean	2.84	2.64
		SE	0.043	0.195
		Median	2.79	2.64
		Min.	1.30	2.44
		Max.	5.08	2.83
	Visit 5 (Week -4)	n	241	2
		Mean	2.84	2.59
		SE	0.043	0.080
		Median	2.83	2.59
		Min.	1.46	2.51
		Max.	4.74	2.67

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Population: ITT Excluding Investigator

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Table 7.65
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS3729943

Treatment: FSC100/50

			C, C	C, G
FEV1 (L)	Visit 6 (Day 1)	n	241	2
		Mean	2.83	2.62
		SE	0.044	0.180
		Median	2.78	2.62
		Min.	1.32	2.44
		Max.	4.95	2.80
	Visit 7 (Week 4)	n	231	2
		Mean	3.03	2.87
		SE	0.050	0.160
		Median	2.97	2.87
		Min.	1.36	2.71
		Max.	5.98	3.03
	Visit 8 (Week 8)	n	224	2
		Mean	3.02	2.88
		SE	0.051	0.160
		Median	2.98	2.88
		Min.	1.20	2.72
		Max.	5.68	3.04
	Visit 9 (Week 12)	n	219	2
		Mean	3.03	2.87
		SE	0.052	0.310
		Median	2.94	2.87
		Min.	1.22	2.56
		Max.	5.75	3.18

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Table 7.65
 Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS3729943

Treatment: FSC100/50

			C, C	C, G

FEV1 (L)	Visit 10 (Week 16)	n	217	2
		Mean	3.03	2.84
		SE	0.052	0.185
		Median	2.97	2.84
		Min.	1.15	2.65
		Max.	5.33	3.02
	Endpoint	n	231	2
		Mean	3.03	2.84
		SE	0.050	0.185
		Median	2.98	2.84
		Min.	1.15	2.65
		Max.	5.33	3.02
	Overall	n	231	2
		Mean	3.03	2.86
		SE	0.049	0.204
		Median	2.93	2.86
		Min.	1.23	2.66
		Max.	5.69	3.07
	Visit 11 (Wash-out)	n	215	2
		Mean	2.86	2.81
		SE	0.050	0.215
		Median	2.82	2.81
		Min.	1.20	2.59
		Max.	4.78	3.02

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Protocol: SFA100062

Population: ITT Excluding Investigator

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Table 7.65
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS3729943

Treatment: FSC100/50

			C, C	C, G
FEV1 change	Visit 7 (Week 4)	n	231	2
		Mean	0.22	0.25
		SE	0.021	0.020
		Median	0.18	0.25
		Min.	-0.80	0.23
		Max.	1.62	0.27
	Visit 8 (Week 8)	n	224	2
		Mean	0.22	0.26
		SE	0.020	0.020
		Median	0.18	0.26
		Min.	-0.54	0.24
		Max.	1.50	0.28
	Visit 9 (Week 12)	n	219	2
		Mean	0.22	0.25
		SE	0.022	0.130
		Median	0.18	0.25
		Min.	-0.64	0.12
		Max.	1.56	0.38
	Visit 10 (Week 16)	n	217	2
		Mean	0.22	0.21
		SE	0.024	0.005
		Median	0.18	0.21
		Min.	-0.74	0.21
		Max.	1.65	0.22

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Table 7.65
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS3729943

Treatment: FSC100/50

			C, C	C, G
FEV1 change	Endpoint	n	231	2
		Mean	0.22	0.21
		SE	0.023	0.005
		Median	0.18	0.21
		Min.	-0.74	0.21
		Max.	1.65	0.22
	Overall	n	231	2
		Mean	0.22	0.24
		SE	0.019	0.024
		Median	0.18	0.24
		Min.	-0.41	0.22
		Max.	1.52	0.27
	Visit 11 (Wash-out)	n	215	2
		Mean	0.06	0.18
		SE	0.020	0.035
		Median	0.06	0.18
		Min.	-1.03	0.15
		Max.	1.53	0.22

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Table 7.65
 Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS3729943

Treatment: Salmeterol

			C, C	C, G

Subjects in treatment			231	1
FEV1 (L)	Visit 2 (Week -16)	n	231	1
		Mean	2.87	2.94
		SE	0.048	
		Median	2.78	2.94
		Min.	1.44	2.94
		Max.	5.09	2.94
	Visit 3 (Week -12)	n	231	1
		Mean	2.89	3.61
		SE	0.049	
		Median	2.79	3.61
		Min.	1.39	3.61
		Max.	5.46	3.61
	Visit 4 (Week -8)	n	231	1
		Mean	2.90	3.13
		SE	0.050	
		Median	2.82	3.13
		Min.	1.44	3.13
		Max.	5.46	3.13
	Visit 5 (Week -4)	n	231	1
		Mean	2.91	3.55
		SE	0.050	
		Median	2.80	3.55
		Min.	1.51	3.55
		Max.	5.66	3.55

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Table 7.65
 Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS3729943

Treatment: Salmeterol

			C, C	C, G
FEV1 (L)	Visit 6 (Day 1)	n	231	1
		Mean	2.89	4.14
		SE	0.050	
		Median	2.80	4.14
		Min.	1.32	4.14
		Max.	4.93	4.14
	Visit 7 (Week 4)	n	221	1
		Mean	3.05	3.66
		SE	0.053	
		Median	2.94	3.66
		Min.	1.22	3.66
		Max.	5.35	3.66
	Visit 8 (Week 8)	n	209	1
		Mean	2.99	3.95
		SE	0.051	
		Median	2.88	3.95
		Min.	1.24	3.95
		Max.	5.36	3.95
	Visit 9 (Week 12)	n	199	1
		Mean	2.99	3.71
		SE	0.052	
		Median	2.95	3.71
		Min.	1.20	3.71
		Max.	4.99	3.71

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Table 7.65
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS3729943

Treatment: Salmeterol

			C, C	C, G
-----			-----	
FEV1 (L)	Visit 10 (Week 16)	n	196	1
		Mean	2.97	4.02
		SE	0.055	
		Median	2.90	4.02
		Min.	1.22	4.02
		Max.	5.15	4.02
	Endpoint	n	221	1
		Mean	3.00	4.02
		SE	0.055	
		Median	2.90	4.02
		Min.	1.22	4.02
		Max.	5.36	4.02
	Overall	n	221	1
		Mean	3.02	3.84
		SE	0.051	
		Median	2.97	3.84
		Min.	1.22	3.84
		Max.	5.16	3.84
	Visit 11 (Wash-out)	n	194	1
		Mean	2.84	3.95
		SE	0.053	
		Median	2.80	3.95
		Min.	1.10	3.95
		Max.	5.32	3.95

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Protocol: SFA100062

Population: ITT Excluding Investigator

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Table 7.65
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS3729943

Treatment: Salmeterol

			C, C	C, G
FEV1 change	Visit 7 (Week 4)	n	221	1
		Mean	0.17	-0.48
		SE	0.023	
		Median	0.13	-0.48
		Min.	-1.33	-0.48
		Max.	2.38	-0.48
	Visit 8 (Week 8)	n	209	1
		Mean	0.13	-0.19
		SE	0.022	
		Median	0.10	-0.19
		Min.	-0.90	-0.19
		Max.	1.73	-0.19
	Visit 9 (Week 12)	n	199	1
		Mean	0.13	-0.43
		SE	0.021	
		Median	0.09	-0.43
		Min.	-0.61	-0.43
		Max.	1.27	-0.43
	Visit 10 (Week 16)	n	196	1
		Mean	0.12	-0.12
		SE	0.025	
		Median	0.08	-0.12
		Min.	-0.90	-0.12
		Max.	2.54	-0.12

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Table 7.65
Summary of Pre-dose FEV1 (L) - ADRB2 Gene SNP RS3729943

Treatment: Salmeterol

		C, C		C, G
FEV1 change	Endpoint	n	221	1
		Mean	0.12	-0.12
		SE	0.023	
		Median	0.09	-0.12
		Min.	-0.90	-0.12
		Max.	2.54	-0.12
	Overall	n	221	1
		Mean	0.14	-0.30
		SE	0.018	
		Median	0.09	-0.30
		Min.	-0.47	-0.30
		Max.	1.19	-0.30
	Visit 11 (Wash-out)	n	194	1
		Mean	-0.01	-0.19
		SE	0.023	
		Median	-0.02	-0.19
		Min.	-1.54	-0.19
		Max.	1.03	-0.19

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Protocol: SFA100062

Population: ITT Excluding Investigator

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Table 7.66
Summary of Pre-dose FEV1 (L) - Poly-C Repeat Group

Treatment: FSC100/50

			<12 Repeats	>=12 Repeats

Subjects in treatment			102	137
FEV1 (L)	Visit 2 (Week -16)	n	102	137
		Mean	2.75	2.88
		SE	0.062	0.062
		Median	2.67	2.87
		Min.	1.44	1.25
		Max.	4.25	5.03
	Visit 3 (Week -12)	n	102	137
		Mean	2.77	2.90
		SE	0.058	0.062
		Median	2.70	2.88
		Min.	1.48	1.45
		Max.	4.37	5.02
	Visit 4 (Week -8)	n	102	137
		Mean	2.77	2.90
		SE	0.060	0.060
		Median	2.71	2.88
		Min.	1.57	1.30
		Max.	4.26	5.08
	Visit 5 (Week -4)	n	102	137
		Mean	2.77	2.91
		SE	0.060	0.059
		Median	2.73	2.92
		Min.	1.62	1.46
		Max.	4.51	4.74

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Population: ITT Excluding Investigator

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Table 7.66
Summary of Pre-dose FEV1 (L) - Poly-C Repeat Group

Treatment: FSC100/50

			<12 Repeats	>=12 Repeats
FEV1 (L)	Visit 6 (Day 1)	n	102	137
		Mean	2.76	2.88
		SE	0.060	0.062
		Median	2.68	2.86
		Min.	1.32	1.33
		Max.	4.18	4.95
	Visit 7 (Week 4)	n	95	134
		Mean	2.93	3.11
		SE	0.068	0.071
		Median	2.90	3.05
		Min.	1.63	1.36
		Max.	4.79	5.98
	Visit 8 (Week 8)	n	93	130
		Mean	2.92	3.11
		SE	0.071	0.071
		Median	2.84	3.03
		Min.	1.64	1.20
		Max.	4.71	5.68
	Visit 9 (Week 12)	n	93	125
		Mean	2.91	3.13
		SE	0.071	0.072
		Median	2.82	3.06
		Min.	1.43	1.22
		Max.	4.69	5.75

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Table 7.66
Summary of Pre-dose FEV1 (L) - Poly-C Repeat Group

Treatment: FSC100/50

			<12 Repeats	>=12 Repeats
FEV1 (L)	Visit 10 (Week 16)	n	92	124
		Mean	2.92	3.11
		SE	0.075	0.071
		Median	2.89	3.08
		Min.	1.62	1.15
		Max.	4.93	5.33
	Endpoint	n	95	134
		Mean	2.92	3.11
		SE	0.073	0.068
		Median	2.88	3.08
		Min.	1.62	1.15
		Max.	4.93	5.33
	Overall	n	95	134
		Mean	2.92	3.11
		SE	0.069	0.068
		Median	2.88	3.05
		Min.	1.61	1.23
		Max.	4.72	5.69
	Visit 11 (Wash-out)	n	92	122
		Mean	2.78	2.93
		SE	0.072	0.068
		Median	2.75	2.89
		Min.	1.27	1.20
		Max.	4.42	4.78

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Table 7.66
Summary of Pre-dose FEV1 (L) - Poly-C Repeat Group

Treatment: FSC100/50

			<12 Repeats	>=12 Repeats
FEV1 change	Visit 7 (Week 4)	n	95	134
		Mean	0.20	0.23
		SE	0.028	0.030
		Median	0.18	0.18
		Min.	-0.67	-0.80
		Max.	0.97	1.62
	Visit 8 (Week 8)	n	93	130
		Mean	0.20	0.24
		SE	0.025	0.029
		Median	0.15	0.20
		Min.	-0.31	-0.54
		Max.	0.85	1.50
	Visit 9 (Week 12)	n	93	125
		Mean	0.18	0.25
		SE	0.027	0.032
		Median	0.13	0.20
		Min.	-0.38	-0.64
		Max.	0.85	1.56
	Visit 10 (Week 16)	n	92	124
		Mean	0.19	0.24
		SE	0.033	0.035
		Median	0.14	0.19
		Min.	-0.74	-0.67
		Max.	1.09	1.65

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Table 7.66
Summary of Pre-dose FEV1 (L) - Poly-C Repeat Group

Treatment: FSC100/50

			<12 Repeats	>=12 Repeats
FEV1 change	Endpoint	n	95	134
		Mean	0.19	0.23
		SE	0.032	0.033
		Median	0.15	0.19
		Min.	-0.74	-0.67
		Max.	1.09	1.65
	Overall	n	95	134
		Mean	0.19	0.24
		SE	0.024	0.027
		Median	0.17	0.19
		Min.	-0.35	-0.41
		Max.	0.85	1.52
	Visit 11 (Wash-out)	n	92	122
		Mean	0.06	0.06
		SE	0.032	0.025
		Median	0.05	0.06
		Min.	-1.03	-0.73
		Max.	1.53	0.84

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Table 7.66
Summary of Pre-dose FEV1 (L) - Poly-C Repeat Group

Treatment: Salmeterol

			<12 Repeats	>=12 Repeats

Subjects in treatment			91	139
FEV1 (L)	Visit 2 (Week -16)	n	91	139
		Mean	2.83	2.90
		SE	0.068	0.065
		Median	2.81	2.77
		Min.	1.61	1.44
		Max.	4.30	5.09
	Visit 3 (Week -12)	n	91	139
		Mean	2.89	2.91
		SE	0.075	0.065
		Median	2.80	2.77
		Min.	1.65	1.39
		Max.	4.63	5.46
	Visit 4 (Week -8)	n	91	139
		Mean	2.88	2.92
		SE	0.074	0.066
		Median	2.74	2.87
		Min.	1.61	1.44
		Max.	4.69	5.46
	Visit 5 (Week -4)	n	91	139
		Mean	2.88	2.95
		SE	0.071	0.068
		Median	2.76	2.84
		Min.	1.65	1.51
		Max.	4.88	5.66

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Table 7.66
Summary of Pre-dose FEV1 (L) - Poly-C Repeat Group

Treatment: Salmeterol

			<12 Repeats	>=12 Repeats
FEV1 (L)	Visit 6 (Day 1)	n	91	139
		Mean	2.89	2.89
		SE	0.077	0.066
		Median	2.80	2.80
		Min.	1.54	1.32
		Max.	4.73	4.93
	Visit 7 (Week 4)	n	86	134
		Mean	3.04	3.06
		SE	0.080	0.071
		Median	2.93	2.97
		Min.	1.63	1.22
		Max.	4.87	5.35
	Visit 8 (Week 8)	n	83	125
		Mean	3.03	2.97
		SE	0.081	0.066
		Median	2.88	2.88
		Min.	1.62	1.24
		Max.	5.36	5.10
	Visit 9 (Week 12)	n	78	121
		Mean	2.98	2.99
		SE	0.076	0.070
		Median	2.92	2.98
		Min.	1.65	1.20
		Max.	4.83	4.99

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Table 7.66
Summary of Pre-dose FEV1 (L) - Poly-C Repeat Group

Treatment: Salmeterol

			<12 Repeats	>=12 Repeats
FEV1 (L)	Visit 10 (Week 16)	n	77	119
		Mean	3.00	2.96
		SE	0.085	0.072
		Median	2.90	2.90
		Min.	1.60	1.22
		Max.	5.13	5.15
	Endpoint	n	86	134
		Mean	3.02	3.01
		SE	0.086	0.072
		Median	2.90	2.91
		Min.	1.60	1.22
		Max.	5.36	5.16
	Overall	n	86	134
		Mean	3.02	3.03
		SE	0.075	0.069
		Median	2.97	2.97
		Min.	1.66	1.22
		Max.	4.80	5.16
	Visit 11 (Wash-out)	n	77	117
		Mean	2.86	2.84
		SE	0.083	0.070
		Median	2.82	2.77
		Min.	1.39	1.10
		Max.	5.32	4.65

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Table 7.66
Summary of Pre-dose FEV1 (L) - Poly-C Repeat Group

Treatment: Salmeterol

			<12 Repeats	>=12 Repeats
FEV1 change	Visit 7 (Week 4)	n	86	134
		Mean	0.14	0.18
		SE	0.048	0.024
		Median	0.09	0.14
		Min.	-1.33	-0.63
		Max.	2.38	1.30
	Visit 8 (Week 8)	n	83	125
		Mean	0.14	0.13
		SE	0.035	0.028
		Median	0.12	0.09
		Min.	-0.84	-0.90
		Max.	1.27	1.73
	Visit 9 (Week 12)	n	78	121
		Mean	0.09	0.15
		SE	0.032	0.028
		Median	0.07	0.11
		Min.	-0.61	-0.60
		Max.	1.17	1.27
	Visit 10 (Week 16)	n	77	119
		Mean	0.10	0.13
		SE	0.046	0.030
		Median	0.05	0.08
		Min.	-0.90	-0.66
		Max.	2.54	1.63

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Table 7.66
Summary of Pre-dose FEV1 (L) - Poly-C Repeat Group

Treatment: Salmeterol

		<12 Repeats		>=12 Repeats	
FEV1 change	Endpoint	n	86	134	
		Mean	0.12	0.13	
		SE	0.043	0.027	
		Median	0.05	0.09	
		Min.	-0.90	-0.66	
		Max.	2.54	1.63	
	Overall	n	86	134	
		Mean	0.12	0.15	
		SE	0.032	0.022	
		Median	0.06	0.10	
		Min.	-0.47	-0.41	
		Max.	1.16	1.19	
	Visit 11 (Wash-out)	n	77	117	
		Mean	-0.05	0.01	
		SE	0.040	0.027	
		Median	-0.04	0.03	
		Min.	-1.54	-0.75	
		Max.	1.02	1.03	

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Table 7.67
Analysis of Pre-dose FEV1 (L) - Poly-C Repeat Group

			<12 vs. ≥12

FSC100/50	Visit 7 (Week 4)	p-value	0.372
		LS Means Diff	-0.04
		95% CI for Diff	(-0.12,0.05)
	Visit 8 (Week 8)	p-value	0.367
		LS Means Diff	-0.04
		95% CI for Diff	(-0.12,0.04)
	Visit 9 (Week 12)	p-value	0.096
		LS Means Diff	-0.07
		95% CI for Diff	(-0.15,0.01)
	Visit 10 (Week 16)	p-value	0.192
LS Means Diff		-0.06	
95% CI for Diff		(-0.16,0.03)	
Endpoint	p-value	0.215	
	LS Means Diff	-0.06	
	95% CI for Diff	(-0.15,0.03)	
Overall	p-value	0.203	
	LS Means Diff	-0.05	
	95% CI for Diff	(-0.12,0.03)	
Visit 11 (Wash-out)	p-value	0.837	
	LS Means Diff	-0.01	
	95% CI for Diff	(-0.09,0.07)	

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and Poly-C repeat group. Least squares mean differences are calculated as <12 Repeats - ≥12 Repeats.

Table 7.67
Analysis of Pre-dose FEV1 (L) - Poly-C Repeat Group

			<12 vs. ≥12
Salmeterol	Visit 7 (Week 4)	p-value	0.465
		LS Means Diff	-0.04
		95% CI for Diff	(-0.13, 0.06)
	Visit 8 (Week 8)	p-value	0.880
		LS Means Diff	0.01
		95% CI for Diff	(-0.08, 0.09)
	Visit 9 (Week 12)	p-value	0.318
		LS Means Diff	-0.04
		95% CI for Diff	(-0.12, 0.04)
	Visit 10 (Week 16)	p-value	0.791
		LS Means Diff	-0.01
		95% CI for Diff	(-0.12, 0.09)
	Endpoint	p-value	0.911
		LS Means Diff	-0.01
		95% CI for Diff	(-0.10, 0.09)
	Overall	p-value	0.591
		LS Means Diff	-0.02
		95% CI for Diff	(-0.09, 0.05)
	Visit 11 (Wash-out)	p-value	0.326
		LS Means Diff	-0.04
		95% CI for Diff	(-0.13, 0.04)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and Poly-C repeat group. Least squares mean differences are calculated as <12 Repeats - ≥12 Repeats.

Table 7.68
Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1432623

Treatment: FSC100/50

				C, C	C, T	T, T
-----				-----		
Subjects in treatment				37	95	110
% Symptom-free days	Double-blind	Baseline	n	36	93	105
			Mean	29.5	36.8	32.0
			SE	5.97	4.11	3.97
			Median	7.1	14.3	0.0
			Min.	0	0	0
			Max.	100	100	100
		Weeks 1-4	n	35	94	110
			Mean	36.4	48.6	47.4
			SE	6.67	4.28	4.03
			Median	17.9	55.4	51.8
			Min.	0	0	0
			Max.	100	100	100
		Weeks 5-8	n	32	92	105
			Mean	39.9	48.9	47.2
			SE	7.08	4.40	4.00
			Median	39.9	53.6	53.6
			Min.	0	0	0
			Max.	100	100	100
		Weeks 9-12	n	30	90	102
			Mean	39.3	49.2	51.1
			SE	7.27	4.45	4.19
			Median	28.6	63.6	54.6
			Min.	0	0	0
			Max.	100	100	100
		Weeks 13-16	n	29	89	99
			Mean	39.9	48.0	51.5
			SE	7.72	4.46	4.25

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Table 7.68
Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1432623

Treatment: FSC100/50

				C, C	C, T	T, T
% Symptom-free days	Double-blind	Weeks 13-16	Median	33.3	50.0	53.6
			Min.	0	0	0
			Max.	100	100	100
		Overall	n	35	95	110
			Mean	37.9	49.3	49.2
			SE	6.63	4.20	3.87
			Median	34.2	58.2	54.3
			Min.	0	0	0
			Max.	99	100	100
	Wash-out	Overall	n	27	88	99
			Mean	36.0	41.5	40.9
			SE	7.90	4.39	4.23
			Median	14.3	28.6	30.8
			Min.	0	0	0
			Max.	100	100	100
% SFD change	Double-blind	Weeks 1-4	n	34	92	105
			Mean	8.4	10.9	14.5
			SE	3.75	2.80	2.90
			Median	0.0	0.0	0.0
			Min.	-25	-39	-43
			Max.	82	96	100
		Weeks 5-8	n	32	90	101
			Mean	10.7	13.2	14.1
			SE	4.19	2.84	3.11
			Median	0.0	0.0	0.0
			Min.	-43	-23	-46
			Max.	82	100	100
		Weeks 9-12	n	30	88	98

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Table 7.68
Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1432623

Treatment: FSC100/50

				C, C	C, T	T, T
-----				-----		
% SFD change	Double-blind	Weeks 9-12	Mean	8.7	13.1	18.4
			SE	4.06	3.15	3.42
			Median	0.0	0.0	0.0
			Min.	-40	-76	-38
			Max.	71	100	100
		Weeks 13-16	n	29	87	95
			Mean	10.7	11.3	18.1
			SE	4.23	3.20	3.67
			Median	0.0	0.0	0.0
			Min.	-33	-78	-71
			Max.	78	100	100
		Overall	n	34	93	105
			Mean	10.0	12.1	16.1
			SE	3.65	2.73	2.93
			Median	0.0	0.0	0.0
			Min.	-35	-44	-27
			Max.	78	99	100
	Wash-out	Overall	n	27	86	95
			Mean	5.4	5.6	8.7
			SE	4.22	2.41	3.09
			Median	0.0	0.0	0.0
			Min.	-64	-55	-64
			Max.	43	100	100

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Table 7.68
Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1432623

Treatment: Salmeterol

				C, C	C, T	T, T
-----				-----		
Subjects in treatment				34	98	100
% Symptom-free days	Double-blind	Baseline	n	33	97	98
			Mean	34.0	36.8	34.2
			SE	7.18	4.15	4.15
			Median	0.0	14.3	7.1
			Min.	0	0	0
			Max.	100	100	100
	Weeks 1-4	n	n	33	96	96
			Mean	39.2	44.1	39.8
			SE	6.72	4.10	4.09
			Median	39.3	46.4	29.2
			Min.	0	0	0
			Max.	100	100	100
	Weeks 5-8	n	n	31	93	93
			Mean	38.7	44.5	43.3
			SE	7.12	4.20	4.13
			Median	32.1	42.9	42.9
			Min.	0	0	0
			Max.	100	100	100
	Weeks 9-12	n	n	28	90	88
			Mean	36.7	44.1	46.0
			SE	7.79	4.41	4.31
			Median	17.9	40.4	46.4
			Min.	0	0	0
			Max.	100	100	100
	Weeks 13-16	n	n	27	88	84
			Mean	39.3	45.6	45.4
			SE	8.07	4.37	4.42

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Table 7.68
Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1432623

Treatment: Salmeterol

				C, C	C, T	T, T
% Symptom-free days	Double-blind	Weeks 13-16	Median	18.5	53.6	43.6
			Min.	0	0	0
			Max.	100	100	100
		Overall	n	33	97	97
			Mean	40.0	45.6	43.0
			SE	6.75	3.98	3.97
			Median	29.5	46.4	38.4
			Min.	0	0	0
			Max.	97	100	100
	Wash-out	Overall	n	27	84	83
			Mean	30.2	42.3	39.2
			SE	8.16	4.68	4.43
			Median	0.0	31.0	21.4
			Min.	0	0	0
			Max.	100	100	100
% SFD change	Double-blind	Weeks 1-4	n	33	95	96
			Mean	5.2	7.5	6.0
			SE	4.45	2.81	2.59
			Median	0.0	0.0	0.0
			Min.	-82	-67	-71
			Max.	64	93	96
		Weeks 5-8	n	31	92	93
			Mean	3.0	8.5	8.1
			SE	5.14	2.81	3.00
			Median	0.0	0.0	0.0
			Min.	-86	-100	-86
			Max.	71	96	96
		Weeks 9-12	n	28	90	88

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Table 7.68
 Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1432623

Treatment: Salmeterol

			C, C	C, T	T, T	

% SFD change	Double-blind	Weeks 9-12	Mean	6.1	9.3	10.1
			SE	4.58	2.65	3.23
			Median	0.0	0.0	0.0
			Min.	-82	-43	-61
			Max.	64	100	100
		Weeks 13-16	n	27	88	84
			Mean	7.6	9.7	9.3
			SE	5.41	2.86	3.40
			Median	0.0	0.0	0.0
			Min.	-79	-38	-86
		Max.	86	100	100	
		Overall	n	33	96	97
			Mean	6.1	8.5	8.5
			SE	4.21	2.48	2.67
			Median	0.0	0.0	0.0
	Min.		-82	-41	-69	
	Max.	65	97	94		
	Wash-out	Overall	n	27	84	83
Mean			-1.5	6.3	3.6	
SE			5.05	3.12	3.02	
Median			0.0	0.0	0.0	
Min.			-86	-57	-71	
Max.			50	93	100	

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Table 7.69
Analysis of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1432623

			C/C vs. C/T	C/C vs. T/T	C/T vs. T/T
FSC100/50	Double-blind	Weeks 1-4	p-value	0.554	0.189
			LS Means Diff	-3.2	-7.0
			95% CI for Diff	(-13.9, 7.5)	(-17.4, 3.5)
		Weeks 5-8	p-value	0.595	0.448
			LS Means Diff	-3.0	-4.3
			95% CI for Diff	(-14.3, 8.2)	(-15.3, 6.8)
		Weeks 9-12	p-value	0.473	0.124
			LS Means Diff	-4.5	-9.5
			95% CI for Diff	(-16.9, 7.9)	(-21.6, 2.6)
		Weeks 13-16	p-value	0.938	0.222
			LS Means Diff	-0.5	-7.9
			95% CI for Diff	(-13.4, 12.4)	(-20.6, 4.8)
	Wash-out	Overall	p-value	0.580	0.188
			LS Means Diff	-2.9	-6.9
			95% CI for Diff	(-13.4, 7.5)	(-17.1, 3.4)
		Overall	p-value	0.979	0.560
			LS Means Diff	-0.1	-3.3
			95% CI for Diff	(-11.3, 11.0)	(-14.3, 7.8)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS1432623. Least squares mean differences are calculated as C/C-C/T, C/C-T/T and C/T-T/T.

Table 7.69
Analysis of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1432623

				C/C vs. C/T	C/C vs. T/T	C/T vs. T/T
Salmeterol	Double-blind	Weeks 1-4	p-value	0.583	0.967	0.491
			LS Means Diff	-2.7	-0.2	2.5
			95% CI for Diff	(-12.6,7.1)	(-10.4,10.0)	(-4.7,9.8)
		Weeks 5-8	p-value	0.298	0.414	0.788
			LS Means Diff	-5.7	-4.6	1.1
			95% CI for Diff	(-16.4,5.1)	(-15.7,6.5)	(-6.8,8.9)
		Weeks 9-12	p-value	0.470	0.411	0.851
			LS Means Diff	-4.1	-4.9	-0.8
			95% CI for Diff	(-15.3,7.1)	(-16.5,6.8)	(-8.7,7.2)
		Weeks 13-16	p-value	0.617	0.687	0.911
			LS Means Diff	-3.0	-2.5	0.5
			95% CI for Diff	(-14.9,8.9)	(-14.9,9.9)	(-8.0,9.0)
	Overall	p-value	0.507	0.702	0.715	
LS Means Diff		-3.1	-1.9	1.3		
95% CI for Diff		(-12.5,6.2)	(-11.5,7.8)	(-5.6,8.1)		
Wash-out	Overall	p-value	0.174	0.601	0.259	
		LS Means Diff	-8.1	-3.2	4.8	
		95% CI for Diff	(-19.7,3.6)	(-15.3,8.9)	(-3.6,13.3)	

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS1432623. Least squares mean differences are calculated as C/C-C/T, C/C-T/T and C/T-T/T.

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Table 7.70
Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1042711

Treatment: FSC100/50

				C, C	C, T	T, T
-----				-----		
Subjects in treatment				23	72	141
% Symptom-free days	Double-blind	Baseline	n	23	70	135
			Mean	31.2	36.9	32.5
			SE	7.05	4.74	3.49
			Median	14.3	14.3	0.0
			Min.	0	0	0
			Max.	86	100	100
		Weeks 1-4	n	22	71	140
			Mean	40.8	51.6	43.7
			SE	8.62	4.96	3.51
			Median	31.3	60.7	42.6
			Min.	0	0	0
			Max.	100	100	100
		Weeks 5-8	n	20	68	135
			Mean	44.3	50.4	44.6
			SE	8.91	5.13	3.52
			Median	48.2	54.8	44.4
			Min.	0	0	0
			Max.	100	100	100
		Weeks 9-12	n	19	66	132
			Mean	42.7	51.7	47.1
			SE	9.39	5.21	3.65
			Median	32.1	66.7	49.1
			Min.	0	0	0
			Max.	100	100	100
		Weeks 13-16	n	19	65	128
			Mean	44.3	50.2	47.0
			SE	9.64	5.21	3.75

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Table 7.70
Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1042711

Treatment: FSC100/50

				C, C	C, T	T, T
% Symptom-free days	Double-blind	Weeks 13-16	Median	42.9	59.3	50.0
			Min.	0	0	0
			Max.	100	100	100
		Overall	n	22	72	140
			Mean	43.2	51.4	45.6
			SE	8.45	4.86	3.40
			Median	42.8	60.4	46.1
			Min.	0	0	0
			Max.	99	100	100
	Wash-out	Overall	n	17	65	127
			Mean	41.6	42.9	37.7
			SE	10.29	5.11	3.65
			Median	33.3	38.5	21.4
			Min.	0	0	0
			Max.	100	100	100
% SFD change	Double-blind	Weeks 1-4	n	22	69	134
			Mean	11.5	14.2	10.2
			SE	4.74	3.13	2.40
			Median	6.5	0.0	0.0
			Min.	-25	-20	-43
			Max.	82	96	96
		Weeks 5-8	n	20	67	130
			Mean	14.9	14.9	11.0
			SE	4.92	3.36	2.50
			Median	7.1	0.0	0.0
			Min.	-4	-18	-46
			Max.	82	100	100
		Weeks 9-12	n	19	65	127

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Table 7.70
 Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1042711

Treatment: FSC100/50

				C, C	C, T	T, T

% SFD change	Double-blind	Weeks 9-12	Mean	12.4	15.6	13.8
			SE	4.75	3.43	2.88
			Median	0.0	0.0	0.0
			Min.	-5	-29	-76
			Max.	71	100	100
		Weeks 13-16	n	19	64	123
			Mean	14.0	14.4	12.8
			SE	5.14	3.55	3.04
			Median	0.0	0.0	0.0
			Min.	-18	-35	-78
			Max.	78	89	100
		Overall	n	22	70	134
			Mean	13.8	14.5	11.9
			SE	4.30	3.09	2.42
			Median	4.8	0.9	0.0
			Min.	-5	-17	-44
			Max.	78	92	99
	Wash-out	Overall	n	17	64	122
			Mean	9.0	7.0	5.1
			SE	4.78	2.45	2.50
			Median	0.0	0.0	0.0
			Min.	-36	-36	-64
			Max.	43	67	100

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Table 7.70
Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1042711

Treatment: Salmeterol

				C, C	C, T	T, T
-----				-----		
Subjects in treatment				25	71	133
% Symptom-free days	Double-blind	Baseline	n	25	71	129
			Mean	38.6	33.2	35.6
			SE	8.37	4.68	3.68
			Median	28.6	0.0	14.3
			Min.	0	0	0
			Max.	100	100	100
		Weeks 1-4	n	25	70	127
			Mean	44.0	42.1	41.4
			SE	7.78	4.86	3.54
			Median	40.7	39.3	35.7
			Min.	0	0	0
			Max.	100	100	100
		Weeks 5-8	n	23	67	124
			Mean	45.2	40.2	44.9
			SE	8.50	4.78	3.64
			Median	39.3	32.1	44.5
			Min.	0	0	0
			Max.	100	100	100
		Weeks 9-12	n	20	66	117
			Mean	40.7	40.9	46.6
			SE	9.27	5.18	3.78
			Median	26.8	23.2	46.4
			Min.	0	0	0
			Max.	100	100	100
		Weeks 13-16	n	20	64	112
			Mean	38.5	42.0	47.7
			SE	9.39	5.18	3.83

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Table 7.70
Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1042711

Treatment: Salmeterol

				C, C	C, T	T, T
% Symptom-free days	Double-blind	Weeks 13-16	Median	12.8	32.1	55.6
			Min.	0	0	0
			Max.	100	100	100
		Overall	n	25	70	129
			Mean	44.0	42.5	44.7
			SE	7.95	4.68	3.45
			Median	31.2	37.4	42.2
			Min.	0	0	0
			Max.	97	100	100
	Wash-out	Overall	n	20	64	107
			Mean	32.3	37.1	42.3
			SE	9.71	5.20	4.05
			Median	0.0	7.4	33.3
			Min.	0	0	0
			Max.	100	100	100
% SFD change	Double-blind	Weeks 1-4	n	25	70	126
			Mean	5.4	8.4	6.5
			SE	5.61	3.06	2.30
			Median	0.0	0.0	0.0
			Min.	-82	-50	-71
			Max.	64	93	96
		Weeks 5-8	n	23	67	123
			Mean	3.9	7.3	9.0
			SE	6.80	3.22	2.53
			Median	0.0	0.0	0.0
			Min.	-86	-100	-86
			Max.	71	96	96
		Weeks 9-12	n	20	66	117

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Table 7.70
 Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1042711

Treatment: Salmeterol

			C, C	C, T	T, T	
% SFD change	Double-blind	Weeks 9-12	Mean	5.7	9.1	10.6
			SE	6.26	2.80	2.73
			Median	0.0	0.0	0.0
			Min.	-82	-43	-61
			Max.	64	100	100
		Weeks 13-16	n	20	64	112
			Mean	3.5	10.0	10.5
			SE	5.79	3.13	2.95
			Median	0.0	0.0	0.0
			Min.	-79	-38	-86
			Max.	60	100	100
		Overall	n	25	70	128
			Mean	5.5	8.9	8.9
			SE	5.42	2.67	2.31
			Median	0.0	0.0	0.0
			Min.	-82	-41	-69
			Max.	65	97	94
	Wash-out	Overall	n	20	64	107
			Mean	-2.7	5.2	5.2
			SE	6.75	3.23	2.76
			Median	0.0	0.0	0.0
			Min.	-86	-57	-71
			Max.	50	93	100

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Table 7.71
Analysis of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1042711

				C/C vs. C/T	C/C vs. T/T	C/T vs. T/T	
FSC100/50	Double-blind	Weeks 1-4	p-value	0.439	0.676	0.551	
			LS Means Diff	-4.9	-2.6	2.4	
			95% CI for Diff	(-17.5,7.6)	(-14.7,9.5)	(-5.4,10.2)	
		Weeks 5-8	p-value	0.818	0.874	0.526	
			LS Means Diff	-1.6	1.0	2.6	
	95% CI for Diff		(-15.0,11.9)	(-12.0,14.1)	(-5.5,10.8)		
	Weeks 9-12	p-value	0.508	0.466	0.944		
		LS Means Diff	-5.0	-5.3	-0.3		
		95% CI for Diff	(-19.8,9.9)	(-19.6,9.0)	(-9.2,8.6)		
	Weeks 13-16	p-value	0.833	0.755	0.880		
LS Means Diff		-1.6	-2.4	-0.7			
95% CI for Diff		(-17.0,13.7)	(-17.2,12.5)	(-10.0,8.5)			
	Overall	p-value	0.628	0.735	0.798		
		LS Means Diff	-3.0	-2.0	1.0		
		95% CI for Diff	(-15.4,9.3)	(-13.9,9.8)	(-6.6,8.6)		
		Wash-out	Overall	p-value	0.944	0.891	0.913
				LS Means Diff	0.5	0.9	0.4
	95% CI for Diff			(-12.5,13.5)	(-11.8,13.6)	(-7.1,8.0)	

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS1042711. Least squares mean differences are calculated as C/C-C/T, C/C-T/T and C/T-T/T.

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Table 7.71
Analysis of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1042711

				C/C vs. C/T	C/C vs. T/T	C/T vs. T/T
Salmeterol	Double-blind	Weeks 1-4	p-value	0.656	0.614	0.940
			LS Means Diff	-2.5	-2.8	-0.3
			95% CI for Diff	(-13.7,8.7)	(-13.8,8.2)	(-7.8,7.2)
		Weeks 5-8	p-value	0.718	0.259	0.264
			LS Means Diff	-2.3	-7.0	-4.7
			95% CI for Diff	(-14.7,10.1)	(-19.1,5.2)	(-12.9,3.6)
		Weeks 9-12	p-value	0.537	0.197	0.295
			LS Means Diff	-4.1	-8.5	-4.4
			95% CI for Diff	(-17.2,9.0)	(-21.5,4.4)	(-12.7,3.9)
	Weeks 13-16	p-value	0.361	0.171	0.492	
		LS Means Diff	-6.4	-9.5	-3.1	
		95% CI for Diff	(-20.2,7.4)	(-23.1,4.1)	(-12.1,5.8)	
	Overall	p-value	0.585	0.324	0.529	
LS Means Diff		-3.0	-5.2	-2.3		
95% CI for Diff		(-13.6,7.7)	(-15.7,5.2)	(-9.4,4.9)		
Wash-out	Overall	p-value	0.247	0.208	0.887	
		LS Means Diff	-8.0	-8.6	-0.6	
		95% CI for Diff	(-21.5,5.6)	(-22.0,4.8)	(-9.5,8.2)	

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS1042711. Least squares mean differences are calculated as C/C-C/T, C/C-T/T and C/T-T/T.

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Table 7.72
Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1042713

Treatment: FSC100/50

				A, A	A, G	G, G
-----				-----		
Subjects in treatment				81	85	77
% Symptom-free days	Double-blind	Baseline	n	75	84	76
			Mean	32.1	34.3	33.7
			SE	4.85	4.55	3.96
			Median	0.0	7.1	24.3
			Min.	0	0	0
			Max.	100	100	100
	Weeks 1-4	n	n	80	85	75
			Mean	43.1	45.5	49.9
			SE	4.68	4.60	4.71
			Median	42.6	46.4	50.0
			Min.	0	0	0
			Max.	100	100	100
	Weeks 5-8	n	n	77	82	71
			Mean	43.5	47.3	49.3
			SE	4.75	4.56	4.88
			Median	44.4	51.8	53.6
			Min.	0	0	0
			Max.	100	100	100
	Weeks 9-12	n	n	73	82	68
			Mean	46.5	48.6	50.5
			SE	4.99	4.65	5.07
			Median	46.4	58.9	58.9
			Min.	0	0	0
			Max.	100	100	100
	Weeks 13-16	n	n	72	79	67
			Mean	48.2	46.3	50.7
			SE	5.18	4.58	5.16

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Table 7.72
Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1042713

Treatment: FSC100/50

				A, A	A, G	G, G

% Symptom-free days	Double-blind	Weeks 13-16	Median	50.9	42.9	53.6
			Min.	0	0	0
			Max.	100	100	100
		Overall	n	80	85	76
			Mean	44.3	47.8	50.3
			SE	4.63	4.37	4.63
			Median	52.3	50.9	58.4
			Min.	0	0	0
			Max.	100	100	100
	Wash-out	Overall	n	71	79	65
			Mean	43.0	36.7	42.0
			SE	5.13	4.49	5.15
			Median	33.3	21.4	38.5
			Min.	0	0	0
			Max.	100	100	100
% SFD change	Double-blind	Weeks 1-4	n	74	84	74
			Mean	9.2	11.7	15.6
			SE	2.97	3.14	3.24
			Median	0.0	0.0	5.6
			Min.	-39	-29	-43
			Max.	100	96	96
		Weeks 5-8	n	72	82	70
			Mean	8.8	14.5	16.1
			SE	3.16	3.30	3.36
			Median	0.0	0.0	0.0
			Min.	-46	-32	-32
			Max.	100	100	100
		Weeks 9-12	n	68	82	67
		[REDACTED]				

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Table 7.72
Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1042713

Treatment: FSC100/50

				A, A	A, G	G, G
-----				-----		
% SFD change	Double-blind	Weeks 9-12	Mean	12.0	15.9	16.4
			SE	3.45	3.79	3.48
			Median	0.0	0.0	5.0
			Min.	-40	-76	-38
			Max.	100	100	100
		Weeks 13-16	n	67	79	66
			Mean	12.0	14.5	16.2
			SE	3.73	4.12	3.32
			Median	0.0	0.0	0.0
			Min.	-50	-78	-35
			Max.	100	100	89
		Overall	n	74	84	75
			Mean	10.0	14.0	16.5
			SE	2.97	3.24	3.07
			Median	0.0	0.0	6.8
			Min.	-35	-44	-23
			Max.	100	99	96
	Wash-out	Overall	n	66	79	64
			Mean	8.3	6.2	6.6
			SE	3.59	3.04	2.64
			Median	0.0	0.0	0.0
			Min.	-64	-55	-43
			Max.	100	100	71

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Table 7.72
Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1042713

Treatment: Salmeterol

				A, A	A, G	G, G
-----				-----		
Subjects in treatment				72	79	81
% Symptom-free days	Double-blind	Baseline	n	69	78	81
			Mean	35.6	37.2	33.1
			SE	5.09	4.55	4.51
			Median	14.3	28.6	0.0
			Min.	0	0	0
			Max.	100	100	100
		Weeks 1-4	n	68	77	80
			Mean	41.1	44.2	39.4
			SE	4.73	4.63	4.47
			Median	41.1	39.3	36.3
			Min.	0	0	0
			Max.	100	100	100
		Weeks 5-8	n	66	75	76
			Mean	43.2	44.8	41.7
			SE	4.87	4.76	4.53
			Median	40.7	42.9	35.7
			Min.	0	0	0
			Max.	100	100	100
		Weeks 9-12	n	62	71	73
			Mean	46.0	45.7	40.4
			SE	5.17	5.04	4.72
			Median	46.4	39.3	25.9
			Min.	0	0	0
			Max.	100	100	100
		Weeks 13-16	n	61	68	70
			Mean	48.4	47.0	39.1
			SE	5.19	5.13	4.71

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Table 7.72
Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1042713

Treatment: Salmeterol

				A, A	A, G	G, G

% Symptom-free days	Double-blind	Weeks 13-16	Median	57.7	48.1	27.1
			Min.	0	0	0
			Max.	100	100	100
		Overall	n	69	77	81
			Mean	44.4	45.2	41.7
			SE	4.63	4.53	4.34
			Median	39.3	42.2	33.6
			Min.	0	0	0
			Max.	100	100	100
	Wash-out	Overall	n	57	67	70
			Mean	42.0	42.3	34.3
			SE	5.40	5.39	4.81
			Median	33.3	21.4	0.0
			Min.	0	0	0
			Max.	100	100	100
% SFD change	Double-blind	Weeks 1-4	n	67	77	80
			Mean	5.7	6.5	7.2
			SE	3.01	3.01	3.07
			Median	0.0	0.0	0.0
			Min.	-43	-67	-82
			Max.	82	96	93
		Weeks 5-8	n	65	75	76
			Mean	8.0	6.4	8.3
			SE	3.56	3.17	3.25
			Median	0.0	0.0	0.0
			Min.	-86	-100	-86
			Max.	96	96	96
		Weeks 9-12	n	62	71	73

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Table 7.72
Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1042713

Treatment: Salmeterol

				A, A	A, G	G, G
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% SFD change	Double-blind	Weeks 9-12	Mean	10.8	8.1	9.1
			SE	3.85	2.90	3.21
			Median	0.0	0.0	0.0
			Min.	-61	-57	-82
			Max.	100	100	100
		Weeks 13-16	n	61	68	70
			Mean	11.2	8.2	8.7
			SE	4.24	3.03	3.40
			Median	0.0	0.0	0.0
			Min.	-86	-50	-79
			Max.	100	86	100
		Overall	n	68	77	81
			Mean	8.4	7.5	8.6
			SE	3.24	2.57	2.91
			Median	0.0	0.0	0.0
			Min.	-69	-45	-82
			Max.	94	94	97
	Wash-out	Overall	n	57	67	70
			Mean	5.2	3.3	3.9
			SE	3.79	2.77	3.77
			Median	0.0	0.0	0.0
			Min.	-57	-57	-86
			Max.	100	86	93

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Table 7.73
Analysis of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1042713

				A/A vs. A/G	A/A vs. G/G	A/G vs. G/G
FSC100/50	Double-blind	Weeks 1-4	p-value	0.656	0.184	0.349
			LS Means Diff	-1.9	-5.9	-4.0
			95% CI for Diff	(-10.3,6.5)	(-14.6,2.8)	(-12.3,4.4)
		Weeks 5-8	p-value	0.250	0.141	0.702
			LS Means Diff	-5.2	-6.9	-1.7
	Wash-out	Weeks 9-12	95% CI for Diff	(-14.0,3.7)	(-16.0,2.3)	(-10.5,7.1)
			p-value	0.587	0.471	0.832
		Weeks 13-16	LS Means Diff	-2.7	-3.7	-1.0
			95% CI for Diff	(-12.3,7.0)	(-13.7,6.4)	(-10.6,8.5)
		Overall	p-value	0.828	0.500	0.626
LS Means Diff			-1.1	-3.6	-2.5	
95% CI for Diff			(-11.1,8.9)	(-14.0,6.9)	(-12.4,7.5)	
Overall		p-value	0.416	0.175	0.555	
		LS Means Diff	-3.4	-5.9	-2.5	
		95% CI for Diff	(-11.7,4.9)	(-14.4,2.6)	(-10.6,5.7)	
Overall		p-value	0.474	0.669	0.789	
		LS Means Diff	3.1	1.9	-1.1	
		95% CI for Diff	(-5.4,11.5)	(-6.9,10.8)	(-9.6,7.3)	

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS1042713. Least squares mean differences are calculated as A/A-A/G, A/A-G/G and A/G-G/G.

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Table 7.73
Analysis of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1042713

				A/A vs. A/G	A/A vs. G/G	A/G vs. G/G
Salmeterol	Double-blind	Weeks 1-4	p-value	0.925	0.918	0.836
			LS Means Diff	-0.4	0.4	0.8
			95% CI for Diff	(-8.6, 7.8)	(-7.8, 8.7)	(-7.0, 8.7)
		Weeks 5-8	p-value	0.663	0.843	0.803
			LS Means Diff	2.0	0.9	-1.1
			95% CI for Diff	(-6.9, 10.9)	(-8.0, 9.8)	(-9.6, 7.4)
		Weeks 9-12	p-value	0.519	0.453	0.912
			LS Means Diff	3.0	3.4	0.5
			95% CI for Diff	(-6.1, 12.0)	(-5.6, 12.5)	(-8.2, 9.1)
		Weeks 13-16	p-value	0.583	0.347	0.681
			LS Means Diff	2.7	4.6	1.9
			95% CI for Diff	(-6.9, 12.3)	(-5.0, 14.3)	(-7.3, 11.2)
	Wash-out	Overall	p-value	0.759	0.758	1.000
			LS Means Diff	1.2	1.2	-0.0
			95% CI for Diff	(-6.6, 9.0)	(-6.5, 9.0)	(-7.4, 7.4)
		Overall	p-value	0.711	0.578	0.845
			LS Means Diff	1.8	2.7	0.9
			95% CI for Diff	(-7.8, 11.4)	(-6.9, 12.3)	(-8.2, 10.0)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS1042713. Least squares mean differences are calculated as A/A-A/G, A/A-G/G and A/G-G/G.

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Table 7.74
Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1042714

Treatment: FSC100/50

				C, C	C, G	G, G
-----				-----		
Subjects in treatment				147	73	23
% Symptom-free days	Double-blind	Baseline	n	141	71	23
			Mean	31.7	37.4	31.2
			SE	3.40	4.70	7.05
			Median	0.0	14.3	14.3
			Min.	0	0	0
			Max.	100	100	86
		Weeks 1-4	n	146	72	22
			Mean	44.4	51.2	40.8
			SE	3.44	4.96	8.62
			Median	42.9	62.5	31.3
			Min.	0	0	0
			Max.	100	100	100
		Weeks 5-8	n	141	69	20
			Mean	45.2	50.2	44.3
			SE	3.45	5.13	8.91
			Median	44.4	56.0	48.2
			Min.	0	0	0
			Max.	100	100	100
		Weeks 9-12	n	137	67	19
			Mean	47.8	51.5	42.7
			SE	3.59	5.19	9.39
			Median	50.0	66.7	32.1
			Min.	0	0	0
			Max.	100	100	100
		Weeks 13-16	n	133	66	19
			Mean	48.2	49.5	44.3
			SE	3.67	5.20	9.64

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Table 7.74
Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1042714

Treatment: FSC100/50

				C, C	C, G	G, G
% Symptom-free days	Double-blind	Weeks 13-16	Median	50.0	57.4	42.9
			Min.	0	0	0
			Max.	100	100	100
		Overall	n	146	73	22
			Mean	46.2	51.0	43.2
			SE	3.34	4.86	8.45
			Median	49.6	60.6	42.8
			Min.	0	0	0
			Max.	100	100	99
	Wash-out	Overall	n	132	66	17
			Mean	38.6	43.5	41.6
			SE	3.62	5.07	10.29
			Median	22.3	40.1	33.3
			Min.	0	0	0
			Max.	100	100	100
% SFD change	Double-blind	Weeks 1-4	n	140	70	22
			Mean	11.7	13.3	11.5
			SE	2.48	3.02	4.74
			Median	0.0	0.0	6.5
			Min.	-43	-20	-25
			Max.	100	96	82
		Weeks 5-8	n	136	68	20
			Mean	12.5	14.2	14.9
			SE	2.57	3.28	4.92
			Median	0.0	0.0	7.1
			Min.	-46	-18	-4
			Max.	100	100	82
		Weeks 9-12	n	132	66	19

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Table 7.74
Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1042714

Treatment: FSC100/50

				C, C	C, G	G, G
-----				-----		
% SFD change	Double-blind	Weeks 9-12	Mean	15.2	14.9	12.4
			SE	2.92	3.38	4.75
			Median	0.0	0.0	0.0
			Min.	-76	-29	-5
			Max.	100	100	71
		Weeks 13-16	n	128	65	19
			Mean	14.8	13.2	14.0
			SE	3.11	3.39	5.14
			Median	0.0	0.0	0.0
			Min.	-78	-35	-18
			Max.	100	89	78
		Overall	n	140	71	22
			Mean	13.4	13.7	13.8
			SE	2.49	3.00	4.30
			Median	0.0	0.9	4.8
			Min.	-44	-17	-5
			Max.	100	92	78
	Wash-out	Overall	n	127	65	17
			Mean	6.6	7.1	9.0
			SE	2.63	2.41	4.78
			Median	0.0	0.0	0.0
			Min.	-64	-36	-36
			Max.	100	67	43

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Table 7.74
Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1042714

Treatment: Salmeterol

				C, C	C, G	G, G
-----				-----		
Subjects in treatment				133	71	25
% Symptom-free days	Double-blind	Baseline	n	129	71	25
			Mean	36.2	33.2	38.6
			SE	3.70	4.68	8.37
			Median	14.3	0.0	28.6
			Min.	0	0	0
			Max.	100	100	100
		Weeks 1-4	n	127	70	25
			Mean	41.1	42.1	44.0
			SE	3.53	4.86	7.78
			Median	35.7	39.3	40.7
			Min.	0	0	0
			Max.	100	100	100
		Weeks 5-8	n	124	67	23
			Mean	44.5	40.2	45.2
			SE	3.66	4.78	8.50
			Median	40.7	32.1	39.3
			Min.	0	0	0
			Max.	100	100	100
		Weeks 9-12	n	118	66	20
			Mean	46.0	40.9	40.7
			SE	3.73	5.18	9.27
			Median	46.4	23.2	26.8
			Min.	0	0	0
			Max.	100	100	100
		Weeks 13-16	n	114	64	20
			Mean	47.1	42.0	38.5
			SE	3.79	5.18	9.39

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Table 7.74
Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1042714

Treatment: Salmeterol

				C, C	C, G	G, G

% Symptom-free days	Double-blind	Weeks 13-16	Median	54.6	32.1	12.8
			Min.	0	0	0
			Max.	100	100	100
		Overall	n	129	70	25
			Mean	44.4	42.5	44.0
			SE	3.45	4.68	7.95
			Median	42.2	37.4	31.2
	Min.		0	0	0	
	Max.		100	100	97	
	Wash-out	Overall	n	109	64	20
			Mean	42.3	37.1	32.3
			SE	3.99	5.20	9.71
			Median	33.3	7.4	0.0
			Min.	0	0	0
Max.			100	100	100	
% SFD change	Double-blind	Weeks 1-4	n	126	70	25
			Mean	5.5	8.4	5.4
			SE	2.35	3.06	5.61
			Median	0.0	0.0	0.0
			Min.	-71	-50	-82
			Max.	96	93	64
		Weeks 5-8	n	123	67	23
			Mean	7.9	7.3	3.9
			SE	2.54	3.22	6.80
			Median	0.0	0.0	0.0
			Min.	-86	-100	-86
			Max.	96	96	71
		Weeks 9-12	n	118	66	20

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Table 7.74
Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1042714

Treatment: Salmeterol

				C, C	C, G	G, G
% SFD change	Double-blind	Weeks 9-12	Mean	9.5	9.1	5.7
			SE	2.68	2.80	6.26
			Median	0.0	0.0	0.0
			Min.	-61	-43	-82
			Max.	100	100	64
		Weeks 13-16	n	114	64	20
			Mean	9.7	10.0	3.5
			SE	2.93	3.13	5.79
			Median	0.0	0.0	0.0
			Min.	-86	-38	-79
		Max.	100	100	60	
		Overall	n	128	70	25
			Mean	8.0	8.9	5.5
			SE	2.33	2.67	5.42
			Median	0.0	0.0	0.0
	Min.		-69	-41	-82	
	Max.	94	97	65		
	Wash-out	Overall	n	109	64	20
			Mean	4.7	5.2	-2.7
			SE	2.74	3.23	6.75
Median			0.0	0.0	0.0	
Min.			-71	-57	-86	
Max.	100	93	50			

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Table 7.75
Analysis of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1042714

			C/C vs. C/G	C/C vs. G/G	C/G vs. G/G
FSC100/50	Double-blind	Weeks 1-4	p-value	0.881	0.594
			LS Means Diff	-0.6	3.4
			95% CI for Diff	(-8.6, 7.4)	(-9.1, 15.8)
		Weeks 5-8	p-value	0.804	0.979
			LS Means Diff	-1.1	-0.2
			95% CI for Diff	(-9.4, 7.3)	(-13.6, 13.2)
		Weeks 9-12	p-value	0.685	0.415
			LS Means Diff	1.9	6.1
			95% CI for Diff	(-7.2, 10.9)	(-8.6, 20.8)
		Weeks 13-16	p-value	0.478	0.607
			LS Means Diff	3.4	4.0
			95% CI for Diff	(-6.0, 12.8)	(-11.2, 19.1)
	Overall		p-value	0.853	0.639
			LS Means Diff	0.7	2.9
			95% CI for Diff	(-7.1, 8.6)	(-9.3, 15.2)
		Wash-out	p-value	0.925	0.967
			LS Means Diff	0.4	-0.3
		Overall	95% CI for Diff	(-7.5, 8.3)	(-13.7, 13.1)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS1042714. Least squares mean differences are calculated as C/C-C/G, C/C-G/G and C/G-G/G.

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Table 7.75
Analysis of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1042714

				C/C vs. C/G	C/C vs. G/G	C/G vs. G/G
Salmeterol	Double-blind	Weeks 1-4	p-value	0.837	0.766	0.668
			LS Means Diff	-0.8	1.7	2.5
			95% CI for Diff	(-8.4,6.8)	(-9.4,12.7)	(-8.8,13.8)
		Weeks 5-8	p-value	0.405	0.358	0.730
			LS Means Diff	3.5	5.7	2.2
			95% CI for Diff	(-4.7,11.7)	(-6.5,17.8)	(-10.3,14.7)
		Weeks 9-12	p-value	0.438	0.264	0.539
			LS Means Diff	3.2	7.3	4.0
			95% CI for Diff	(-5.0,11.4)	(-5.5,20.0)	(-8.9,17.0)
		Weeks 13-16	p-value	0.649	0.227	0.368
			LS Means Diff	2.1	8.4	6.3
			95% CI for Diff	(-6.8,10.9)	(-5.2,22.0)	(-7.5,20.1)
	Overall	p-value	0.729	0.434	0.593	
LS Means Diff		1.3	4.2	2.9		
95% CI for Diff		(-5.9,8.4)	(-6.3,14.7)	(-7.8,13.6)		
Wash-out	Overall	p-value	0.986	0.243	0.253	
		LS Means Diff	0.1	7.9	7.9	
		95% CI for Diff	(-8.7,8.8)	(-5.4,21.3)	(-5.7,21.4)	

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS1042714. Least squares mean differences are calculated as C/C-C/G, C/C-G/G and C/G-G/G.

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Table 7.76
Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1042718

Treatment: FSC100/50

				A, A	A, C	C, C
-----				-----		
Subjects in treatment				17	78	148
% Symptom-free days	Double-blind	Baseline	n	17	78	140
			Mean	34.5	36.4	31.6
			SE	8.75	4.38	3.42
			Median	28.6	14.3	0.0
			Min.	0	0	0
			Max.	100	100	100
	Weeks 1-4	n	n	17	77	146
			Mean	52.6	49.4	43.5
			SE	9.61	4.83	3.43
			Median	60.7	53.6	42.9
			Min.	0	0	0
			Max.	100	100	100
	Weeks 5-8	n	n	16	75	139
			Mean	53.6	48.7	44.7
			SE	10.12	4.84	3.49
			Median	61.1	53.6	48.1
			Min.	0	0	0
			Max.	100	100	100
	Weeks 9-12	n	n	16	73	134
			Mean	56.3	49.8	46.9
			SE	10.22	4.95	3.64
			Median	60.7	57.1	50.8
			Min.	0	0	0
			Max.	100	100	100
	Weeks 13-16	n	n	15	72	131
			Mean	55.3	49.4	46.9
			SE	10.38	5.02	3.69

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Table 7.76
Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1042718

Treatment: FSC100/50

				A, A	A, C	C, C

% Symptom-free days	Double-blind	Weeks 13-16	Median	53.6	51.8	48.0
			Min.	0	0	0
			Max.	100	100	100
		Overall	n	17	78	146
			Mean	53.8	50.6	45.0
			SE	9.26	4.65	3.37
			Median	58.6	57.2	51.1
			Min.	0	0	0
			Max.	99	100	100
	Wash-out	Overall	n	15	71	129
			Mean	38.7	40.5	40.5
			SE	11.38	4.75	3.71
			Median	7.1	30.8	21.4
			Min.	0	0	0
			Max.	100	100	100
% SFD change	Double-blind	Weeks 1-4	n	17	77	138
			Mean	18.1	12.6	11.2
			SE	7.98	3.40	2.17
			Median	10.7	0.0	0.0
			Min.	-43	-29	-39
			Max.	96	94	100
		Weeks 5-8	n	16	75	133
			Mean	17.0	14.2	12.2
			SE	8.46	3.47	2.33
			Median	5.4	0.0	0.0
			Min.	-32	-32	-46
			Max.	100	100	100
		Weeks 9-12	n	16	73	128

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Table 7.76
Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1042718

Treatment: FSC100/50

				A, A	A, C	C, C
-----				-----		
% SFD change	Double-blind	Weeks 9-12	Mean	19.7	14.8	14.2
			SE	9.15	3.84	2.55
			Median	12.5	0.0	0.0
			Min.	-38	-76	-40
			Max.	100	100	100
		Weeks 13-16	n	15	72	125
			Mean	17.2	15.2	13.4
			SE	7.82	4.27	2.64
			Median	0.0	1.4	0.0
			Min.	-18	-78	-50
			Max.	89	100	100
		Overall	n	17	78	138
			Mean	19.4	14.2	12.4
			SE	7.67	3.37	2.17
			Median	9.8	0.4	0.0
			Min.	-23	-44	-35
			Max.	96	99	100
	Wash-out	Overall	n	15	71	123
			Mean	0.6	7.1	7.6
			SE	7.27	3.25	2.26
			Median	0.0	0.0	0.0
			Min.	-43	-55	-64
			Max.	71	100	100

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Table 7.76
Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1042718

Treatment: Salmeterol

				A, A	A, C	C, C
-----				-----		
Subjects in treatment				21	68	143
% Symptom-free days	Double-blind	Baseline	n	21	67	140
			Mean	26.5	35.0	36.7
			SE	8.94	4.90	3.49
			Median	0.0	14.3	14.3
			Min.	0	0	0
			Max.	100	100	100
	Weeks 1-4	n	n	20	67	138
			Mean	23.9	44.6	42.6
			SE	7.97	5.08	3.33
			Median	0.0	42.9	41.8
			Min.	0	0	0
			Max.	100	100	100
	Weeks 5-8	n	n	20	64	133
			Mean	35.4	45.2	43.4
			SE	8.90	5.20	3.41
			Median	17.9	44.6	42.9
			Min.	0	0	0
			Max.	100	100	100
	Weeks 9-12	n	n	20	62	124
			Mean	39.1	43.8	44.7
			SE	8.98	5.26	3.71
			Median	29.6	34.3	43.7
			Min.	0	0	0
			Max.	100	100	100
	Weeks 13-16	n	n	18	59	122
			Mean	33.3	45.7	45.8
			SE	8.55	5.34	3.74

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Table 7.76
Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1042718

Treatment: Salmeterol

				A, A	A, C	C, C
% Symptom-free days	Double-blind	Weeks 13-16	Median	20.4	55.6	43.6
			Min.	0	0	0
			Max.	100	100	100
		Overall	n	21	67	139
			Mean	33.5	45.2	44.5
			SE	8.26	4.91	3.27
			Median	14.5	43.8	41.1
			Min.	0	0	0
			Max.	100	100	100
		Wash-out	n	18	58	118
			Mean	24.8	42.9	39.8
			SE	8.50	5.54	3.88
			Median	0.0	39.3	19.0
			Min.	0	0	0
			Max.	100	100	100
% SFD change	Double-blind	Weeks 1-4	n	20	67	137
			Mean	1.1	9.6	5.8
			SE	4.74	3.83	2.05
			Median	0.0	0.0	0.0
			Min.	-71	-67	-82
			Max.	33	96	82
		Weeks 5-8	n	20	64	132
			Mean	7.6	10.6	6.1
			SE	5.76	3.50	2.47
			Median	1.8	0.0	0.0
			Min.	-71	-71	-100
			Max.	57	96	96
		Weeks 9-12	n	20	62	124

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Table 7.76
 Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1042718

Treatment: Salmeterol

				A, A	A, C	C, C
% SFD change	Double-blind	Weeks 9-12	Mean	11.3	8.5	9.3
			SE	6.65	3.55	2.40
			Median	0.0	0.0	0.0
			Min.	-61	-57	-82
			Max.	60	100	100
		Weeks 13-16	n	18	59	122
			Mean	7.9	10.1	9.0
			SE	7.01	3.80	2.59
			Median	0.0	0.0	0.0
			Min.	-71	-50	-86
			Max.	69	100	100
		Overall	n	21	67	138
			Mean	6.9	10.1	7.4
			SE	5.35	3.31	2.07
			Median	0.9	0.0	0.0
			Min.	-68	-45	-82
			Max.	47	97	94
	Wash-out	Overall	n	18	58	118
			Mean	-0.6	7.1	3.2
			SE	7.02	3.88	2.45
			Median	0.0	0.0	0.0
			Min.	-71	-57	-86
			Max.	43	93	100

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Table 7.77
Analysis of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1042718

				A/A vs. A/C	A/A vs. C/C	A/C vs. C/C
FSC100/50	Double-blind	Weeks 1-4	p-value	0.229	0.097	0.447
			LS Means Diff	8.8	11.7	2.9
			95% CI for Diff	(-5.6,23.1)	(-2.1,25.5)	(-4.6,10.5)
		Weeks 5-8	p-value	0.429	0.215	0.426
			LS Means Diff	6.1	9.3	3.2
			95% CI for Diff	(-9.1,21.4)	(-5.4,24.1)	(-4.7,11.1)
		Weeks 9-12	p-value	0.259	0.166	0.681
			LS Means Diff	9.4	11.2	1.8
			95% CI for Diff	(-7.0,25.8)	(-4.7,27.1)	(-6.8,10.4)
		Weeks 13-16	p-value	0.418	0.236	0.512
			LS Means Diff	7.1	10.1	3.0
			95% CI for Diff	(-10.2,24.5)	(-6.7,27.0)	(-6.0,12.0)
		Overall	p-value	0.234	0.086	0.371
			LS Means Diff	8.5	11.9	3.4
			95% CI for Diff	(-5.6,22.6)	(-1.7,25.5)	(-4.0,10.8)
	Wash-out	Overall	p-value	0.614	0.659	0.887
LS Means Diff			-3.7	-3.2	0.6	
95% CI for Diff			(-18.4,10.9)	(-17.4,11.0)	(-7.1,8.2)	

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS1042718. Least squares mean differences are calculated as A/A-A/C, A/A-C/C and A/C-C/C.

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Table 7.77
Analysis of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1042718

				A/A vs. A/C	A/A vs. C/C	A/C vs. C/C
Salmeterol	Double-blind	Weeks 1-4	p-value	0.130	0.314	0.342
			LS Means Diff	-9.8	-6.2	3.5
			95% CI for Diff	(-22.4,2.9)	(-18.4,5.9)	(-3.8,10.8)
		Weeks 5-8	p-value	0.652	0.856	0.292
			LS Means Diff	-3.1	1.2	4.3
			95% CI for Diff	(-16.5,10.4)	(-11.7,14.0)	(-3.7,12.2)
		Weeks 9-12	p-value	0.715	0.753	0.916
			LS Means Diff	2.5	2.1	-0.4
			95% CI for Diff	(-11.0,15.9)	(-10.8,14.9)	(-8.5,7.6)
		Weeks 13-16	p-value	0.556	0.646	0.796
			LS Means Diff	-4.4	-3.3	1.1
			95% CI for Diff	(-19.2,10.3)	(-17.4,10.8)	(-7.5,9.7)
		Overall	p-value	0.525	0.829	0.468
	LS Means Diff		-3.8	-1.2	2.6	
95% CI for Diff	(-15.5,7.9)		(-12.5,10.0)	(-4.4,9.5)		
Wash-out	Overall	p-value	0.130	0.250	0.483	
		LS Means Diff	-11.1	-8.1	3.0	
		95% CI for Diff	(-25.5,3.3)	(-21.9,5.7)	(-5.5,11.5)	

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS1042718. Least squares mean differences are calculated as A/A-A/C, A/A-C/C and A/C-C/C.

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Table 7.78
Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1042719

Treatment: FSC100/50

				C, C	C, G	G, G
Subjects in treatment				28	99	116
% Symptom-free days	Double-blind	Baseline	n	27	97	111
			Mean	36.0	33.7	32.5
			SE	7.09	3.91	3.91
			Median	28.6	14.3	0.0
			Min.	0	0	0
			Max.	100	100	100
			Weeks 1-4	n	28	98
		Mean		53.5	46.8	43.7
		SE		7.79	4.14	3.96
		Median		62.2	49.1	42.6
		Min.		0	0	0
		Max.		100	100	100
		Weeks 5-8		n	26	96
			Mean	52.7	46.5	45.3
			SE	8.30	4.09	4.07
			Median	68.5	50.0	50.0
			Min.	0	0	0
			Max.	100	100	100
			Weeks 9-12	n	26	93
		Mean		53.6	48.4	47.3
		SE		8.06	4.27	4.24
		Median		60.7	53.6	54.6
		Min.		0	0	0
		Max.		100	100	100
Weeks 13-16	n	26		90	102	
	Mean	54.5	47.9	47.0		
	SE	7.85	4.35	4.32		

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Table 7.78
Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1042719

Treatment: FSC100/50

				C, C	C, G	G, G
% Symptom-free days	Double-blind	Weeks 13-16	Median	62.8	50.0	45.4
			Min.	0	0	0
			Max.	100	100	100
		Overall	n	28	99	114
			Mean	53.9	48.2	45.1
			SE	7.51	3.96	3.93
			Median	64.6	56.3	51.1
			Min.	0	0	0
			Max.	99	100	100
	Wash-out	Overall	n	26	89	100
			Mean	41.2	39.9	40.6
			SE	8.21	4.29	4.25
			Median	29.7	28.6	22.3
			Min.	0	0	0
			Max.	100	100	100
% SFD change	Double-blind	Weeks 1-4	n	27	96	109
			Mean	16.3	12.6	10.7
			SE	6.13	2.97	2.39
			Median	3.6	0.0	0.0
			Min.	-43	-39	-36
			Max.	96	93	100
		Weeks 5-8	n	26	94	104
			Mean	15.3	14.3	11.7
			SE	6.39	2.96	2.67
			Median	0.0	0.0	0.0
			Min.	-32	-32	-46
			Max.	100	100	100
		Weeks 9-12	n	26	91	100

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Table 7.78
Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1042719

Treatment: FSC100/50

				C, C	C, G	G, G
-----				-----		
% SFD change	Double-blind	Weeks 9-12	Mean	16.3	15.4	14.0
			SE	6.62	3.42	2.84
			Median	8.9	0.0	0.0
			Min.	-38	-76	-40
			Max.	100	100	100
		Weeks 13-16	n	26	88	98
			Mean	17.2	14.2	13.5
			SE	5.84	3.93	2.78
			Median	1.8	0.0	0.0
			Min.	-28	-78	-33
			Max.	89	100	100
		Overall	n	27	97	109
			Mean	16.8	14.2	12.1
			SE	5.90	2.96	2.40
			Median	8.1	0.9	0.0
			Min.	-23	-44	-35
			Max.	96	98	100
	Wash-out	Overall	n	26	87	96
			Mean	3.8	7.9	6.9
			SE	4.92	2.81	2.68
			Median	0.0	0.0	0.0
			Min.	-43	-55	-64
			Max.	71	100	100

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Table 7.78
Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1042719

Treatment: Salmeterol

				C, C	C, G	G, G
-----				-----		
Subjects in treatment				25	90	117
% Symptom-free days	Double-blind	Baseline	n	25	89	114
			Mean	22.9	38.7	35.3
			SE	7.47	4.35	3.87
			Median	0.0	14.3	14.3
			Min.	0	0	0
			Max.	100	100	100
	Weeks 1-4	n	n	24	89	112
			Mean	22.5	48.0	40.5
			SE	6.27	4.37	3.71
			Median	1.8	46.4	39.3
			Min.	0	0	0
			Max.	100	100	100
	Weeks 5-8	n	n	24	85	108
			Mean	32.3	48.7	41.3
			SE	7.30	4.42	3.83
			Median	14.3	57.1	35.7
			Min.	0	0	0
			Max.	100	100	100
	Weeks 9-12	n	n	24	82	100
			Mean	35.5	49.1	41.7
			SE	7.15	4.66	4.13
			Median	28.6	52.8	26.8
			Min.	0	0	0
			Max.	100	100	100
	Weeks 13-16	n	n	21	80	98
			Mean	31.6	49.2	43.7
			SE	7.61	4.63	4.16

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Table 7.78
Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1042719

Treatment: Salmeterol

				C, C	C, G	G, G
% Symptom-free days	Double-blind	Weeks 13-16	Median	18.5	58.9	33.9
			Min.	0	0	0
			Max.	100	100	100
		Overall	n	25	89	113
			Mean	31.1	48.6	42.6
			SE	6.70	4.26	3.64
			Median	14.5	51.4	31.5
			Min.	0	0	0
			Max.	100	100	100
	Wash-out	Overall	n	21	79	94
			Mean	22.1	46.1	37.4
			SE	6.78	4.75	4.38
			Median	0.0	57.1	11.3
			Min.	0	0	0
			Max.	100	100	100
% SFD change	Double-blind	Weeks 1-4	n	24	89	111
			Mean	2.9	9.3	5.1
			SE	5.41	3.02	2.29
			Median	0.0	0.0	0.0
			Min.	-71	-67	-82
			Max.	54	96	82
		Weeks 5-8	n	24	85	107
			Mean	8.5	9.7	5.7
			SE	5.91	2.99	2.74
			Median	1.8	0.0	0.0
			Min.	-71	-86	-100
			Max.	82	96	96
		Weeks 9-12	n	24	82	100

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Table 7.78
Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1042719

Treatment: Salmeterol

				C, C	C, G	G, G
% SFD change	Double-blind	Weeks 9-12	Mean	11.7	9.9	8.1
			SE	6.30	3.12	2.57
			Median	0.0	0.0	0.0
			Min.	-61	-61	-82
			Max.	70	100	100
		Weeks 13-16	n	21	80	98
			Mean	10.5	9.8	8.6
			SE	7.25	3.25	2.81
			Median	0.0	0.0	0.0
			Min.	-71	-86	-79
			Max.	89	100	100
		Overall	n	25	89	112
			Mean	8.3	9.9	6.7
			SE	5.44	2.77	2.26
			Median	1.8	0.0	0.0
			Min.	-68	-69	-82
			Max.	74	97	94
	Wash-out	Overall	n	21	79	94
			Mean	1.0	6.6	2.6
			SE	7.00	3.14	2.76
			Median	0.0	0.0	0.0
			Min.	-71	-57	-86
			Max.	71	93	100

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Table 7.79
Analysis of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1042719

				C/C vs. C/G	C/C vs. G/G	C/G vs. G/G	
FSC100/50	Double-blind	Weeks 1-4	p-value	0.334	0.168	0.531	
			LS Means Diff	5.6	8.0	2.3	
			95% CI for Diff	(-5.8,17.1)	(-3.4,19.3)	(-5.0,9.7)	
		Weeks 5-8	p-value	0.591	0.326	0.494	
			LS Means Diff	3.3	6.0	2.7	
	95% CI for Diff		(-8.8,15.4)	(-6.0,18.0)	(-5.0,10.4)		
	Weeks 9-12	p-value	0.629	0.461	0.700		
		LS Means Diff	3.2	4.8	1.6		
		95% CI for Diff	(-9.8,16.2)	(-8.1,17.8)	(-6.8,10.1)		
	Weeks 13-16	p-value	0.393	0.300	0.794		
LS Means Diff		5.8	7.0	1.2			
95% CI for Diff		(-7.6,19.3)	(-6.3,20.3)	(-7.6,9.9)			
	Overall	p-value	0.429	0.209	0.476		
		LS Means Diff	4.5	7.2	2.6		
		95% CI for Diff	(-6.8,15.8)	(-4.0,18.3)	(-4.6,9.8)		
		Wash-out	Overall	p-value	0.706	0.837	0.791
				LS Means Diff	-2.2	-1.2	1.0
	95% CI for Diff			(-13.5,9.2)	(-12.4,10.1)	(-6.4,8.4)	

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS1042719. Least squares mean differences are calculated as C/C-C/G, C/C-G/G and C/G-G/G.

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Table 7.79
Analysis of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1042719

				C/C vs. C/G	C/C vs. G/G	C/G vs. G/G
Salmeterol	Double-blind	Weeks 1-4	p-value	0.075	0.315	0.184
			LS Means Diff	-10.5	-5.8	4.7
			95% CI for Diff	(-22.0, 1.1)	(-17.0, 5.5)	(-2.3, 11.7)
		Weeks 5-8	p-value	0.440	0.952	0.183
			LS Means Diff	-4.8	0.4	5.2
	Wash-out	Weeks 9-12	95% CI for Diff	(-17.1, 7.5)	(-11.6, 12.3)	(-2.5, 12.8)
			p-value	0.796	0.787	0.410
		Weeks 13-16	LS Means Diff	-1.6	1.6	3.3
			95% CI for Diff	(-13.9, 10.7)	(-10.4, 13.7)	(-4.5, 11.1)
			p-value	0.503	0.786	0.506
	Double-blind	Weeks 1-4	LS Means Diff	-4.6	-1.8	2.8
			95% CI for Diff	(-18.2, 9.0)	(-15.1, 11.4)	(-5.5, 11.1)
			p-value	0.345	0.802	0.258
		Weeks 5-8	LS Means Diff	-5.1	-1.3	3.8
			95% CI for Diff	(-15.9, 5.6)	(-11.8, 9.1)	(-2.8, 10.4)
	Wash-out	Weeks 9-12	p-value	0.100	0.346	0.240
			LS Means Diff	-11.1	-6.2	4.9
		Weeks 13-16	95% CI for Diff	(-24.3, 2.2)	(-19.2, 6.8)	(-3.3, 13.0)
			p-value	0.100	0.346	0.240
			LS Means Diff	-11.1	-6.2	4.9

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS1042719. Least squares mean differences are calculated as C/C-C/G, C/C-G/G and C/G-G/G.

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Table 7.80
Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS17778257

Treatment: FSC100/50

				A, A	A, T	T, T
-----				-----		
Subjects in treatment				100	88	55
% Symptom-free days	Double-blind	Baseline	n	98	87	50
			Mean	33.2	33.8	33.0
			SE	3.55	4.59	5.95
			Median	17.1	0.0	0.0
			Min.	0	0	0
			Max.	100	100	100
		Weeks 1-4	n	97	88	55
			Mean	46.1	45.0	47.8
			SE	4.09	4.60	5.70
			Median	50.0	42.9	59.3
			Min.	0	0	0
			Max.	100	100	100
		Weeks 5-8	n	92	86	52
			Mean	46.8	46.4	46.6
			SE	4.27	4.53	5.74
			Median	51.8	44.4	55.4
			Min.	0	0	0
			Max.	100	100	100
		Weeks 9-12	n	88	86	49
			Mean	47.0	49.0	50.5
			SE	4.40	4.58	6.16
			Median	54.5	58.9	53.6
			Min.	0	0	0
			Max.	100	100	100
		Weeks 13-16	n	86	83	49
			Mean	47.2	46.9	52.7
			SE	4.54	4.52	6.31

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Table 7.80
Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS17778257

Treatment: FSC100/50

				A, A	A, T	T, T

% Symptom-free days	Double-blind	Weeks 13-16	Median	50.0	42.9	78.6
			Min.	0	0	0
			Max.	100	100	100
		Overall	n	98	88	55
			Mean	46.6	47.8	48.2
			SE	4.05	4.35	5.62
			Median	48.6	50.9	61.5
			Min.	0	0	0
			Max.	100	100	100
	Wash-out	Overall	n	84	82	49
			Mean	39.6	36.8	47.7
			SE	4.43	4.55	6.16
			Median	28.6	17.9	50.0
			Min.	0	0	0
			Max.	100	100	100
% SFD change	Double-blind	Weeks 1-4	n	95	87	50
			Mean	12.5	11.2	13.1
			SE	2.80	3.07	3.73
			Median	0.0	0.0	0.0
			Min.	-43	-39	-25
			Max.	96	96	100
		Weeks 5-8	n	91	85	48
			Mean	13.6	14.2	10.7
			SE	2.97	3.02	4.31
			Median	0.0	0.0	0.0
			Min.	-43	-32	-46
			Max.	100	100	100
		Weeks 9-12	n	87	85	45

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Table 7.80
Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS17778257

Treatment: FSC100/50

				A, A	A, T	T, T
-----				-----		
% SFD change	Double-blind	Weeks 9-12	Mean	12.7	16.8	15.2
			SE	3.19	3.49	4.51
			Median	0.0	0.0	0.0
			Min.	-76	-29	-24
			Max.	100	100	100
		Weeks 13-16	n	85	82	45
			Mean	13.0	14.8	15.6
			SE	3.13	3.79	4.94
			Median	0.0	0.0	0.0
			Min.	-78	-71	-33
			Max.	100	100	100
		Overall	n	96	87	50
			Mean	13.3	14.1	12.9
			SE	2.77	2.99	3.92
			Median	0.9	0.9	0.0
			Min.	-44	-28	-20
			Max.	99	98	100
	Wash-out	Overall	n	83	81	45
			Mean	4.7	6.8	11.4
			SE	2.71	2.58	4.83
			Median	0.0	0.0	0.0
			Min.	-64	-41	-64
			Max.	100	100	100

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Table 7.80
Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS17778257

Treatment: Salmeterol

				A, A	A, T	T, T
-----				-----		
Subjects in treatment				100	86	46
% Symptom-free days	Double-blind	Baseline	n	99	84	45
			Mean	34.1	37.1	34.3
			SE	4.10	4.47	6.19
			Median	0.0	21.4	14.3
			Min.	0	0	0
			Max.	100	100	100
		Weeks 1-4	n	98	83	44
			Mean	39.8	43.5	41.8
			SE	4.02	4.45	5.90
			Median	36.3	39.3	39.3
			Min.	0	0	0
			Max.	100	100	100
		Weeks 5-8	n	94	81	42
			Mean	42.1	43.6	44.7
			SE	4.10	4.62	5.89
			Median	35.7	42.9	46.4
			Min.	0	0	0
			Max.	100	100	100
		Weeks 9-12	n	91	75	40
			Mean	41.3	44.2	49.1
			SE	4.26	4.90	6.30
			Median	25.9	44.4	50.9
			Min.	0	0	0
			Max.	100	100	100
		Weeks 13-16	n	87	72	40
			Mean	42.1	45.1	49.5
			SE	4.26	4.99	6.44

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Table 7.80
Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS17778257

Treatment: Salmeterol

				A, A	A, T	T, T

% Symptom-free days	Double-blind	Weeks 13-16	Median	39.3	40.0	60.4
			Min.	0	0	0
			Max.	100	100	100
		Overall	n	99	84	44
			Mean	42.5	44.2	45.4
			SE	3.90	4.38	5.72
			Median	33.6	41.6	45.3
			Min.	0	0	0
			Max.	100	100	100
	Wash-out	Overall	n	86	69	39
			Mean	36.6	41.4	41.6
			SE	4.51	5.17	6.41
			Median	3.6	23.1	28.6
			Min.	0	0	0
			Max.	100	100	100
% SFD change	Double-blind	Weeks 1-4	n	98	82	44
			Mean	6.3	6.6	6.8
			SE	2.78	2.83	3.73
			Median	0.0	0.0	0.0
			Min.	-82	-50	-43
			Max.	93	96	82
		Weeks 5-8	n	94	80	42
			Mean	7.7	6.3	9.7
			SE	2.76	3.10	4.87
			Median	0.0	0.0	0.0
			Min.	-86	-100	-86
			Max.	96	96	96
		Weeks 9-12	n	91	75	40

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Table 7.80
Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS17778257

Treatment: Salmeterol

				A, A	A, T	T, T
-----				-----		
% SFD change	Double-blind	Weeks 9-12	Mean	8.5	8.3	12.7
			SE	2.75	2.91	5.23
			Median	0.0	0.0	0.3
			Min.	-82	-57	-61
			Max.	100	100	100
		Weeks 13-16	n	87	72	40
			Mean	9.5	6.8	13.1
			SE	3.12	2.76	5.72
			Median	0.0	0.0	0.0
			Min.	-79	-50	-86
			Max.	100	82	100
		Overall	n	99	83	44
			Mean	8.3	6.8	10.4
			SE	2.53	2.56	4.28
			Median	0.0	0.0	1.5
			Min.	-82	-45	-69
			Max.	97	94	94
	Wash-out	Overall	n	86	69	39
			Mean	4.0	2.9	6.1
			SE	3.27	2.85	4.67
			Median	0.0	0.0	0.0
			Min.	-86	-57	-57
			Max.	93	86	100

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Table 7.81
Analysis of Percent of Symptom-Free Days - ADRB2 Gene SNP RS17778257

				A/A vs. A/T	A/A vs. T/T	A/T vs. T/T
FSC100/50	Double-blind	Weeks 1-4	p-value	0.583	0.958	0.686
			LS Means Diff	2.2	0.2	-1.9
			95% CI for Diff	(-5.7, 10.0)	(-9.0, 9.5)	(-11.4, 7.5)
		Weeks 5-8	p-value	0.968	0.487	0.512
			LS Means Diff	0.2	3.5	3.3
			95% CI for Diff	(-8.1, 8.4)	(-6.3, 13.3)	(-6.6, 13.2)
		Weeks 9-12	p-value	0.510	0.906	0.670
			LS Means Diff	-3.0	-0.6	2.3
			95% CI for Diff	(-11.9, 5.9)	(-11.5, 10.2)	(-8.5, 13.2)
		Weeks 13-16	p-value	0.896	0.796	0.881
			LS Means Diff	-0.6	-1.5	-0.9
			95% CI for Diff	(-10.0, 8.7)	(-12.7, 9.8)	(-12.1, 10.4)
	Wash-out	Overall	p-value	0.996	0.733	0.733
			LS Means Diff	-0.0	1.6	1.6
			95% CI for Diff	(-7.7, 7.7)	(-7.6, 10.7)	(-7.7, 10.9)
		Overall	p-value	0.845	0.255	0.327
			LS Means Diff	-0.8	-5.5	-4.7
			95% CI for Diff	(-8.7, 7.1)	(-14.9, 4.0)	(-14.1, 4.7)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS17778257. Least squares mean differences are calculated as A/A-A/T, A/A-T/T and A/T-T/T.

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Table 7.81
Analysis of Percent of Symptom-Free Days - ADRB2 Gene SNP RS17778257

				A/A vs. A/T	A/A vs. T/T	A/T vs. T/T
Salmeterol	Double-blind	Weeks 1-4	p-value	0.890	0.887	0.799
			LS Means Diff	-0.5	0.7	1.2
			95% CI for Diff	(-7.9,6.9)	(-8.4,9.7)	(-7.9,10.3)
		Weeks 5-8	p-value	0.627	0.948	0.644
			LS Means Diff	2.0	-0.3	-2.3
			95% CI for Diff	(-6.1,10.0)	(-10.1,9.5)	(-12.1,7.5)
		Weeks 9-12	p-value	0.917	0.493	0.443
			LS Means Diff	0.4	-3.5	-3.9
			95% CI for Diff	(-7.8,8.6)	(-13.5,6.5)	(-13.9,6.1)
		Weeks 13-16	p-value	0.691	0.469	0.296
			LS Means Diff	1.8	-3.9	-5.6
			95% CI for Diff	(-7.0,10.5)	(-14.4,6.6)	(-16.2,5.0)
		Overall	p-value	0.669	0.895	0.634
			LS Means Diff	1.5	-0.6	-2.1
95% CI for Diff			(-5.4,8.5)	(-9.1,8.0)	(-10.7,6.5)	
Wash-out		Overall	p-value	0.817	0.851	0.707
			LS Means Diff	1.0	-1.0	-2.0
			95% CI for Diff	(-7.7,9.7)	(-11.4,9.4)	(-12.6,8.5)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS17778257. Least squares mean differences are calculated as A/A-A/T, A/A-T/T and A/T-T/T.

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Table 7.82
Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS11168070

Treatment: FSC100/50

				C, C	C, G	G, G
-----				-----		
Subjects in treatment				147	73	23
% Symptom-free days	Double-blind	Baseline	n	141	71	23
			Mean	31.7	37.4	31.2
			SE	3.40	4.70	7.05
			Median	0.0	14.3	14.3
			Min.	0	0	0
			Max.	100	100	86
		Weeks 1-4	n	146	72	22
			Mean	44.4	51.2	40.8
			SE	3.44	4.96	8.62
			Median	42.9	62.5	31.3
			Min.	0	0	0
			Max.	100	100	100
		Weeks 5-8	n	141	69	20
			Mean	45.2	50.2	44.3
			SE	3.45	5.13	8.91
			Median	44.4	56.0	48.2
			Min.	0	0	0
			Max.	100	100	100
		Weeks 9-12	n	137	67	19
			Mean	47.8	51.5	42.7
			SE	3.59	5.19	9.39
			Median	50.0	66.7	32.1
			Min.	0	0	0
			Max.	100	100	100
		Weeks 13-16	n	133	66	19
			Mean	48.2	49.5	44.3
			SE	3.67	5.20	9.64

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Table 7.82
 Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS11168070

Treatment: FSC100/50

				C, C	C, G	G, G

% Symptom-free days	Double-blind	Weeks 13-16	Median	50.0	57.4	42.9
			Min.	0	0	0
			Max.	100	100	100
		Overall	n	146	73	22
			Mean	46.2	51.0	43.2
			SE	3.34	4.86	8.45
			Median	49.6	60.6	42.8
			Min.	0	0	0
			Max.	100	100	99
	Wash-out	Overall	n	132	66	17
			Mean	38.6	43.5	41.6
			SE	3.62	5.07	10.29
			Median	22.3	40.1	33.3
			Min.	0	0	0
			Max.	100	100	100
% SFD change	Double-blind	Weeks 1-4	n	140	70	22
			Mean	11.7	13.3	11.5
			SE	2.48	3.02	4.74
			Median	0.0	0.0	6.5
			Min.	-43	-20	-25
			Max.	100	96	82
		Weeks 5-8	n	136	68	20
			Mean	12.5	14.2	14.9
			SE	2.57	3.28	4.92
			Median	0.0	0.0	7.1
			Min.	-46	-18	-4
			Max.	100	100	82
		Weeks 9-12	n	132	66	19

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Table 7.82
Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS11168070

Treatment: FSC100/50

				C, C	C, G	G, G
-----				-----		
% SFD change	Double-blind	Weeks 9-12	Mean	15.2	14.9	12.4
			SE	2.92	3.38	4.75
			Median	0.0	0.0	0.0
			Min.	-76	-29	-5
			Max.	100	100	71
		Weeks 13-16	n	128	65	19
			Mean	14.8	13.2	14.0
			SE	3.11	3.39	5.14
			Median	0.0	0.0	0.0
			Min.	-78	-35	-18
			Max.	100	89	78
		Overall	n	140	71	22
			Mean	13.4	13.7	13.8
			SE	2.49	3.00	4.30
			Median	0.0	0.9	4.8
			Min.	-44	-17	-5
			Max.	100	92	78
	Wash-out	Overall	n	127	65	17
			Mean	6.6	7.1	9.0
			SE	2.63	2.41	4.78
			Median	0.0	0.0	0.0
			Min.	-64	-36	-36
			Max.	100	67	43

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Table 7.82
Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS11168070

Treatment: Salmeterol

				C, C	C, G	G, G
-----				-----		
Subjects in treatment				136	71	25
% Symptom-free days	Double-blind	Baseline	n	132	71	25
			Mean	35.7	33.2	38.6
			SE	3.63	4.68	8.37
			Median	14.3	0.0	28.6
			Min.	0	0	0
			Max.	100	100	100
		Weeks 1-4	n	130	70	25
			Mean	40.8	42.1	44.0
			SE	3.49	4.86	7.78
			Median	35.7	39.3	40.7
			Min.	0	0	0
			Max.	100	100	100
		Weeks 5-8	n	127	67	23
			Mean	44.4	40.2	45.2
			SE	3.59	4.78	8.50
			Median	42.9	32.1	39.3
			Min.	0	0	0
			Max.	100	100	100
		Weeks 9-12	n	120	66	20
			Mean	46.1	40.9	40.7
			SE	3.71	5.18	9.27
			Median	46.4	23.2	26.8
			Min.	0	0	0
			Max.	100	100	100
		Weeks 13-16	n	115	64	20
			Mean	47.2	42.0	38.5
			SE	3.76	5.18	9.39

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Table 7.82
Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS11168070

Treatment: Salmeterol

				C, C	C, G	G, G
% Symptom-free days	Double-blind	Weeks 13-16	Median	55.6	32.1	12.8
			Min.	0	0	0
			Max.	100	100	100
		Overall	n	132	70	25
			Mean	44.2	42.5	44.0
			SE	3.39	4.68	7.95
			Median	40.7	37.4	31.2
	Wash-out	Overall	Min.	0	0	0
			Max.	100	100	97
			n	110	64	20
% SFD change	Double-blind	Weeks 1-4	Mean	41.9	37.1	32.3
			SE	3.97	5.20	9.71
			Median	31.0	7.4	0.0
			Min.	0	0	0
			Max.	100	100	100
		Weeks 5-8	n	129	70	25
			Mean	5.7	8.4	5.4
			SE	2.32	3.06	5.61
			Median	0.0	0.0	0.0
			Min.	-71	-50	-82
			Max.	96	93	64
		Weeks 9-12	n	126	67	23
			Mean	8.3	7.3	3.9
			SE	2.51	3.22	6.80
			Median	0.0	0.0	0.0
			Min.	-86	-100	-86
			Max.	96	96	71

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Table 7.82
Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS11168070

Treatment: Salmeterol

				C, C	C, G	G, G
-----				-----		
% SFD change	Double-blind	Weeks 9-12	Mean	9.9	9.1	5.7
			SE	2.69	2.80	6.26
			Median	0.0	0.0	0.0
			Min.	-61	-43	-82
			Max.	100	100	64
		Weeks 13-16	n	115	64	20
			Mean	9.8	10.0	3.5
			SE	2.91	3.13	5.79
			Median	0.0	0.0	0.0
			Min.	-86	-38	-79
			Max.	100	100	60
		Overall	n	131	70	25
			Mean	8.3	8.9	5.5
			SE	2.29	2.67	5.42
			Median	0.0	0.0	0.0
			Min.	-69	-41	-82
			Max.	94	97	65
	Wash-out	Overall	n	110	64	20
			Mean	4.6	5.2	-2.7
			SE	2.72	3.23	6.75
			Median	0.0	0.0	0.0
			Min.	-71	-57	-86
			Max.	100	93	50

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Table 7.83
Analysis of Percent of Symptom-Free Days - ADRB2 Gene SNP RS11168070

				C/C vs. C/G	C/C vs. G/G	C/G vs. G/G
FSC100/50	Double-blind	Weeks 1-4	p-value	0.881	0.594	0.545
			LS Means Diff	-0.6	3.4	4.0
			95% CI for Diff	(-8.6, 7.4)	(-9.1, 15.8)	(-9.0, 16.9)
		Weeks 5-8	p-value	0.804	0.979	0.901
			LS Means Diff	-1.1	-0.2	0.9
			95% CI for Diff	(-9.4, 7.3)	(-13.6, 13.2)	(-13.0, 14.8)
		Weeks 9-12	p-value	0.685	0.415	0.586
			LS Means Diff	1.9	6.1	4.2
			95% CI for Diff	(-7.2, 10.9)	(-8.6, 20.8)	(-11.0, 19.4)
		Weeks 13-16	p-value	0.478	0.607	0.943
			LS Means Diff	3.4	4.0	0.6
			95% CI for Diff	(-6.0, 12.8)	(-11.2, 19.1)	(-15.1, 16.3)
	Wash-out	Overall	p-value	0.853	0.639	0.735
			LS Means Diff	0.7	2.9	2.2
			95% CI for Diff	(-7.1, 8.6)	(-9.3, 15.2)	(-10.6, 14.9)
		Overall	p-value	0.925	0.967	0.925
			LS Means Diff	0.4	-0.3	-0.7
			95% CI for Diff	(-7.5, 8.3)	(-13.7, 13.1)	(-14.4, 13.1)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS11168070. Least squares mean differences are calculated as C/C-C/G, C/C-G/G and C/G-G/G.

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Table 7.83
Analysis of Percent of Symptom-Free Days - ADRB2 Gene SNP RS11168070

				C/C vs. C/G	C/C vs. G/G	C/G vs. G/G	
Salmeterol	Double-blind	Weeks 1-4	p-value	0.863	0.749	0.667	
			LS Means Diff	-0.7	1.8	2.5	
			95% CI for Diff	(-8.2,6.9)	(-9.3,12.9)	(-8.9,13.8)	
		Weeks 5-8	p-value	0.376	0.342	0.732	
			LS Means Diff	3.7	5.9	2.2	
	95% CI for Diff		(-4.5,11.9)	(-6.3,18.0)	(-10.3,14.6)		
	Weeks 9-12	p-value	0.400	0.253	0.549		
		LS Means Diff	3.5	7.5	4.0		
		95% CI for Diff	(-4.7,11.8)	(-5.4,20.5)	(-9.1,17.1)		
	Weeks 13-16	p-value	0.627	0.220	0.369		
LS Means Diff		2.2	8.5	6.3			
95% CI for Diff		(-6.7,11.1)	(-5.1,22.1)	(-7.5,20.1)			
	Overall	p-value	0.694	0.418	0.596		
		LS Means Diff	1.4	4.3	2.9		
		95% CI for Diff	(-5.7,8.6)	(-6.2,14.8)	(-7.8,13.6)		
		Wash-out	Overall	p-value	0.992	0.248	0.251
				LS Means Diff	-0.0	7.8	7.9
	95% CI for Diff			(-8.8,8.7)	(-5.5,21.2)	(-5.6,21.4)	

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS11168070. Least squares mean differences are calculated as C/C-C/G, C/C-G/G and C/G-G/G.

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Table 7.84
Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS9325122

Treatment: FSC100/50

				C, C	C, T	T, T
-----				-----		
Subjects in treatment				23	65	145
% Symptom-free days	Double-blind	Baseline	n	23	63	139
			Mean	32.4	37.6	31.5
			SE	7.47	5.01	3.40
			Median	14.3	14.3	0.0
			Min.	0	0	0
			Max.	100	100	100
		Weeks 1-4	n	22	64	144
			Mean	40.4	51.4	44.3
			SE	8.59	5.41	3.46
			Median	31.3	64.3	42.9
			Min.	0	0	0
			Max.	100	100	100
		Weeks 5-8	n	20	61	139
			Mean	43.8	50.0	45.2
			SE	8.82	5.61	3.47
			Median	48.2	53.6	44.4
			Min.	0	0	0
			Max.	100	100	100
		Weeks 9-12	n	19	59	135
			Mean	41.9	51.5	48.0
			SE	9.17	5.73	3.63
			Median	32.1	66.7	50.0
			Min.	0	0	0
			Max.	100	100	100
		Weeks 13-16	n	19	59	131
			Mean	42.1	50.1	48.4
			SE	9.33	5.66	3.70

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Table 7.84
Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS9325122

Treatment: FSC100/50

				C, C	C, T	T, T
% Symptom-free days	Double-blind	Weeks 13-16	Median	42.9	64.3	50.0
			Min.	0	0	0
			Max.	100	100	100
		Overall	n	22	65	144
			Mean	42.3	51.2	46.3
			SE	8.31	5.31	3.36
			Median	42.8	62.1	49.6
			Min.	0	0	0
			Max.	99	100	100
	Wash-out	Overall	n	17	59	130
			Mean	42.5	44.8	38.5
			SE	9.60	5.51	3.64
			Median	35.7	41.7	22.3
			Min.	0	0	0
			Max.	100	100	100
% SFD change	Double-blind	Weeks 1-4	n	22	62	138
			Mean	9.8	13.2	11.9
			SE	4.27	3.09	2.52
			Median	3.0	0.0	0.0
			Min.	-25	-20	-43
			Max.	67	96	100
		Weeks 5-8	n	20	60	134
			Mean	12.9	14.0	12.7
			SE	4.56	3.32	2.60
			Median	5.4	0.0	0.0
			Min.	-11	-18	-46
			Max.	67	100	100
		Weeks 9-12	n	19	58	130

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Table 7.84
Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS9325122

Treatment: FSC100/50

				C, C	C, T	T, T
-----				-----		
% SFD change	Double-blind	Weeks 9-12	Mean	10.1	14.7	15.6
			SE	4.64	3.48	2.95
			Median	0.0	0.0	0.0
			Min.	-11	-29	-76
			Max.	67	100	100
		Weeks 13-16	n	19	58	126
			Mean	10.3	13.1	15.3
			SE	4.12	3.52	3.14
			Median	0.0	0.0	0.0
			Min.	-18	-35	-78
			Max.	43	89	100
		Overall	n	22	63	138
			Mean	11.6	13.6	13.7
			SE	3.83	3.05	2.52
			Median	1.4	0.9	0.0
			Min.	-7	-17	-44
			Max.	61	92	100
	Wash-out	Overall	n	17	58	125
			Mean	8.2	7.7	6.7
			SE	5.21	2.62	2.67
			Median	0.0	0.0	0.0
			Min.	-36	-36	-64
			Max.	43	67	100

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Table 7.84
Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS9325122

Treatment: Salmeterol

				C, C	C, T	T, T
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Subjects in treatment				27	63	129
% Symptom-free days	Double-blind	Baseline	n	27	63	125
			Mean	37.0	32.3	36.8
			SE	8.19	4.89	3.74
			Median	14.3	0.0	14.3
			Min.	0	0	0
			Max.	100	100	100
		Weeks 1-4	n	27	62	123
			Mean	41.0	41.8	42.0
			SE	7.60	5.14	3.60
			Median	39.3	42.9	35.7
			Min.	0	0	0
			Max.	100	100	100
		Weeks 5-8	n	25	60	120
			Mean	40.7	41.2	44.0
			SE	8.00	5.20	3.69
			Median	35.7	32.1	40.7
			Min.	0	0	0
			Max.	100	100	100
		Weeks 9-12	n	23	58	113
			Mean	39.6	40.9	45.9
			SE	8.78	5.53	3.82
			Median	25.0	23.2	46.4
			Min.	0	0	0
			Max.	100	100	100
		Weeks 13-16	n	23	57	109
			Mean	37.7	42.2	46.8
			SE	8.87	5.52	3.88

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Table 7.84
Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS9325122

Treatment: Salmeterol

				C, C	C, T	T, T
% Symptom-free days	Double-blind	Weeks 13-16	Median	7.1	32.1	53.6
			Min.	0	0	0
			Max.	100	100	100
		Overall	n	27	62	125
			Mean	40.8	42.6	44.7
			SE	7.70	4.98	3.51
			Median	29.7	38.7	42.2
			Min.	0	0	0
			Max.	97	100	100
	Wash-out	Overall	n	23	57	104
			Mean	32.1	37.1	42.0
			SE	9.07	5.53	4.09
			Median	0.0	7.1	31.0
			Min.	0	0	0
			Max.	100	100	100
% SFD change	Double-blind	Weeks 1-4	n	27	62	122
			Mean	4.0	8.9	5.8
			SE	5.11	3.34	2.33
			Median	0.0	0.0	0.0
			Min.	-82	-50	-71
			Max.	64	93	96
		Weeks 5-8	n	25	60	119
			Mean	1.3	8.2	7.6
			SE	6.00	3.65	2.55
			Median	0.0	0.0	0.0
			Min.	-86	-100	-86
			Max.	71	96	96
		Weeks 9-12	n	23	58	113

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Table 7.84
Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS9325122

Treatment: Salmeterol

				C, C	C, T	T, T
-----				-----		
% SFD change	Double-blind	Weeks 9-12	Mean	5.4	9.4	9.4
			SE	5.44	3.12	2.75
			Median	0.0	0.0	0.0
			Min.	-82	-43	-61
			Max.	64	100	100
		Weeks 13-16	n	23	57	109
			Mean	3.5	11.2	8.4
			SE	5.03	3.58	2.87
			Median	0.0	0.0	0.0
			Min.	-79	-38	-86
			Max.	60	100	100
		Overall	n	27	62	124
			Mean	3.8	9.8	7.7
			SE	4.86	3.01	2.32
			Median	0.0	0.0	0.0
			Min.	-82	-41	-69
			Max.	65	97	94
	Wash-out	Overall	n	23	57	104
			Mean	-2.1	6.1	3.7
			SE	5.86	3.70	2.77
			Median	0.0	0.0	0.0
			Min.	-86	-57	-71
			Max.	50	93	100

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Table 7.85
Analysis of Percent of Symptom-Free Days - ADRB2 Gene SNP RS9325122

			C/C vs. C/T	C/C vs. T/T	C/T vs. T/T
FSC100/50	Double-blind	Weeks 1-4	p-value	0.411	0.353
			LS Means Diff	-5.4	-5.9
			95% CI for Diff	(-18.5, 7.6)	(-18.3, 6.5)
		Weeks 5-8	p-value	0.729	0.707
			LS Means Diff	-2.4	-2.5
			95% CI for Diff	(-16.4, 11.5)	(-15.9, 10.8)
		Weeks 9-12	p-value	0.447	0.204
			LS Means Diff	-5.9	-9.4
			95% CI for Diff	(-21.3, 9.4)	(-24.1, 5.2)
		Weeks 13-16	p-value	0.603	0.254
			LS Means Diff	-4.2	-8.7
			95% CI for Diff	(-19.9, 11.6)	(-23.8, 6.3)
	Wash-out	Overall	p-value	0.526	0.332
			LS Means Diff	-4.1	-6.0
			95% CI for Diff	(-16.9, 8.7)	(-18.2, 6.2)
		Overall	p-value	0.909	0.895
			LS Means Diff	-0.8	-0.9
			95% CI for Diff	(-15.0, 13.4)	(-14.6, 12.8)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS9325122. Least squares mean differences are calculated as C/C-C/T, C/C-T/T and C/T-T/T.

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Table 7.85
Analysis of Percent of Symptom-Free Days - ADRB2 Gene SNP RS9325122

				C/C vs. C/T	C/C vs. T/T	C/T vs. T/T
Salmeterol	Double-blind	Weeks 1-4	p-value	0.366	0.480	0.756
			LS Means Diff	-5.2	-3.9	1.3
			95% CI for Diff	(-16.4, 6.1)	(-14.8, 7.0)	(-6.7, 9.2)
		Weeks 5-8	p-value	0.303	0.172	0.679
			LS Means Diff	-6.5	-8.3	-1.8
			95% CI for Diff	(-18.9, 5.9)	(-20.3, 3.6)	(-10.5, 6.9)
		Weeks 9-12	p-value	0.471	0.286	0.645
			LS Means Diff	-4.7	-6.7	-2.1
			95% CI for Diff	(-17.4, 8.1)	(-19.1, 5.7)	(-10.9, 6.8)
		Weeks 13-16	p-value	0.252	0.285	0.881
			LS Means Diff	-7.7	-7.0	0.7
			95% CI for Diff	(-20.9, 5.5)	(-19.8, 5.9)	(-8.6, 10.0)
	Wash-out	Overall	p-value	0.258	0.262	0.947
			LS Means Diff	-6.2	-5.9	0.3
			95% CI for Diff	(-16.9, 4.6)	(-16.3, 4.5)	(-7.3, 7.8)
		Overall	p-value	0.249	0.392	0.654
			LS Means Diff	-7.7	-5.6	2.1
			95% CI for Diff	(-20.8, 5.4)	(-18.4, 7.2)	(-7.2, 11.4)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS9325122. Least squares mean differences are calculated as C/C-C/T, C/C-T/T and C/T-T/T.

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Table 7.86
 Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1800888

Treatment: FSC100/50

				C, C	C, T

Subjects in treatment				240	3
% Symptom-free days	Double-blind	Baseline	n	232	3
			Mean	33.5	23.8
			SE	2.60	17.17
			Median	7.1	14.3
			Min.	0	0
			Max.	100	57
		Weeks 1-4	n	237	3
			Mean	46.0	51.2
			SE	2.71	26.11
			Median	48.1	67.9
			Min.	0	0
			Max.	100	86
		Weeks 5-8	n	227	3
			Mean	46.6	48.1
			SE	2.74	25.21
			Median	50.0	59.3
			Min.	0	0
			Max.	100	85
		Weeks 9-12	n	220	3
			Mean	48.4	55.9
			SE	2.83	28.39
			Median	54.6	75.0
			Min.	0	0
			Max.	100	93
		Weeks 13-16	n	216	2
			Mean	48.4	38.5
			SE	2.87	38.46

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Table 7.86
 Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1800888

Treatment: FSC100/50

				C, C	C, T
% Symptom-free days	Double-blind	Weeks 13-16	Median	50.0	38.5
			Min.	0	0
			Max.	100	77
		Overall	n	238	3
			Mean	47.4	51.4
			SE	2.63	25.79
			Median	51.6	73.5
			Min.	0	0
			Max.	100	81
	Wash-out	Overall	n	213	2
			Mean	40.3	50.0
			SE	2.83	50.00
			Median	28.6	50.0
			Min.	0	0
			Max.	100	100
% SFD change	Double-blind	Weeks 1-4	n	229	3
			Mean	11.9	27.4
			SE	1.82	15.48
			Median	0.0	28.6
			Min.	-43	0
			Max.	100	54
		Weeks 5-8	n	221	3
			Mean	13.1	24.3
			SE	1.92	13.11
			Median	0.0	28.0
			Min.	-46	0
			Max.	100	45
		Weeks 9-12	n	214	3

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Table 7.86
 Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1800888

Treatment: FSC100/50

CC100/00

			C, C	C, T	

% SFD change	Double-blind	Weeks 9-12	Mean	14.6	32.1
			SE	2.09	23.69
			Median	0.0	17.9
			Min.	-76	0
			Max.	100	78
		Weeks 13-16	n	210	2
			Mean	14.3	9.9
			SE	2.21	9.89
			Median	0.0	9.9
			Min.	-78	0
			Max.	100	20
		Overall	n	230	3
			Mean	13.3	27.6
			SE	1.81	17.21
			Median	0.0	23.6
			Min.	-44	0
			Max.	100	59
	Wash-out	Overall	n	207	2
			Mean	6.8	21.4
			SE	1.81	21.43
			Median	0.0	21.4
			Min.	-64	0
			Max.	100	43

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Table 7.86
Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1800888

Treatment: Salmeterol

				C, C	C, T

Subjects in treatment				226	6
% Symptom-free days	Double-blind	Baseline	n	222	6
			Mean	35.3	33.3
			SE	2.73	21.08
			Median	14.3	0.0
			Min.	0	0
			Max.	100	100
		Weeks 1-4	n	219	6
			Mean	41.5	42.3
			SE	2.68	20.13
			Median	39.3	26.8
			Min.	0	0
			Max.	100	100
		Weeks 5-8	n	212	5
			Mean	42.9	57.1
			SE	2.73	22.84
			Median	37.1	82.1
			Min.	0	0
			Max.	100	100
		Weeks 9-12	n	201	5
			Mean	43.6	54.8
			SE	2.89	22.31
			Median	36.4	70.4
			Min.	0	0
			Max.	100	100
		Weeks 13-16	n	194	5
			Mean	44.3	57.8
			SE	2.91	23.67

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Table 7.86
Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1800888

Treatment: Salmeterol

				C, C	C, T

% Symptom-free days	Double-blind	Weeks 13-16	Median	43.6	88.9
			Min.	0	0
			Max.	100	100
		Overall	n	221	6
			Mean	43.6	45.9
			SE	2.61	20.64
			Median	39.3	37.3
			Min.	0	0
			Max.	100	100
	Wash-out	Overall	n	189	5
			Mean	38.9	54.3
			SE	3.02	22.77
			Median	21.4	71.4
			Min.	0	0
			Max.	100	100
% SFD change	Double-blind	Weeks 1-4	n	218	6
			Mean	6.4	8.9
			SE	1.78	8.93
			Median	0.0	0.0
			Min.	-82	0
			Max.	96	54
		Weeks 5-8	n	211	5
			Mean	7.3	17.1
			SE	1.92	16.26
			Median	0.0	0.0
			Min.	-100	0
			Max.	96	82
		Weeks 9-12	n	201	5

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Table 7.86
 Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS1800888

Treatment: Salmeterol

			C, C	C, T	
% SFD change	Double-blind	Weeks 9-12	Mean	9.1	14.8
			SE	1.92	13.91
			Median	0.0	0.0
			Min.	-82	0
			Max.	100	70
		Weeks 13-16	n	194	5
			Mean	9.0	17.8
			SE	2.05	17.78
			Median	0.0	0.0
			Min.	-86	0
			Max.	100	89
		Overall	n	220	6
			Mean	8.0	12.6
			SE	1.69	12.21
			Median	0.0	0.4
			Min.	-82	0
			Max.	97	74
	Wash-out	Overall	n	189	5
			Mean	3.8	14.3
			SE	2.01	14.29
			Median	0.0	0.0
			Min.	-86	0
			Max.	100	71

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Table 7.87
Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS3729943

Treatment: FSC100/50

				C, C	C, G

Subjects in treatment				241	2
% Symptom-free days	Double-blind	Baseline	n	233	2
			Mean	33.3	42.9
			SE	2.59	14.29
			Median	0.0	42.9
			Min.	0	29
			Max.	100	57
		Weeks 1-4	n	238	2
			Mean	46.0	57.1
			SE	2.70	32.14
			Median	48.1	57.1
			Min.	0	25
			Max.	100	89
		Weeks 5-8	n	228	2
			Mean	46.5	62.3
			SE	2.74	26.59
			Median	51.8	62.3
			Min.	0	36
			Max.	100	89
		Weeks 9-12	n	221	2
			Mean	48.4	60.7
			SE	2.83	39.29
			Median	55.6	60.7
			Min.	0	21
			Max.	100	100
		Weeks 13-16	n	216	2
			Mean	48.2	62.5
			SE	2.87	37.50

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Table 7.87
Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS3729943

Treatment: FSC100/50

				C, C	C, G

% Symptom-free days	Double-blind	Weeks 13-16	Median	50.0	62.5
			Min.	0	25
			Max.	100	100
		Overall	n	239	2
			Mean	47.3	60.6
			SE	2.63	33.83
			Median	51.8	60.6
			Min.	0	27
			Max.	100	94
	Wash-out	Overall	n	213	2
			Mean	40.5	25.3
			SE	2.85	17.58
			Median	28.6	25.3
			Min.	0	8
			Max.	100	43
% SFD change	Double-blind	Weeks 1-4	n	230	2
			Mean	12.1	14.3
			SE	1.82	17.86
			Median	0.0	14.3
			Min.	-43	-4
			Max.	100	32
		Weeks 5-8	n	222	2
			Mean	13.1	19.4
			SE	1.91	12.30
			Median	0.0	19.4
			Min.	-46	7
			Max.	100	32
		Weeks 9-12	n	215	2

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Table 7.87
 Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS3729943

Treatment: FSC100/50

CC100/00

			C, C	C, G	

% SFD change	Double-blind	Weeks 9-12	Mean	14.8	17.9
			SE	2.10	25.00
			Median	0.0	17.9
			Min.	-76	-7
			Max.	100	43
		Weeks 13-16	n	210	2
			Mean	14.2	19.6
			SE	2.20	23.21
			Median	0.0	19.6
			Min.	-78	-4
			Max.	100	43
		Overall	n	231	2
			Mean	13.5	17.8
			SE	1.81	19.54
			Median	0.0	17.8
			Min.	-44	-2
			Max.	100	37
	Wash-out	Overall	n	207	2
			Mean	7.2	-17.6
			SE	1.81	3.30
			Median	0.0	-17.6
			Min.	-64	-21
			Max.	100	-14

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Table 7.87
 Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS3729943

Treatment: Salmeterol

				C, C	C, G

Subjects in treatment				231	1
% Symptom-free days	Double-blind	Baseline	n	227	1
			Mean	35.4	0.0
			SE	2.71	
			Median	14.3	0.0
			Min.	0	0
			Max.	100	0
		Weeks 1-4	n	224	1
			Mean	41.7	0.0
			SE	2.66	
			Median	39.3	0.0
			Min.	0	0
			Max.	100	0
		Weeks 5-8	n	216	1
			Mean	43.4	3.7
			SE	2.72	
			Median	38.9	3.7
			Min.	0	4
			Max.	100	4
		Weeks 9-12	n	205	1
			Mean	44.1	10.7
			SE	2.87	
			Median	39.3	10.7
			Min.	0	11
			Max.	100	11
		Weeks 13-16	n	198	1
			Mean	44.5	64.3
			SE	2.90	

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Table 7.87
 Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS3729943

Treatment: Salmeterol

				C, C	C, G
% Symptom-free days	Double-blind	Weeks 13-16	Median	43.6	64.3
			Min.	0	64
			Max.	100	64
		Overall	n	226	1
			Mean	43.8	20.0
			SE	2.60	
			Median	40.2	20.0
			Min.	0	20
			Max.	100	20
	Wash-out	Overall	n	193	1
			Mean	39.5	0.0
			SE	3.00	
			Median	21.4	0.0
			Min.	0	0
			Max.	100	0
% SFD change	Double-blind	Weeks 1-4	n	223	1
			Mean	6.5	0.0
			SE	1.76	
			Median	0.0	0.0
			Min.	-82	0
			Max.	96	0
		Weeks 5-8	n	215	1
			Mean	7.6	3.7
			SE	1.91	
			Median	0.0	3.7
			Min.	-100	4
			Max.	96	4
		Weeks 9-12	n	205	1

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Table 7.87
 Summary of Percent of Symptom-Free Days - ADRB2 Gene SNP RS3729943

Treatment: Salmeterol

			C, C	C, G	

% SFD change	Double-blind	Weeks 9-12	Mean	9.2	10.7
			SE	1.91	
			Median	0.0	10.7
			Min.	-82	11
			Max.	100	11
		Weeks 13-16	n	198	1
			Mean	9.0	64.3
			SE	2.03	
			Median	0.0	64.3
			Min.	-86	64
			Max.	100	64
		Overall	n	225	1
			Mean	8.1	20.0
			SE	1.68	
			Median	0.0	20.0
			Min.	-82	20
			Max.	97	20
	Wash-out	Overall	n	193	1
			Mean	4.1	0.0
			SE	2.00	
			Median	0.0	0.0
			Min.	-86	0
			Max.	100	0

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Table 7.88
Summary of Percent of Symptom-Free Days - Poly-C Repeat Group

Treatment: FSC100/50

				<12 Repeats	>=12 Repeats

Subjects in treatment				102	137
% Symptom-free days	Double-blind	Baseline	n	101	130
			Mean	33.5	33.2
			SE	3.82	3.56
			Median	14.3	0.0
			Min.	0	0
			Max.	100	100
		Weeks 1-4	n	100	136
			Mean	46.1	46.3
			SE	4.11	3.63
			Median	48.2	48.1
			Min.	0	0
			Max.	100	100
		Weeks 5-8	n	95	132
			Mean	45.9	47.6
			SE	4.30	3.57
			Median	53.6	51.8
			Min.	0	0
			Max.	100	100
		Weeks 9-12	n	92	128
			Mean	45.7	51.0
			SE	4.36	3.73
			Median	50.9	57.1
			Min.	0	0
			Max.	100	100
		Weeks 13-16	n	92	123
			Mean	45.7	50.6

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Table 7.88
Summary of Percent of Symptom-Free Days - Poly-C Repeat Group

Treatment: FSC100/50

				<12 Repeats	>=12 Repeats
% Symptom-free days	Double-blind	Weeks 13-16	SE	4.34	3.84
			Median	44.6	55.6
			Min.	0	0
			Max.	100	100
		Overall	n	100	137
			Mean	46.5	48.4
			SE	4.07	3.49
			Median	51.3	53.8
			Min.	0	0
			Max.	100	100
	Wash-out	Overall	n	89	123
			Mean	38.8	41.6
			SE	4.39	3.76
			Median	21.4	33.3
			Min.	0	0
			Max.	100	100
% SFD change	Double-blind	Weeks 1-4	n	99	129
			Mean	12.2	12.4
			SE	2.72	2.49
			Median	0.0	0.0
			Min.	-39	-43
			Max.	100	96
		Weeks 5-8	n	95	126
			Mean	12.6	13.8
			SE	2.85	2.61
			Median	0.0	0.0
			Min.	-43	-46
			Max.	100	100

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Table 7.88
Summary of Percent of Symptom-Free Days - Poly-C Repeat Group

Treatment: FSC100/50

CC100/00

				<12 Repeats	>=12 Repeats
% SFD change	Double-blind	Weeks 9-12	n	92	122
			Mean	12.6	16.8
			SE	3.24	2.79
			Median	0.0	0.0
			Min.	-76	-29
			Max.	100	100
		Weeks 13-16	n	92	117
			Mean	12.6	15.6
			SE	3.21	3.06
			Median	0.0	0.0
			Min.	-78	-71
			Max.	100	100
		Overall	n	99	130
			Mean	12.6	14.6
			SE	2.74	2.45
			Median	0.9	0.0
			Min.	-44	-27
			Max.	100	98
	Wash-out	Overall	n	89	117
			Mean	6.0	7.6
			SE	2.89	2.35
			Median	0.0	0.0
			Min.	-64	-64
			Max.	100	100

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Table 7.88
Summary of Percent of Symptom-Free Days - Poly-C Repeat Group

Treatment: Salmeterol

				<12 Repeats	>=12 Repeats

Subjects in treatment				91	139
% Symptom-free days	Double-blind	Baseline	n	90	136
			Mean	33.7	35.9
			SE	4.28	3.53
			Median	0.0	14.3
			Min.	0	0
			Max.	100	100
		Weeks 1-4	n	87	136
			Mean	39.9	42.2
			SE	4.17	3.47
			Median	35.7	40.0
			Min.	0	0
			Max.	100	100
		Weeks 5-8	n	84	131
			Mean	44.1	42.1
			SE	4.30	3.54
			Median	37.1	35.7
			Min.	0	0
			Max.	100	100
		Weeks 9-12	n	81	123
			Mean	43.7	43.4
			SE	4.46	3.78
			Median	42.9	25.9
			Min.	0	0
			Max.	100	100
		Weeks 13-16	n	77	121
			Mean	43.7	44.4

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Table 7.88
 Summary of Percent of Symptom-Free Days - Poly-C Repeat Group

Treatment: Salmeterol

				<12 Repeats	>=12 Repeats
% Symptom-free days	Double-blind	Weeks 13-16	SE	4.52	3.80
			Median	39.3	40.7
			Min.	0	0
			Max.	100	100
		Overall	n	88	137
			Mean	43.6	43.3
			SE	4.06	3.39
			Median	41.6	35.1
			Min.	0	0
			Max.	100	100
	Wash-out	Overall	n	76	117
			Mean	32.9	42.3
			SE	4.66	3.88
			Median	0.0	28.6
			Min.	0	0
			Max.	100	100
% SFD change	Double-blind	Weeks 1-4	n	87	135
			Mean	6.2	6.7
			SE	2.98	2.18
			Median	0.0	0.0
			Min.	-82	-50
			Max.	68	96
		Weeks 5-8	n	84	130
			Mean	9.0	6.6
			SE	2.96	2.52
			Median	0.6	0.0
			Min.	-86	-100
			Max.	82	96

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Table 7.88
Summary of Percent of Symptom-Free Days - Poly-C Repeat Group

Treatment: Salmeterol

			<12 Repeats	>=12 Repeats
% SFD change	Double-blind	Weeks 9-12	n	81
			Mean	11.1
			SE	3.23
			Median	0.0
			Min.	-82
			Max.	100
		Weeks 13-16	n	77
			Mean	11.0
			SE	3.34
			Median	0.0
			Min.	-79
			Max.	89
		Overall	n	88
			Mean	9.1
			SE	2.72
			Median	0.9
			Min.	-82
			Max.	74
	Wash-out	Overall	n	76
			Mean	0.1
			SE	3.26
			Median	0.0
			Min.	-86
			Max.	86

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Table 7.89
Analysis of Percent of Symptom-Free Days - Poly-C Repeat Group

				<12 vs. ≥12
FSC100/50	Double-blind	Weeks 1-4	p-value	0.919
			LS Means Diff	0.4
			95% CI for Diff	(-6.8, 7.6)
		Weeks 5-8	p-value	0.821
			LS Means Diff	-0.9
			95% CI for Diff	(-8.4, 6.7)
		Weeks 9-12	p-value	0.387
			LS Means Diff	-3.6
			95% CI for Diff	(-11.8, 4.6)
		Weeks 13-16	p-value	0.537
			LS Means Diff	-2.7
			95% CI for Diff	(-11.2, 5.8)
	Wash-out	Overall	p-value	0.678
			LS Means Diff	-1.5
			95% CI for Diff	(-8.6, 5.6)
		Overall	p-value	0.704
			LS Means Diff	-1.4
			95% CI for Diff	(-8.6, 5.8)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and Poly-C repeat group. Least squares mean differences are calculated as <12 Repeats - ≥12 Repeats.

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Table 7.89
Analysis of Percent of Symptom-Free Days - Poly-C Repeat Group

				<12 vs. ≥12

Salmeterol	Double-blind	Weeks 1-4	p-value	0.820
			LS Means Diff	-0.8
			95% CI for Diff	(-7.5,6.0)
		Weeks 5-8	p-value	0.466
			LS Means Diff	2.7
			95% CI for Diff	(-4.6,10.0)
		Weeks 9-12	p-value	0.417
			LS Means Diff	3.1
			95% CI for Diff	(-4.4,10.5)
		Weeks 13-16	p-value	0.567
			LS Means Diff	2.3
			95% CI for Diff	(-5.6,10.2)
		Overall	p-value	0.611
			LS Means Diff	1.6
			95% CI for Diff	(-4.7,8.0)
	Wash-out	Overall	p-value	0.126
			LS Means Diff	-6.0
			95% CI for Diff	(-13.7,1.7)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and Poly-C repeat group. Least squares mean differences are calculated as <12 Repeats - ≥12 Repeats.

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Table 7.90
 Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1432623

Treatment: FSC100/50

				C, C	C, T	T, T
-----				-----		
Subjects in treatment				37	95	110
Ipratropium use	Double-blind	Baseline	n	36	91	104
			Mean	1.02	0.96	1.25
			SE	0.183	0.107	0.123
			Median	0.50	0.71	1.14
			Min.	0.0	0.0	0.0
			Max.	4.0	4.6	5.9
		Weeks 1-4	n	33	94	109
			Mean	0.71	0.56	0.61
			SE	0.148	0.072	0.074
			Median	0.39	0.29	0.29
			Min.	0.0	0.0	0.0
			Max.	2.9	3.3	2.8
		Weeks 5-8	n	33	89	105
			Mean	0.53	0.53	0.55
			SE	0.118	0.077	0.073
			Median	0.29	0.21	0.15
			Min.	0.0	0.0	0.0
			Max.	2.0	3.6	3.0
		Weeks 9-12	n	30	89	101
			Mean	0.67	0.52	0.58
			SE	0.144	0.074	0.074
			Median	0.41	0.18	0.21
			Min.	0.0	0.0	0.0
			Max.	2.2	2.9	2.8
		Weeks 13-16	n	29	89	99
			Mean	0.66	0.50	0.61
			SE	0.156	0.077	0.080

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Table 7.90
Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1432623

Treatment: FSC100/50

				C, C	C, T	T, T

Ipratropium use	Double-blind	Weeks 13-16	Median	0.37	0.18	0.21
			Min.	0.0	0.0	0.0
			Max.	2.9	3.9	3.6
		Overall	n	34	95	109
			Mean	0.60	0.53	0.57
			SE	0.120	0.067	0.067
			Median	0.32	0.23	0.25
			Min.	0.0	0.0	0.0
			Max.	2.0	2.8	3.0
	Wash-out	Overall	n	27	87	98
			Mean	0.61	0.68	0.83
			SE	0.150	0.096	0.099
			Median	0.29	0.33	0.48
			Min.	0.0	0.0	0.0
			Max.	2.6	4.4	4.9
Ipratropium change	Double-blind	Weeks 1-4	n	33	91	104
			Mean	-0.38	-0.41	-0.65
			SE	0.151	0.089	0.116
			Median	-0.21	-0.11	-0.23
			Min.	-3.5	-4.2	-5.9
			Max.	1.9	0.9	0.9
		Weeks 5-8	n	33	86	100
			Mean	-0.56	-0.49	-0.71
			SE	0.183	0.097	0.120
			Median	-0.18	-0.29	-0.29
			Min.	-3.7	-4.2	-5.9
			Max.	0.8	1.5	1.2
		Weeks 9-12	n	30	85	96

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Table 7.90
 Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1432623

Treatment: FSC100/50

ment: TSC100750

				C, C	C, T	T, T
Ipratropium change	Double-blind	Weeks 9-12	Mean	-0.45	-0.49	-0.67
			SE	0.197	0.111	0.115
			Median	-0.02	-0.29	-0.29
			Min.	-3.9	-4.1	-5.0
			Max.	1.7	1.8	2.0
		Weeks 13-16	n	29	85	94
			Mean	-0.50	-0.50	-0.65
			SE	0.199	0.102	0.116
			Median	-0.21	-0.29	-0.32
			Min.	-3.9	-4.3	-5.0
		Max.	1.1	1.3	2.0	
		Overall	n	34	91	104
			Mean	-0.46	-0.46	-0.69
			SE	0.158	0.090	0.116
			Median	-0.21	-0.20	-0.25
			Min.	-3.5	-4.1	-5.9
		Max.	1.4	1.1	1.0	
Wash-out	Overall	n	26	84	94	
		Mean	-0.45	-0.34	-0.48	
		SE	0.199	0.103	0.106	
		Median	-0.21	-0.14	-0.14	
		Min.	-3.1	-4.0	-5.0	
		Max.	1.2	2.0	1.6	

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Table 7.90
Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1432623

Treatment: Salmeterol

				C, C	C, T	T, T
-----				-----		
Subjects in treatment				34	98	100
Ipratropium use	Double-blind	Baseline	n	31	96	97
			Mean	1.02	1.12	1.05
			SE	0.236	0.138	0.100
			Median	0.29	0.57	0.86
			Min.	0.0	0.0	0.0
			Max.	4.7	6.7	4.0
		Weeks 1-4	n	33	94	97
			Mean	0.71	0.62	0.89
			SE	0.151	0.077	0.088
			Median	0.29	0.32	0.50
			Min.	0.0	0.0	0.0
			Max.	3.1	2.8	3.1
		Weeks 5-8	n	31	92	93
			Mean	0.63	0.65	0.82
			SE	0.138	0.085	0.086
			Median	0.21	0.30	0.50
			Min.	0.0	0.0	0.0
			Max.	2.6	4.4	3.5
		Weeks 9-12	n	28	89	88
			Mean	0.64	0.59	0.68
			SE	0.164	0.074	0.072
			Median	0.11	0.32	0.44
			Min.	0.0	0.0	0.0
			Max.	3.1	2.5	2.9
		Weeks 13-16	n	28	87	83
			Mean	0.65	0.54	0.65
			SE	0.163	0.070	0.076

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Table 7.90
 Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1432623

Treatment: Salmeterol

				C, C	C, T	T, T

Ipratropium use	Double-blind	Weeks 13-16	Median	0.22	0.22	0.36
			Min.	0.0	0.0	0.0
			Max.	3.3	2.2	2.4
		Overall	n	33	96	97
			Mean	0.67	0.59	0.79
			SE	0.144	0.067	0.076
			Median	0.29	0.35	0.55
			Min.	0.0	0.0	0.0
			Max.	3.0	2.3	3.0
	Wash-out	Overall	n	27	85	83
			Mean	0.75	0.77	0.90
			SE	0.159	0.124	0.098
			Median	0.43	0.36	0.57
			Min.	0.0	0.0	0.0
			Max.	2.0	8.0	3.6
Ipratropium change	Double-blind	Weeks 1-4	n	31	93	96
			Mean	-0.28	-0.51	-0.15
			SE	0.151	0.125	0.065
			Median	-0.04	-0.18	0.00
			Min.	-2.9	-6.1	-2.8
			Max.	1.9	1.3	1.4
		Weeks 5-8	n	29	91	92
			Mean	-0.26	-0.49	-0.22
			SE	0.127	0.135	0.080
			Median	-0.14	-0.07	0.00
			Min.	-1.7	-6.2	-2.9
			Max.	1.2	2.4	1.6
		Weeks 9-12	n	26	89	87

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Table 7.90
 Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1432623

Treatment: Salmeterol

				C, C	C, T	T, T
Ipratropium change	Double-blind	Weeks 9-12	Mean	-0.34	-0.58	-0.36
			SE	0.126	0.123	0.078
			Median	-0.23	-0.21	-0.07
			Min.	-1.6	-6.0	-2.9
			Max.	1.2	1.1	1.1
		Weeks 13-16	n	26	87	82
			Mean	-0.33	-0.63	-0.40
			SE	0.118	0.131	0.087
			Median	-0.25	-0.26	-0.21
			Min.	-1.6	-5.4	-2.4
		Max.	0.9	1.1	1.9	
		Overall	n	31	95	96
			Mean	-0.31	-0.53	-0.26
			SE	0.120	0.119	0.068
			Median	-0.08	-0.13	-0.02
			Min.	-1.9	-5.9	-2.7
		Max.	0.8	1.1	1.4	
Wash-out	Overall	n	25	85	82	
		Mean	-0.08	-0.39	-0.15	
		SE	0.160	0.120	0.082	
		Median	-0.14	-0.14	0.00	
		Min.	-1.6	-4.6	-2.3	
		Max.	1.9	1.4	2.3	

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Table 7.91
Analysis of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1432623

				C/C vs. C/T	C/C vs. T/T	C/T vs. T/T
FSC100/50	Double-blind	Weeks 1-4	p-value	0.387	0.210	0.613
			LS Means Diff	0.12	0.16	0.05
			95% CI for Diff	(-0.15,0.38)	(-0.09,0.42)	(-0.14,0.24)
		Weeks 5-8	p-value	0.859	0.757	0.509
			LS Means Diff	-0.02	0.04	0.07
			95% CI for Diff	(-0.29,0.24)	(-0.22,0.30)	(-0.13,0.26)
		Weeks 9-12	p-value	0.344	0.339	0.988
			LS Means Diff	0.14	0.13	-0.00
			95% CI for Diff	(-0.15,0.42)	(-0.14,0.41)	(-0.20,0.20)
		Weeks 13-16	p-value	0.416	0.598	0.674
			LS Means Diff	0.12	0.08	-0.04
95% CI for Diff	(-0.17,0.42)		(-0.21,0.37)	(-0.25,0.16)		
Overall	p-value	0.601	0.388	0.656		
	LS Means Diff	0.06	0.10	0.04		
	95% CI for Diff	(-0.18,0.30)	(-0.13,0.34)	(-0.13,0.21)		
Wash-out	Overall	p-value	0.484	0.416	0.879	
		LS Means Diff	-0.12	-0.13	-0.02	
		95% CI for Diff	(-0.45,0.21)	(-0.46,0.19)	(-0.24,0.21)	

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS1432623. Least squares mean differences are calculated as C/C-C/T, C/C-T/T and C/T-T/T.

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Table 7.91
Analysis of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1432623

				C/C vs. C/T	C/C vs. T/T	C/T vs. T/T
Salmeterol	Double-blind	Weeks 1-4	p-value	0.201	0.296	0.001
			LS Means Diff	0.17	-0.14	-0.31
			95% CI for Diff	(-0.09,0.43)	(-0.41,0.13)	(-0.50,-0.13)
		Weeks 5-8	p-value	0.389	0.761	0.102
			LS Means Diff	0.13	-0.05	-0.17
			95% CI for Diff	(-0.16,0.41)	(-0.34,0.25)	(-0.38,0.03)
		Weeks 9-12	p-value	0.199	0.740	0.176
			LS Means Diff	0.16	0.04	-0.12
			95% CI for Diff	(-0.08,0.40)	(-0.21,0.29)	(-0.28,0.05)
		Weeks 13-16	p-value	0.137	0.855	0.069
			LS Means Diff	0.19	0.02	-0.17
			95% CI for Diff	(-0.06,0.44)	(-0.24,0.28)	(-0.34,0.01)
	Overall	p-value	0.142	0.626	0.006	
		LS Means Diff	0.17	-0.06	-0.22	
95% CI for Diff		(-0.06,0.39)	(-0.28,0.17)	(-0.38,-0.06)		
Wash-out	Overall	p-value	0.355	0.505	0.023	
		LS Means Diff	0.16	-0.12	-0.28	
		95% CI for Diff	(-0.18,0.50)	(-0.48,0.23)	(-0.52,-0.04)	

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS1432623. Least squares mean differences are calculated as C/C-C/T, C/C-T/T and C/T-T/T.

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Table 7.92
Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1042711

Treatment: FSC100/50

				C, C	C, T	T, T
-----				-----		
Subjects in treatment				23	72	141
Ipratropium use	Double-blind	Baseline	n	23	69	133
			Mean	0.99	1.03	1.15
			SE	0.213	0.136	0.103
			Median	0.57	0.57	1.00
			Min.	0.0	0.0	0.0
			Max.	4.0	4.6	5.9
		Weeks 1-4	n	21	70	139
			Mean	0.63	0.54	0.63
			SE	0.177	0.089	0.064
			Median	0.39	0.21	0.29
			Min.	0.0	0.0	0.0
			Max.	2.9	3.3	2.8
		Weeks 5-8	n	21	65	135
			Mean	0.49	0.50	0.57
			SE	0.143	0.091	0.064
			Median	0.29	0.14	0.19
			Min.	0.0	0.0	0.0
			Max.	2.0	3.6	3.0
		Weeks 9-12	n	19	65	131
			Mean	0.65	0.42	0.63
			SE	0.178	0.080	0.066
			Median	0.43	0.14	0.29
			Min.	0.0	0.0	0.0
			Max.	2.1	2.5	2.9
		Weeks 13-16	n	19	65	128
			Mean	0.67	0.44	0.62
			SE	0.199	0.090	0.069

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Table 7.92
Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1042711

Treatment: FSC100/50

				C, C	C, T	T, T
Ipratropium use	Double-blind	Weeks 13-16	Median	0.37	0.14	0.22
			Min.	0.0	0.0	0.0
			Max.	2.9	3.9	3.6
		Overall	n	22	71	139
			Mean	0.57	0.48	0.60
			SE	0.147	0.077	0.060
			Median	0.35	0.20	0.25
			Min.	0.0	0.0	0.0
			Max.	2.0	2.8	3.0
	Wash-out	Overall	n	16	65	126
			Mean	0.35	0.66	0.84
			SE	0.141	0.110	0.086
			Median	0.14	0.29	0.57
			Min.	0.0	0.0	0.0
			Max.	2.0	4.4	4.9
Ipratropium change	Double-blind	Weeks 1-4	n	21	69	132
			Mean	-0.42	-0.48	-0.54
			SE	0.183	0.105	0.097
			Median	-0.29	-0.20	-0.18
			Min.	-3.5	-4.2	-5.9
			Max.	0.8	0.9	1.9
		Weeks 5-8	n	21	64	128
			Mean	-0.55	-0.59	-0.61
			SE	0.223	0.127	0.098
			Median	-0.21	-0.29	-0.29
			Min.	-3.7	-4.2	-5.9
			Max.	0.5	1.5	1.2
		Weeks 9-12	n	19	63	124

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Table 7.92
Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1042711

Treatment: FSC100/50

				C, C	C, T	T, T
-----				-----		
Ipratropium change	Double-blind	Weeks 9-12	Mean	-0.41	-0.65	-0.54
			SE	0.201	0.143	0.097
			Median	-0.03	-0.29	-0.29
			Min.	-3.4	-4.1	-5.0
			Max.	0.6	1.8	2.0
		Weeks 13-16	n	19	63	121
			Mean	-0.39	-0.63	-0.55
			SE	0.209	0.132	0.097
			Median	-0.21	-0.39	-0.29
			Min.	-3.6	-4.3	-5.0
			Max.	0.6	1.3	2.0
		Overall	n	22	69	132
			Mean	-0.44	-0.56	-0.58
			SE	0.174	0.114	0.096
			Median	-0.25	-0.29	-0.22
			Min.	-3.5	-4.1	-5.9
			Max.	0.3	1.1	1.4
	Wash-out	Overall	n	16	63	120
			Mean	-0.46	-0.41	-0.39
			SE	0.225	0.133	0.087
			Median	-0.29	-0.19	-0.11
			Min.	-2.9	-4.0	-5.0
			Max.	0.9	2.0	1.6

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Table 7.92

Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1042711

Treatment: Salmeterol

				C, C	C, T	T, T
Subjects in treatment				25	71	133
Ipratropium use	Double-blind	Baseline	n	23	71	127
			Mean	0.92	1.11	1.10
			SE	0.262	0.159	0.098
			Median	0.29	0.57	0.86
			Min.	0.0	0.0	0.0
			Max.	4.7	6.7	4.6
		Weeks 1-4	n	25	69	127
			Mean	0.68	0.58	0.85
			SE	0.178	0.083	0.077
			Median	0.29	0.36	0.50
			Min.	0.0	0.0	0.0
			Max.	3.1	2.7	3.1
		Weeks 5-8	n	23	67	123
			Mean	0.48	0.61	0.82
			SE	0.140	0.086	0.080
			Median	0.14	0.43	0.43
			Min.	0.0	0.0	0.0
			Max.	2.0	2.8	4.4
		Weeks 9-12	n	20	66	116
			Mean	0.46	0.54	0.71
			SE	0.160	0.079	0.069
			Median	0.09	0.30	0.44
			Min.	0.0	0.0	0.0
			Max.	2.0	2.0	3.1
Weeks 13-16	n	20	64	111		
	Mean	0.51	0.53	0.66		
	SE	0.158	0.083	0.069		

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Table 7.92

Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1042711

Treatment: Salmeterol

				C, C	C, T	T, T
Ipratropium use	Double-blind	Weeks 13-16	Median	0.11	0.24	0.36
			Min.	0.0	0.0	0.0
			Max.	2.0	2.2	3.3
		Overall	n	25	70	128
			Mean	0.58	0.56	0.77
			SE	0.160	0.072	0.068
			Median	0.25	0.39	0.55
			Min.	0.0	0.0	0.0
			Max.	3.0	2.2	3.0
	Wash-out	Overall	n	20	64	108
			Mean	0.63	0.82	0.85
			SE	0.181	0.154	0.085
			Median	0.15	0.35	0.59
			Min.	0.0	0.0	0.0
			Max.	2.0	8.0	3.6
Ipratropium change	Double-blind	Weeks 1-4	n	23	69	125
			Mean	-0.19	-0.52	-0.25
			SE	0.151	0.144	0.073
			Median	-0.04	-0.14	0.00
			Min.	-2.2	-6.1	-3.9
			Max.	1.9	1.3	1.3
		Weeks 5-8	n	21	67	121
			Mean	-0.26	-0.51	-0.28
			SE	0.134	0.155	0.082
			Median	-0.14	-0.05	0.00
			Min.	-1.7	-6.2	-4.2
			Max.	1.2	2.2	2.4
		Weeks 9-12	n	18	66	115

Table 7.92
 Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1042711

Treatment: Salmeterol

				C, C	C, T	T, T
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Ipratropium change	Double-blind	Weeks 9-12	Mean	-0.38	-0.60	-0.40
			SE	0.119	0.146	0.076
			Median	-0.16	-0.27	-0.21
			Min.	-1.6	-6.0	-3.4
			Max.	0.2	1.1	1.2
		Weeks 13-16	n	18	64	110
			Mean	-0.33	-0.62	-0.45
			SE	0.126	0.150	0.085
			Median	-0.18	-0.24	-0.22
			Min.	-1.6	-5.4	-3.7
			Max.	0.4	1.1	1.9
		Overall	n	23	70	126
			Mean	-0.29	-0.54	-0.32
			SE	0.123	0.140	0.071
			Median	-0.04	-0.16	-0.10
			Min.	-1.8	-5.9	-3.6
			Max.	0.5	1.1	1.4
Wash-out	Overall	Overall	n	18	64	107
			Mean	-0.19	-0.34	-0.22
			SE	0.172	0.130	0.087
			Median	-0.14	-0.14	-0.05
			Min.	-1.6	-4.1	-4.6
			Max.	1.9	1.4	2.3

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Table 7.93
Analysis of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1042711

				C/C vs. C/T	C/C vs. T/T	C/T vs. T/T
FSC100/50	Double-blind	Weeks 1-4	p-value	0.467	0.366	0.814
			LS Means Diff	0.12	0.14	0.02
			95% CI for Diff	(-0.20,0.44)	(-0.17,0.45)	(-0.17,0.22)
		Weeks 5-8	p-value	0.919	0.869	0.927
			LS Means Diff	0.02	0.03	0.01
			95% CI for Diff	(-0.31,0.35)	(-0.29,0.34)	(-0.20,0.21)
		Weeks 9-12	p-value	0.128	0.373	0.271
			LS Means Diff	0.26	0.15	-0.12
			95% CI for Diff	(-0.08,0.61)	(-0.18,0.48)	(-0.32,0.09)
		Weeks 13-16	p-value	0.165	0.435	0.295
LS Means Diff	0.25		0.14	-0.12		
95% CI for Diff	(-0.11,0.61)		(-0.21,0.48)	(-0.33,0.10)		
Overall	p-value	0.350	0.434	0.772		
	LS Means Diff	0.14	0.11	-0.03		
	95% CI for Diff	(-0.15,0.43)	(-0.17,0.39)	(-0.21,0.15)		
Wash-out	Overall	p-value	0.433	0.233	0.494	
		LS Means Diff	-0.16	-0.25	-0.08	
		95% CI for Diff	(-0.58,0.25)	(-0.65,0.16)	(-0.32,0.15)	

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS1042711. Least squares mean differences are calculated as C/C-C/T, C/C-T/T and C/T-T/T.

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Table 7.93
Analysis of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1042711

				C/C vs. C/T	C/C vs. T/T	C/T vs. T/T
Salmeterol	Double-blind	Weeks 1-4	p-value	0.133	0.973	0.026
			LS Means Diff	0.23	0.01	-0.23
			95% CI for Diff	(-0.07,0.54)	(-0.30,0.31)	(-0.43,-0.03)
		Weeks 5-8	p-value	0.655	0.800	0.280
			LS Means Diff	0.08	-0.04	-0.12
			95% CI for Diff	(-0.26,0.41)	(-0.37,0.29)	(-0.34,0.10)
		Weeks 9-12	p-value	0.411	0.808	0.344
			LS Means Diff	0.12	0.04	-0.08
			95% CI for Diff	(-0.17,0.41)	(-0.25,0.32)	(-0.26,0.09)
		Weeks 13-16	p-value	0.288	0.547	0.461
			LS Means Diff	0.16	0.09	-0.07
			95% CI for Diff	(-0.14,0.46)	(-0.21,0.39)	(-0.26,0.12)
	Overall	p-value	0.193	0.806	0.104	
		LS Means Diff	0.17	0.03	-0.14	
95% CI for Diff		(-0.09,0.43)	(-0.22,0.29)	(-0.31,0.03)		
Wash-out	Overall	p-value	0.861	0.641	0.308	
		LS Means Diff	0.04	-0.10	-0.13	
		95% CI for Diff	(-0.37,0.44)	(-0.51,0.31)	(-0.39,0.12)	

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS1042711. Least squares mean differences are calculated as C/C-C/T, C/C-T/T and C/T-T/T.

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Table 7.94
Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1042713

Treatment: FSC100/50

				A, A	A, G	G, G
-----				-----		
Subjects in treatment				81	85	77
Ipratropium use	Double-blind	Baseline	n	76	82	74
			Mean	0.97	1.22	1.09
			SE	0.121	0.144	0.123
			Median	0.57	0.86	0.86
			Min.	0.0	0.0	0.0
			Max.	4.0	5.0	5.9
		Weeks 1-4	n	80	82	75
			Mean	0.55	0.67	0.59
			SE	0.078	0.093	0.082
			Median	0.21	0.29	0.36
			Min.	0.0	0.0	0.0
			Max.	2.8	3.3	2.9
		Weeks 5-8	n	77	79	72
			Mean	0.50	0.57	0.55
			SE	0.080	0.090	0.078
			Median	0.15	0.14	0.29
			Min.	0.0	0.0	0.0
			Max.	2.5	3.6	2.5
		Weeks 9-12	n	73	81	67
			Mean	0.54	0.55	0.61
			SE	0.085	0.081	0.090
			Median	0.21	0.21	0.36
			Min.	0.0	0.0	0.0
			Max.	2.9	2.8	2.5
		Weeks 13-16	n	72	79	67
			Mean	0.48	0.62	0.61
			SE	0.080	0.092	0.098

Table 7.94
Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1042713

Treatment: FSC100/50

				A, A	A, G	G, G

Ipratropium use	Double-blind	Weeks 13-16	Median	0.13	0.29	0.21
			Min.	0.0	0.0	0.0
			Max.	2.2	3.9	3.4
		Overall	n	80	83	76
			Mean	0.51	0.59	0.57
			SE	0.072	0.081	0.076
			Median	0.24	0.22	0.33
			Min.	0.0	0.0	0.0
			Max.	2.3	3.0	2.2
	Wash-out	Overall	n	71	78	64
			Mean	0.65	0.80	0.75
			SE	0.103	0.108	0.118
			Median	0.29	0.43	0.36
			Min.	0.0	0.0	0.0
			Max.	4.0	4.4	4.9
Ipratropium change	Double-blind	Weeks 1-4	n	75	82	72
			Mean	-0.45	-0.55	-0.53
			SE	0.120	0.115	0.116
			Median	0.00	-0.21	-0.25
			Min.	-3.6	-4.9	-5.9
			Max.	1.9	0.8	0.9
		Weeks 5-8	n	72	79	69
			Mean	-0.48	-0.70	-0.62
			SE	0.120	0.124	0.129
			Median	-0.11	-0.29	-0.29
			Min.	-4.0	-5.0	-5.9
			Max.	1.2	0.4	1.5
		Weeks 9-12	n	68	80	64

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Table 7.94

Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1042713

Treatment: FSC100/50

				A, A	A, G	G, G
-----				-----		
Ipratropium change	Double-blind	Weeks 9-12	Mean	-0.47	-0.71	-0.48
			SE	0.132	0.135	0.109
			Median	-0.07	-0.43	-0.25
			Min.	-4.0	-5.0	-3.4
			Max.	1.8	2.0	1.8
		Weeks 13-16	n	67	78	64
			Mean	-0.53	-0.68	-0.47
			SE	0.124	0.136	0.107
			Median	-0.07	-0.43	-0.29
			Min.	-4.0	-5.0	-3.6
			Max.	1.3	2.0	1.3
		Overall	n	75	82	73
			Mean	-0.48	-0.64	-0.55
			SE	0.117	0.120	0.115
			Median	-0.06	-0.29	-0.29
			Min.	-3.8	-5.0	-5.9
			Max.	1.4	1.0	1.1
	Wash-out	Overall	n	66	77	62
			Mean	-0.41	-0.51	-0.30
			SE	0.116	0.134	0.096
			Median	0.00	-0.29	-0.21
			Min.	-4.0	-5.0	-2.9
			Max.	1.2	1.6	2.0

Table 7.94

Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1042713

Treatment: Salmeterol

				A, A	A, G	G, G
-----				-----		
Subjects in treatment				72	79	81
Ipratropium use	Double-blind	Baseline	n	69	77	78
			Mean	0.98	1.15	1.10
			SE	0.129	0.149	0.135
			Median	0.43	0.71	0.64
			Min.	0.0	0.0	0.0
			Max.	4.3	6.7	4.7
		Weeks 1-4	n	68	76	80
			Mean	0.72	0.79	0.74
			SE	0.094	0.097	0.096
			Median	0.33	0.50	0.37
			Min.	0.0	0.0	0.0
			Max.	2.5	3.0	3.1
		Weeks 5-8	n	66	74	76
			Mean	0.76	0.70	0.70
			SE	0.110	0.091	0.091
			Median	0.29	0.39	0.41
			Min.	0.0	0.0	0.0
			Max.	4.4	2.8	3.5
		Weeks 9-12	n	62	70	73
			Mean	0.64	0.59	0.67
			SE	0.094	0.079	0.087
			Median	0.36	0.34	0.35
			Min.	0.0	0.0	0.0
			Max.	3.1	2.1	2.9
		Weeks 13-16	n	61	67	70
			Mean	0.57	0.56	0.67
			SE	0.094	0.081	0.085

Table 7.94

Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1042713

Treatment: Salmeterol

				A, A	A, G	G, G
-----				-----		
Ipratropium use	Double-blind	Weeks 13-16	Median	0.25	0.21	0.34
			Min.	0.0	0.0	0.0
			Max.	3.3	2.1	2.4
		Overall	n	69	76	81
			Mean	0.67	0.68	0.70
			SE	0.086	0.083	0.083
			Median	0.36	0.39	0.46
			Min.	0.0	0.0	0.0
			Max.	2.4	3.0	3.0
	Wash-out	Overall	n	58	67	70
			Mean	0.71	0.86	0.88
			SE	0.106	0.151	0.106
			Median	0.44	0.43	0.54
			Min.	0.0	0.0	0.0
			Max.	3.1	8.0	3.1
Ipratropium change	Double-blind	Weeks 1-4	n	67	76	77
			Mean	-0.26	-0.34	-0.36
			SE	0.105	0.128	0.098
			Median	0.00	-0.07	-0.07
			Min.	-3.4	-6.1	-4.1
			Max.	1.4	1.3	1.9
		Weeks 5-8	n	65	74	73
			Mean	-0.23	-0.42	-0.37
			SE	0.120	0.141	0.098
			Median	0.00	-0.07	-0.07
			Min.	-3.4	-6.2	-2.9
			Max.	2.4	2.2	1.3
		Weeks 9-12	n	62	70	70

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Table 7.94

Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1042713

Treatment: Salmeterol

				A, A	A, G	G, G
-----				-----		
Ipratropium change	Double-blind	Weeks 9-12	Mean	-0.35	-0.56	-0.44
			SE	0.115	0.130	0.095
			Median	-0.04	-0.29	-0.14
			Min.	-3.4	-6.0	-2.9
			Max.	1.2	0.9	1.1
		Weeks 13-16	n	61	67	67
			Mean	-0.41	-0.60	-0.46
			SE	0.120	0.141	0.105
			Median	-0.07	-0.26	-0.21
			Min.	-3.2	-5.4	-4.2
			Max.	1.9	1.0	1.1
		Overall	n	68	76	78
			Mean	-0.29	-0.45	-0.39
			SE	0.103	0.125	0.088
			Median	0.00	-0.14	-0.09
			Min.	-3.4	-5.9	-3.4
			Max.	1.4	0.8	1.1
	Wash-out	Overall	n	58	67	67
			Mean	-0.21	-0.30	-0.23
			SE	0.120	0.118	0.114
			Median	0.00	-0.14	-0.03
			Min.	-3.4	-4.6	-4.1
			Max.	1.7	1.4	2.3

Table 7.95
Analysis of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1042713

				A/A vs. A/G	A/A vs. G/G	A/G vs. G/G
FSC100/50	Double-blind	Weeks 1-4	p-value	0.359	0.742	0.561
			LS Means Diff	-0.10	-0.04	0.06
			95% CI for Diff	(-0.30,0.11)	(-0.25,0.18)	(-0.15,0.27)
		Weeks 5-8	p-value	0.879	0.883	0.999
			LS Means Diff	-0.02	-0.02	0.00
			95% CI for Diff	(-0.23,0.20)	(-0.24,0.20)	(-0.21,0.21)
		Weeks 9-12	p-value	0.856	0.591	0.459
			LS Means Diff	0.02	-0.06	-0.08
			95% CI for Diff	(-0.20,0.24)	(-0.29,0.17)	(-0.30,0.14)
		Weeks 13-16	p-value	0.484	0.283	0.677
			LS Means Diff	-0.08	-0.13	-0.05
			95% CI for Diff	(-0.31,0.15)	(-0.37,0.11)	(-0.28,0.18)
	Wash-out	Overall	p-value	0.631	0.597	0.950
			LS Means Diff	-0.05	-0.05	-0.01
			95% CI for Diff	(-0.24,0.14)	(-0.25,0.14)	(-0.19,0.18)
		Overall	p-value	0.493	0.200	0.513
			LS Means Diff	-0.09	-0.17	-0.08
			95% CI for Diff	(-0.33,0.16)	(-0.43,0.09)	(-0.33,0.17)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS1042713. Least squares mean differences are calculated as A/A-A/G, A/A-G/G and A/G-G/G.

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Table 7.95
Analysis of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1042713

				A/A vs. A/G	A/A vs. G/G	A/G vs. G/G		
Salmeterol	Double-blind	Weeks 1-4	p-value	0.769	0.951	0.809		
			LS Means Diff	-0.03	-0.01	0.03		
			95% CI for Diff	(-0.25,0.19)	(-0.23,0.21)	(-0.19,0.24)		
		Weeks 5-8	p-value	0.656	0.688	0.967		
			LS Means Diff	0.05	0.05	-0.00		
			95% CI for Diff	(-0.18,0.29)	(-0.19,0.28)	(-0.23,0.22)		
		Weeks 9-12	p-value	0.567	0.591	0.249		
			LS Means Diff	0.06	-0.05	-0.11		
			95% CI for Diff	(-0.14,0.25)	(-0.25,0.14)	(-0.29,0.08)		
		Weeks 13-16	p-value	0.818	0.253	0.152		
LS Means Diff	0.02		-0.12	-0.14				
95% CI for Diff	(-0.18,0.23)		(-0.32,0.09)	(-0.34,0.05)				
	Wash-out	Overall	p-value	0.891	0.709	0.595		
			LS Means Diff	0.01	-0.03	-0.05		
			95% CI for Diff	(-0.17,0.20)	(-0.22,0.15)	(-0.22,0.13)		
		Overall	p-value	0.913	0.587	0.646		
			LS Means Diff	-0.02	-0.08	-0.06		
			95% CI for Diff	(-0.29,0.26)	(-0.36,0.20)	(-0.33,0.20)		

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS1042713. Least squares mean differences are calculated as A/A-A/G, A/A-G/G and A/G-G/G.

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Table 7.96

Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1042714

Treatment: FSC100/50

				C, C	C, G	G, G
Subjects in treatment				147	73	23
Ipratropium use	Double-blind	Baseline	n	139	70	23
			Mean	1.15	1.02	0.99
			SE	0.100	0.135	0.213
			Median	1.00	0.57	0.57
			Min.	0.0	0.0	0.0
			Max.	5.9	4.6	4.0
		Weeks 1-4	n	145	71	21
			Mean	0.63	0.54	0.63
			SE	0.063	0.088	0.177
			Median	0.29	0.21	0.39
			Min.	0.0	0.0	0.0
			Max.	2.8	3.3	2.9
		Weeks 5-8	n	141	66	21
			Mean	0.56	0.51	0.49
			SE	0.062	0.090	0.143
			Median	0.19	0.15	0.29
			Min.	0.0	0.0	0.0
			Max.	3.0	3.6	2.0
		Weeks 9-12	n	136	66	19
			Mean	0.61	0.44	0.65
			SE	0.065	0.080	0.178
			Median	0.29	0.14	0.43
			Min.	0.0	0.0	0.0
			Max.	2.9	2.5	2.1
Weeks 13-16	n	133	66	19		
	Mean	0.61	0.46	0.67		
	SE	0.067	0.089	0.199		

Table 7.96

Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1042714

Treatment: FSC100/50

				C, C	C, G	G, G
Ipratropium use	Double-blind	Weeks 13-16	Median	0.21	0.14	0.37
			Min.	0.0	0.0	0.0
			Max.	3.6	3.9	2.9
		Overall	n	145	72	22
			Mean	0.59	0.49	0.57
			SE	0.058	0.076	0.147
			Median	0.25	0.22	0.35
			Min.	0.0	0.0	0.0
			Max.	3.0	2.8	2.0
	Wash-out	Overall	n	131	66	16
			Mean	0.82	0.65	0.35
			SE	0.084	0.109	0.141
			Median	0.50	0.30	0.14
			Min.	0.0	0.0	0.0
			Max.	4.9	4.4	2.0
Ipratropium change	Double-blind	Weeks 1-4	n	138	70	21
			Mean	-0.55	-0.47	-0.42
			SE	0.095	0.103	0.183
			Median	-0.12	-0.17	-0.29
			Min.	-5.9	-4.2	-3.5
			Max.	1.9	0.9	0.8
		Weeks 5-8	n	134	65	21
			Mean	-0.62	-0.58	-0.55
			SE	0.096	0.125	0.223
			Median	-0.29	-0.29	-0.21
			Min.	-5.9	-4.2	-3.7
			Max.	1.2	1.5	0.5
		Weeks 9-12	n	129	64	19
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Table 7.96

Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1042714

Treatment: FSC100/50

				C, C	C, G	G, G
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Ipratropium change	Double-blind	Weeks 9-12	Mean	-0.56	-0.62	-0.41
			SE	0.096	0.141	0.201
			Median	-0.29	-0.29	-0.03
			Min.	-5.0	-4.1	-3.4
			Max.	2.0	1.8	0.6
		Weeks 13-16	n	126	64	19
			Mean	-0.57	-0.60	-0.39
			SE	0.095	0.129	0.209
			Median	-0.29	-0.29	-0.21
			Min.	-5.0	-4.3	-3.6
			Max.	2.0	1.3	0.6
		Overall	n	138	70	22
			Mean	-0.59	-0.54	-0.44
			SE	0.094	0.112	0.174
			Median	-0.22	-0.28	-0.25
			Min.	-5.9	-4.1	-3.5
			Max.	1.4	1.1	0.3
Wash-out	Overall	Overall	n	125	64	16
			Mean	-0.42	-0.40	-0.46
			SE	0.087	0.131	0.225
			Median	-0.14	-0.17	-0.29
			Min.	-5.0	-4.0	-2.9
			Max.	1.6	2.0	0.9

Table 7.96

Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1042714

Treatment: Salmeterol

				C, C	C, G	G, G
Subjects in treatment				133	71	25
Ipratropium use	Double-blind	Baseline	n	127	71	23
			Mean	1.09	1.11	0.92
			SE	0.098	0.159	0.262
			Median	0.71	0.57	0.29
			Min.	0.0	0.0	0.0
			Max.	4.6	6.7	4.7
		Weeks 1-4	n	127	69	25
			Mean	0.84	0.58	0.68
			SE	0.076	0.083	0.178
			Median	0.50	0.36	0.29
			Min.	0.0	0.0	0.0
			Max.	3.1	2.7	3.1
		Weeks 5-8	n	123	67	23
			Mean	0.82	0.61	0.48
			SE	0.080	0.086	0.140
			Median	0.43	0.43	0.14
			Min.	0.0	0.0	0.0
			Max.	4.4	2.8	2.0
		Weeks 9-12	n	117	66	20
			Mean	0.71	0.54	0.46
			SE	0.068	0.079	0.160
			Median	0.44	0.30	0.09
			Min.	0.0	0.0	0.0
			Max.	3.1	2.0	2.0
Weeks 13-16	n	113	64	20		
	Mean	0.66	0.53	0.51		
	SE	0.068	0.083	0.158		

Table 7.96

Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1042714

Treatment: Salmeterol

				C, C	C, G	G, G
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Ipratropium use	Double-blind	Weeks 13-16	Median	0.36	0.24	0.11
			Min.	0.0	0.0	0.0
			Max.	3.3	2.2	2.0
		Overall	n	128	70	25
			Mean	0.77	0.56	0.58
			SE	0.067	0.072	0.160
			Median	0.55	0.39	0.25
			Min.	0.0	0.0	0.0
			Max.	3.0	2.2	3.0
	Wash-out	Overall	n	109	64	20
			Mean	0.86	0.82	0.63
			SE	0.084	0.154	0.181
			Median	0.62	0.35	0.15
			Min.	0.0	0.0	0.0
			Max.	3.6	8.0	2.0
Ipratropium change	Double-blind	Weeks 1-4	n	125	69	23
			Mean	-0.25	-0.52	-0.19
			SE	0.074	0.144	0.151
			Median	0.00	-0.14	-0.04
			Min.	-3.9	-6.1	-2.2
			Max.	1.4	1.3	1.9
		Weeks 5-8	n	121	67	21
			Mean	-0.27	-0.51	-0.26
			SE	0.084	0.155	0.134
			Median	0.00	-0.05	-0.14
			Min.	-4.2	-6.2	-1.7
			Max.	2.4	2.2	1.2
		Weeks 9-12	n	116	66	18

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Table 7.96

Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1042714

Treatment: Salmeterol

				C, C	C, G	G, G
-----				-----		
Ipratropium change	Double-blind	Weeks 9-12	Mean	-0.38	-0.60	-0.38
			SE	0.077	0.146	0.119
			Median	-0.16	-0.27	-0.16
			Min.	-3.4	-6.0	-1.6
			Max.	1.2	1.1	0.2
		Weeks 13-16	n	112	64	18
			Mean	-0.45	-0.62	-0.33
			SE	0.086	0.150	0.126
			Median	-0.21	-0.24	-0.18
			Min.	-3.7	-5.4	-1.6
			Max.	1.9	1.1	0.4
		Overall	n	126	70	23
			Mean	-0.32	-0.54	-0.29
			SE	0.072	0.140	0.123
			Median	-0.05	-0.16	-0.04
			Min.	-3.6	-5.9	-1.8
			Max.	1.4	1.1	0.5
	Wash-out	Overall	n	108	64	18
			Mean	-0.20	-0.34	-0.19
			SE	0.087	0.130	0.172
			Median	0.00	-0.14	-0.14
			Min.	-4.6	-4.1	-1.6
			Max.	2.3	1.4	1.9

Table 7.97
Analysis of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1042714

				C/C vs. C/G	C/C vs. G/G	C/G vs. G/G
FSC100/50	Double-blind	Weeks 1-4	p-value	0.714	0.377	0.530
			LS Means Diff	-0.04	-0.14	-0.10
			95% CI for Diff	(-0.23,0.16)	(-0.45,0.17)	(-0.42,0.22)
		Weeks 5-8	p-value	0.825	0.878	0.991
			LS Means Diff	-0.02	-0.02	-0.00
			95% CI for Diff	(-0.22,0.18)	(-0.34,0.29)	(-0.33,0.32)
		Weeks 9-12	p-value	0.403	0.369	0.173
			LS Means Diff	0.09	-0.15	-0.24
			95% CI for Diff	(-0.12,0.29)	(-0.48,0.18)	(-0.58,0.10)
		Weeks 13-16	p-value	0.440	0.412	0.209
LS Means Diff	0.08		-0.14	-0.23		
95% CI for Diff	(-0.13,0.30)		(-0.49,0.20)	(-0.58,0.13)		
	Overall	p-value	0.928	0.438	0.422	
		LS Means Diff	0.01	-0.11	-0.12	
		95% CI for Diff	(-0.17,0.19)	(-0.39,0.17)	(-0.41,0.17)	
	Wash-out	Overall	p-value	0.627	0.251	0.393
			LS Means Diff	0.06	0.24	0.18
			95% CI for Diff	(-0.17,0.29)	(-0.17,0.64)	(-0.23,0.59)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS1042714. Least squares mean differences are calculated as C/C-C/G, C/C-G/G and C/G-G/G.

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Table 7.97
Analysis of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1042714

				C/C vs. C/G	C/C vs. G/G	C/G vs. G/G
Salmeterol Double-blind	Weeks 1-4	p-value		0.023	1.000	0.138
		LS Means Diff		0.23	-0.00	-0.23
		95% CI for Diff		(0.03, 0.43)	(-0.30, 0.30)	(-0.54, 0.07)
	Weeks 5-8	p-value		0.246	0.738	0.678
		LS Means Diff		0.13	0.06	-0.07
		95% CI for Diff		(-0.09, 0.35)	(-0.28, 0.39)	(-0.41, 0.27)
	Weeks 9-12	p-value		0.255	0.918	0.426
		LS Means Diff		0.10	-0.02	-0.12
		95% CI for Diff		(-0.07, 0.28)	(-0.30, 0.27)	(-0.41, 0.17)
	Weeks 13-16	p-value		0.373	0.636	0.307
		LS Means Diff		0.08	-0.07	-0.16
		95% CI for Diff		(-0.10, 0.27)	(-0.37, 0.23)	(-0.46, 0.15)
	Overall	p-value		0.088	0.871	0.204
		LS Means Diff		0.15	-0.02	-0.17
		95% CI for Diff		(-0.02, 0.31)	(-0.28, 0.24)	(-0.43, 0.09)
Wash-out	Overall	p-value		0.268	0.599	0.866
		LS Means Diff		0.14	0.11	-0.03
		95% CI for Diff		(-0.11, 0.40)	(-0.30, 0.52)	(-0.44, 0.37)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS1042714. Least squares mean differences are calculated as C/C-C/G, C/C-G/G and C/G-G/G.

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Table 7.98
Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1042718

Treatment: FSC100/50

				A, A	A, C	C, C
-----				-----		
Subjects in treatment				17	78	148
Ipratropium use	Double-blind	Baseline	n	15	77	140
			Mean	1.60	1.07	1.05
			SE	0.376	0.126	0.096
			Median	1.43	0.86	0.57
			Min.	0.0	0.0	0.0
			Max.	5.9	5.0	4.6
		Weeks 1-4	n	17	77	143
			Mean	0.73	0.62	0.58
			SE	0.191	0.085	0.063
			Median	0.43	0.25	0.29
			Min.	0.0	0.0	0.0
			Max.	2.0	2.7	3.3
		Weeks 5-8	n	17	73	138
			Mean	0.65	0.59	0.50
			SE	0.186	0.086	0.061
			Median	0.21	0.21	0.21
			Min.	0.0	0.0	0.0
			Max.	2.1	3.0	3.6
		Weeks 9-12	n	16	71	134
			Mean	0.68	0.64	0.51
			SE	0.188	0.091	0.061
			Median	0.46	0.29	0.20
			Min.	0.0	0.0	0.0
			Max.	2.0	2.8	2.9
		Weeks 13-16	n	15	71	132
			Mean	0.77	0.64	0.51
			SE	0.201	0.097	0.064

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Table 7.98
Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1042718

Treatment: FSC100/50

				A, A	A, C	C, C
Ipratropium use	Double-blind	Weeks 13-16	Median	0.57	0.22	0.20
			Min.	0.0	0.0	0.0
			Max.	2.0	3.6	3.9
		Overall	n	17	77	145
			Mean	0.68	0.61	0.52
			SE	0.175	0.081	0.055
			Median	0.50	0.25	0.23
			Min.	0.0	0.0	0.0
			Max.	2.0	3.0	2.8
	Wash-out	Overall	n	15	70	128
			Mean	1.29	0.73	0.67
			SE	0.351	0.088	0.083
			Median	0.93	0.57	0.29
			Min.	0.0	0.0	0.0
			Max.	4.9	2.6	4.4
Ipratropium change	Double-blind	Weeks 1-4	n	15	77	137
			Mean	-0.95	-0.45	-0.50
			SE	0.401	0.107	0.085
			Median	-0.64	-0.07	-0.21
			Min.	-5.9	-4.9	-4.2
			Max.	0.3	0.9	1.9
		Weeks 5-8	n	15	73	132
			Mean	-1.04	-0.54	-0.58
			SE	0.384	0.116	0.091
			Median	-0.79	-0.39	-0.26
			Min.	-5.9	-5.0	-4.2
			Max.	0.3	1.5	1.2
		Weeks 9-12	n	14	71	127
	[REDACTED]					

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Table 7.98
Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1042718

Treatment: FSC100/50

				A, A	A, C	C, C
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Ipratropium change	Double-blind	Weeks 9-12	Mean	-0.76	-0.47	-0.60
			SE	0.213	0.125	0.099
			Median	-0.48	-0.36	-0.21
			Min.	-2.3	-5.0	-4.1
			Max.	0.3	2.0	1.8
		Weeks 13-16	n	13	71	125
			Mean	-0.69	-0.46	-0.61
			SE	0.185	0.129	0.094
			Median	-0.50	-0.29	-0.29
			Min.	-1.7	-5.0	-4.3
			Max.	0.3	2.0	1.3
		Overall	n	15	77	138
			Mean	-1.03	-0.47	-0.56
			SE	0.384	0.109	0.085
			Median	-0.65	-0.27	-0.18
			Min.	-5.9	-5.0	-4.1
			Max.	0.3	1.1	1.4
Wash-out	Overall	Overall	n	14	70	121
			Mean	-0.32	-0.39	-0.44
			SE	0.149	0.115	0.095
			Median	-0.21	-0.21	-0.14
			Min.	-1.1	-5.0	-4.0
			Max.	0.4	2.0	1.6

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Table 7.98

Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1042718

Treatment: Salmeterol

				A, A	A, C	C, C
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Subjects in treatment				21	68	143
Ipratropium use	Double-blind	Baseline	n	20	66	138
			Mean	1.32	1.24	0.97
			SE	0.249	0.145	0.103
			Median	1.43	1.00	0.43
			Min.	0.0	0.0	0.0
			Max.	3.7	4.6	6.7
		Weeks 1-4	n	21	65	138
			Mean	1.17	0.82	0.65
			SE	0.207	0.108	0.065
			Median	1.00	0.50	0.29
			Min.	0.0	0.0	0.0
			Max.	3.1	3.0	3.1
		Weeks 5-8	n	20	63	133
			Mean	1.09	0.79	0.63
			SE	0.216	0.100	0.069
			Median	1.04	0.43	0.29
			Min.	0.0	0.0	0.0
			Max.	3.5	2.4	4.4
		Weeks 9-12	n	20	61	124
			Mean	0.94	0.76	0.52
			SE	0.169	0.094	0.060
			Median	1.00	0.50	0.23
			Min.	0.0	0.0	0.0
			Max.	2.9	2.1	3.1
		Weeks 13-16	n	18	58	122
			Mean	0.98	0.69	0.50
			SE	0.150	0.095	0.061

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Table 7.98
Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1042718

Treatment: Salmeterol

				A, A	A, C	C, C
Ipratropium use	Double-blind	Weeks 13-16	Median	1.04	0.34	0.21
			Min.	0.0	0.0	0.0
			Max.	2.4	2.2	3.3
		Overall	n	21	66	139
			Mean	1.03	0.80	0.58
			SE	0.164	0.095	0.057
			Median	1.00	0.55	0.29
			Min.	0.0	0.0	0.0
			Max.	3.0	3.0	3.0
	Wash-out	Overall	n	18	58	119
			Mean	1.36	0.89	0.71
			SE	0.196	0.122	0.095
			Median	1.26	0.52	0.29
			Min.	0.0	0.0	0.0
			Max.	3.1	3.6	8.0
Ipratropium change	Double-blind	Weeks 1-4	n	20	65	135
			Mean	-0.14	-0.42	-0.30
			SE	0.137	0.121	0.085
			Median	0.00	-0.21	0.00
			Min.	-1.6	-4.1	-6.1
			Max.	1.0	1.3	1.9
		Weeks 5-8	n	19	63	130
			Mean	-0.26	-0.44	-0.31
			SE	0.183	0.119	0.095
			Median	0.00	-0.08	-0.04
			Min.	-2.0	-4.2	-6.2
			Max.	1.3	1.1	2.4
		Weeks 9-12	n	19	61	122

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Table 7.98

Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1042718

Treatment: Salmeterol

				A, A	A, C	C, C
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Ipratropium change	Double-blind	Weeks 9-12	Mean	-0.42	-0.47	-0.46
			SE	0.170	0.108	0.092
			Median	-0.06	-0.29	-0.20
			Min.	-2.3	-2.9	-6.0
			Max.	0.5	1.1	1.2
		Weeks 13-16	n	17	58	120
			Mean	-0.44	-0.54	-0.47
			SE	0.173	0.135	0.092
			Median	-0.60	-0.25	-0.21
			Min.	-2.1	-4.2	-5.4
			Max.	0.6	1.1	1.9
		Overall	n	20	66	136
			Mean	-0.29	-0.44	-0.37
			SE	0.137	0.110	0.083
			Median	-0.11	-0.17	-0.04
			Min.	-1.7	-3.6	-5.9
			Max.	0.6	1.1	1.4
	Wash-out	Overall	n	17	58	117
			Mean	-0.05	-0.34	-0.23
			SE	0.229	0.131	0.083
			Median	0.00	-0.14	-0.07
			Min.	-1.4	-4.6	-3.7
			Max.	2.3	1.3	1.9

Table 7.99
Analysis of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1042718

				A/A vs. A/C	A/A vs. C/C	A/C vs. C/C
FSC100/50	Double-blind	Weeks 1-4	p-value	0.268	0.315	0.788
			LS Means Diff	-0.21	-0.18	0.03
			95% CI for Diff	(-0.58, 0.16)	(-0.54, 0.18)	(-0.16, 0.21)
		Weeks 5-8	p-value	0.287	0.478	0.458
			LS Means Diff	-0.20	-0.13	0.07
			95% CI for Diff	(-0.57, 0.17)	(-0.49, 0.23)	(-0.12, 0.26)
		Weeks 9-12	p-value	0.237	0.567	0.216
			LS Means Diff	-0.23	-0.11	0.12
			95% CI for Diff	(-0.62, 0.15)	(-0.49, 0.27)	(-0.07, 0.32)
		Weeks 13-16	p-value	0.707	0.742	0.157
			LS Means Diff	-0.08	0.07	0.15
			95% CI for Diff	(-0.50, 0.34)	(-0.34, 0.47)	(-0.06, 0.35)
	Wash-out	Overall	p-value	0.162	0.366	0.296
			LS Means Diff	-0.24	-0.15	0.09
			95% CI for Diff	(-0.58, 0.10)	(-0.48, 0.18)	(-0.08, 0.26)
		Overall	p-value	0.066	0.033	0.634
			LS Means Diff	0.40	0.46	0.05
			95% CI for Diff	(-0.03, 0.84)	(0.04, 0.88)	(-0.17, 0.27)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS1042718. Least squares mean differences are calculated as A/A-A/C, A/A-C/C and A/C-C/C.

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Table 7.99
Analysis of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1042718

				A/A vs. A/C	A/A vs. C/C	A/C vs. C/C
Salmeterol	Double-blind	Weeks 1-4	p-value	0.089	0.048	0.742
			LS Means Diff	0.29	0.32	0.03
			95% CI for Diff	(-0.04,0.62)	(0.00,0.64)	(-0.16,0.23)
		Weeks 5-8	p-value	0.396	0.330	0.886
			LS Means Diff	0.15	0.17	0.02
			95% CI for Diff	(-0.20,0.51)	(-0.17,0.51)	(-0.20,0.23)
	Weeks 9-12	p-value	0.712	0.203	0.152	
		LS Means Diff	0.05	0.18	0.12	
		95% CI for Diff	(-0.23,0.34)	(-0.10,0.45)	(-0.05,0.30)	
	Weeks 13-16	p-value	0.246	0.061	0.270	
		LS Means Diff	0.18	0.29	0.10	
		95% CI for Diff	(-0.13,0.50)	(-0.01,0.59)	(-0.08,0.28)	
Wash-out	Overall	p-value	0.379	0.118	0.290	
		LS Means Diff	0.13	0.21	0.09	
		95% CI for Diff	(-0.15,0.41)	(-0.05,0.48)	(-0.08,0.25)	
	Overall	p-value	0.039	0.020	0.743	
		LS Means Diff	0.44	0.48	0.04	
		95% CI for Diff	(0.02,0.86)	(0.08,0.88)	(-0.20,0.28)	

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS1042718. Least squares mean differences are calculated as A/A-A/C, A/A-C/C and A/C-C/C.

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Table 7.100

Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1042719

Treatment: FSC100/50

100100/00

				C, C	C, G	G, G
Subjects in treatment				28	99	116
Ipratropium use	Double-blind	Baseline	n	26	97	109
			Mean	1.57	1.11	0.97
			SE	0.246	0.122	0.100
			Median	1.57	0.86	0.57
			Min.	0.0	0.0	0.0
			Max.	5.9	5.0	4.6
			Weeks 1-4	n	28	98
		Mean		0.76	0.57	0.59
		SE		0.154	0.068	0.076
		Median		0.46	0.29	0.21
		Min.		0.0	0.0	0.0
		Max.		2.4	2.7	3.3
		Weeks 5-8		n	27	93
			Mean	0.71	0.54	0.49
			SE	0.153	0.071	0.071
			Median	0.30	0.29	0.14
			Min.	0.0	0.0	0.0
			Max.	2.1	3.0	3.6
			Weeks 9-12	n	26	91
		Mean		0.87	0.53	0.52
		SE		0.163	0.070	0.072
		Median		0.66	0.29	0.14
		Min.		0.0	0.0	0.0
		Max.		2.4	2.8	2.9
		Weeks 13-16		n	26	90
			Mean	0.90	0.53	0.52
			SE	0.180	0.073	0.077

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Table 7.100

Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1042719

Treatment: FSC100/50

				C, C	C, G	G, G

Ipratropium use	Double-blind	Weeks 13-16	Median	0.64	0.21	0.14
			Min.	0.0	0.0	0.0
			Max.	3.4	3.6	3.9
		Overall	n	28	98	113
			Mean	0.77	0.53	0.53
			SE	0.145	0.064	0.065
			Median	0.53	0.25	0.22
			Min.	0.0	0.0	0.0
			Max.	2.2	3.0	2.8
	Wash-out	Overall	n	26	87	100
			Mean	1.12	0.73	0.64
			SE	0.229	0.090	0.090
			Median	0.82	0.43	0.25
			Min.	0.0	0.0	0.0
			Max.	4.9	3.9	4.4
Ipratropium change	Double-blind	Weeks 1-4	n	26	97	106
			Mean	-0.85	-0.53	-0.41
			SE	0.244	0.110	0.085
			Median	-0.50	-0.11	-0.14
			Min.	-5.9	-4.9	-3.1
			Max.	0.3	0.9	1.9
		Weeks 5-8	n	25	92	103
			Mean	-0.90	-0.62	-0.51
			SE	0.244	0.118	0.095
			Median	-0.76	-0.29	-0.21
			Min.	-5.9	-5.0	-4.0
			Max.	0.3	1.5	1.2
		Weeks 9-12	n	24	90	98

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Table 7.100

Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1042719

Treatment: FSC100/50

				C, C	C, G	G, G
-----				-----		
Ipratropium change	Double-blind	Weeks 9-12	Mean	-0.57	-0.59	-0.53
			SE	0.187	0.119	0.108
			Median	-0.43	-0.29	-0.21
			Min.	-2.3	-5.0	-4.1
			Max.	2.0	1.8	1.8
		Weeks 13-16	n	24	89	96
			Mean	-0.51	-0.61	-0.54
			SE	0.193	0.123	0.098
			Median	-0.43	-0.29	-0.25
			Min.	-2.2	-5.0	-4.0
			Max.	2.0	1.3	1.1
		Overall	n	26	97	107
			Mean	-0.85	-0.57	-0.48
			SE	0.248	0.109	0.088
			Median	-0.50	-0.23	-0.13
			Min.	-5.9	-5.0	-3.8
			Max.	1.0	1.1	1.4
	Wash-out	Overall	n	25	86	94
			Mean	-0.40	-0.39	-0.44
			SE	0.117	0.112	0.106
			Median	-0.29	-0.14	-0.10
			Min.	-1.9	-5.0	-4.0
			Max.	0.4	2.0	1.6

Table 7.100

Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1042719

Treatment: Salmeterol

				C, C	C, G	G, G
Subjects in treatment				25	90	117
Ipratropium use	Double-blind	Baseline	n	24	88	112
			Mean	1.42	1.12	0.97
			SE	0.240	0.122	0.116
			Median	1.43	0.77	0.43
			Min.	0.0	0.0	0.0
			Max.	4.0	4.6	6.7
		Weeks 1-4	n	25	87	112
			Mean	1.15	0.73	0.68
			SE	0.182	0.089	0.074
			Median	1.00	0.32	0.36
			Min.	0.0	0.0	0.0
			Max.	3.1	3.0	3.1
		Weeks 5-8	n	24	84	108
			Mean	1.07	0.70	0.66
			SE	0.186	0.084	0.079
			Median	0.89	0.33	0.29
			Min.	0.0	0.0	0.0
			Max.	3.5	2.4	4.4
		Weeks 9-12	n	24	81	100
			Mean	0.94	0.66	0.53
			SE	0.149	0.081	0.067
			Median	1.00	0.36	0.29
			Min.	0.0	0.0	0.0
			Max.	2.9	2.5	3.1
Weeks 13-16	n	21	79	98		
	Mean	0.96	0.63	0.50		
	SE	0.149	0.081	0.067		

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Table 7.100

Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1042719

Treatment: Salmeterol

				C, C	C, G	G, G
Ipratropium use	Double-blind	Weeks 13-16	Median	1.00	0.29	0.21
			Min.	0.0	0.0	0.0
			Max.	2.4	2.3	3.3
		Overall	n	25	88	113
			Mean	1.01	0.71	0.59
			SE	0.147	0.080	0.065
			Median	0.92	0.38	0.29
			Min.	0.0	0.0	0.0
			Max.	3.0	3.0	3.0
	Wash-out	Overall	n	21	79	95
			Mean	1.38	0.86	0.67
			SE	0.175	0.107	0.107
			Median	1.36	0.43	0.29
			Min.	0.0	0.0	0.0
			Max.	3.1	3.6	8.0
Ipratropium change	Double-blind	Weeks 1-4	n	24	87	109
			Mean	-0.26	-0.39	-0.28
			SE	0.149	0.100	0.097
			Median	0.00	-0.18	0.00
			Min.	-2.2	-4.1	-6.1
			Max.	1.0	1.3	1.9
		Weeks 5-8	n	23	84	105
			Mean	-0.37	-0.42	-0.28
			SE	0.186	0.101	0.108
			Median	0.00	-0.05	-0.07
			Min.	-2.5	-4.2	-6.2
			Max.	1.3	1.6	2.4
		Weeks 9-12	n	23	81	98

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Table 7.100

Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1042719

Treatment: Salmeterol

				C, C	C, G	G, G
Ipratropium change	Double-blind	Weeks 9-12	Mean	-0.51	-0.46	-0.44
			SE	0.163	0.093	0.106
			Median	-0.24	-0.21	-0.20
			Min.	-2.3	-2.9	-6.0
			Max.	0.4	1.1	1.2
		Weeks 13-16	n	20	79	96
			Mean	-0.63	-0.49	-0.47
			SE	0.169	0.112	0.106
			Median	-0.62	-0.21	-0.18
			Min.	-2.1	-4.2	-5.4
		Max.	0.3	1.9	1.2	
		Overall	n	24	88	110
			Mean	-0.40	-0.41	-0.35
			SE	0.145	0.093	0.095
			Median	-0.24	-0.14	-0.06
			Min.	-2.3	-3.6	-5.9
		Max.	0.6	1.4	1.3	
Wash-out	Overall	n	20	79	93	
		Mean	-0.18	-0.25	-0.26	
		SE	0.215	0.108	0.095	
		Median	0.00	-0.14	-0.07	
		Min.	-2.0	-4.6	-3.7	
		Max.	2.3	1.7	1.9	

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Table 7.101
Analysis of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1042719

				C/C vs. C/G	C/C vs. G/G	C/G vs. G/G	
FSC100/50	Double-blind	Weeks 1-4	p-value	0.887	0.557	0.482	
			LS Means Diff	-0.02	-0.09	-0.06	
			95% CI for Diff	(-0.31,0.27)	(-0.37,0.20)	(-0.25,0.12)	
		Weeks 5-8	p-value	0.973	0.977	0.920	
			LS Means Diff	-0.01	0.00	0.01	
	95% CI for Diff		(-0.30,0.29)	(-0.29,0.30)	(-0.18,0.20)		
	Weeks 9-12	p-value	0.231	0.187	0.854		
		LS Means Diff	0.18	0.20	0.02		
		95% CI for Diff	(-0.12,0.48)	(-0.10,0.50)	(-0.17,0.21)		
	Weeks 13-16	p-value	0.121	0.111	0.953		
LS Means Diff		0.25	0.25	0.01			
95% CI for Diff		(-0.07,0.56)	(-0.06,0.57)	(-0.19,0.21)			
	Overall	p-value	0.735	0.781	0.922		
		LS Means Diff	0.04	0.04	-0.01		
		95% CI for Diff	(-0.22,0.31)	(-0.22,0.30)	(-0.17,0.16)		
		Wash-out	Overall	p-value	0.166	0.053	0.403
				LS Means Diff	0.23	0.33	0.09
	95% CI for Diff			(-0.10,0.57)	(-0.00,0.66)	(-0.12,0.31)	

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS1042719. Least squares mean differences are calculated as C/C-C/G, C/C-G/G and C/G-G/G.

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Table 7.101
Analysis of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1042719

				C/C vs. C/G	C/C vs. G/G	C/G vs. G/G
Salmeterol	Double-blind	Weeks 1-4	p-value	0.067	0.076	0.889
			LS Means Diff	0.28	0.27	-0.01
			95% CI for Diff	(-0.02, 0.59)	(-0.03, 0.57)	(-0.20, 0.17)
		Weeks 5-8	p-value	0.261	0.361	0.710
			LS Means Diff	0.19	0.15	-0.04
			95% CI for Diff	(-0.14, 0.51)	(-0.17, 0.47)	(-0.24, 0.16)
		Weeks 9-12	p-value	0.458	0.177	0.352
			LS Means Diff	0.10	0.18	0.08
			95% CI for Diff	(-0.16, 0.36)	(-0.08, 0.43)	(-0.09, 0.24)
		Weeks 13-16	p-value	0.316	0.098	0.300
			LS Means Diff	0.15	0.24	0.09
			95% CI for Diff	(-0.14, 0.43)	(-0.04, 0.52)	(-0.08, 0.26)
	Wash-out	Overall	p-value	0.301	0.135	0.476
			LS Means Diff	0.13	0.19	0.06
			95% CI for Diff	(-0.12, 0.39)	(-0.06, 0.44)	(-0.10, 0.21)
		Overall	p-value	0.083	0.026	0.439
			LS Means Diff	0.34	0.43	0.09
			95% CI for Diff	(-0.04, 0.72)	(0.05, 0.81)	(-0.14, 0.32)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS1042719. Least squares mean differences are calculated as C/C-C/G, C/C-G/G and C/G-G/G.

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Table 7.102

Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS17778257

Treatment: FSC100/50

				A, A	A, T	T, T
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Subjects in treatment				100	88	55
Ipratropium use	Double-blind	Baseline	n	96	84	52
			Mean	1.05	1.21	1.00
			SE	0.107	0.140	0.153
			Median	0.86	0.86	0.57
			Min.	0.0	0.0	0.0
			Max.	5.9	5.0	4.0
		Weeks 1-4	n	96	86	55
			Mean	0.62	0.70	0.43
			SE	0.074	0.090	0.086
			Median	0.35	0.29	0.15
			Min.	0.0	0.0	0.0
			Max.	2.9	3.3	2.8
		Weeks 5-8	n	93	83	52
			Mean	0.55	0.61	0.41
			SE	0.068	0.093	0.087
			Median	0.29	0.14	0.09
			Min.	0.0	0.0	0.0
			Max.	2.5	3.6	2.5
		Weeks 9-12	n	87	85	49
			Mean	0.61	0.61	0.40
			SE	0.078	0.086	0.085
			Median	0.36	0.18	0.14
			Min.	0.0	0.0	0.0
			Max.	2.5	2.9	2.4
		Weeks 13-16	n	86	83	49
			Mean	0.60	0.66	0.36
			SE	0.083	0.093	0.082

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Table 7.102

Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS17778257

Treatment: FSC100/50

				A, A	A, T	T, T

Ipratropium use	Double-blind	Weeks 13-16	Median	0.29	0.27	0.11
			Min.	0.0	0.0	0.0
			Max.	3.4	3.9	2.2
		Overall	n	97	87	55
			Mean	0.58	0.64	0.40
			SE	0.066	0.083	0.074
			Median	0.35	0.23	0.22
			Min.	0.0	0.0	0.0
			Max.	2.2	3.0	2.3
	Wash-out	Overall	n	84	80	49
			Mean	0.75	0.85	0.52
			SE	0.096	0.117	0.105
			Median	0.54	0.35	0.15
			Min.	0.0	0.0	0.0
			Max.	4.9	4.4	3.6
Ipratropium change	Double-blind	Weeks 1-4	n	93	84	52
			Mean	-0.47	-0.53	-0.55
			SE	0.097	0.118	0.148
			Median	-0.21	-0.13	-0.16
			Min.	-5.9	-4.9	-3.6
			Max.	1.9	0.9	0.9
		Weeks 5-8	n	90	81	49
			Mean	-0.57	-0.66	-0.55
			SE	0.109	0.120	0.160
			Median	-0.29	-0.29	-0.21
			Min.	-5.9	-5.0	-4.0
			Max.	1.5	1.1	1.2
		Weeks 9-12	n	84	82	46

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Table 7.102

Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS17778257

Treatment: FSC100/50

				A, A	A, T	T, T
-----				-----		
Ipratropium change	Double-blind	Weeks 9-12	Mean	-0.45	-0.67	-0.59
			SE	0.101	0.130	0.169
			Median	-0.25	-0.34	-0.14
			Min.	-3.9	-5.0	-4.0
			Max.	1.8	2.0	1.7
		Weeks 13-16	n	83	80	46
			Mean	-0.47	-0.63	-0.63
			SE	0.099	0.131	0.155
			Median	-0.29	-0.29	-0.18
			Min.	-3.9	-5.0	-4.0
			Max.	1.3	2.0	0.5
		Overall	n	94	84	52
			Mean	-0.51	-0.61	-0.58
			SE	0.099	0.117	0.150
			Median	-0.29	-0.26	-0.17
			Min.	-5.9	-5.0	-3.8
			Max.	1.4	1.0	0.9
	Wash-out	Overall	n	81	78	46
			Mean	-0.32	-0.48	-0.48
			SE	0.091	0.128	0.147
			Median	-0.19	-0.14	-0.13
			Min.	-3.1	-5.0	-4.0
			Max.	2.0	1.6	0.7

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Table 7.102

Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS17778257

Treatment: Salmeterol

				A, A	A, T	T, T
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Subjects in treatment				100	86	46
Ipratropium use	Double-blind	Baseline	n	95	84	45
			Mean	1.16	1.07	0.93
			SE	0.130	0.133	0.144
			Median	0.57	0.64	0.57
			Min.	0.0	0.0	0.0
			Max.	4.7	6.7	4.0
		Weeks 1-4	n	97	83	44
			Mean	0.76	0.73	0.75
			SE	0.088	0.089	0.116
			Median	0.43	0.46	0.33
			Min.	0.0	0.0	0.0
			Max.	3.1	3.0	2.3
		Weeks 5-8	n	93	81	42
			Mean	0.74	0.70	0.72
			SE	0.084	0.096	0.118
			Median	0.43	0.29	0.29
			Min.	0.0	0.0	0.0
			Max.	3.5	4.4	2.5
		Weeks 9-12	n	90	75	40
			Mean	0.73	0.56	0.55
			SE	0.084	0.074	0.098
			Median	0.37	0.36	0.36
			Min.	0.0	0.0	0.0
			Max.	3.1	2.5	2.5
		Weeks 13-16	n	87	72	39
			Mean	0.70	0.53	0.52
			SE	0.082	0.074	0.108

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Table 7.102

Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS17778257

Treatment: Salmeterol

				A, A	A, T	T, T
Ipratropium use	Double-blind	Weeks 13-16	Median	0.37	0.21	0.24
			Min.	0.0	0.0	0.0
			Max.	3.3	2.0	2.3
		Overall	n	98	84	44
			Mean	0.74	0.64	0.65
			SE	0.077	0.078	0.100
			Median	0.48	0.38	0.32
			Min.	0.0	0.0	0.0
			Max.	3.0	3.0	2.3
	Wash-out	Overall	n	86	70	39
			Mean	0.89	0.80	0.71
			SE	0.096	0.142	0.137
			Median	0.57	0.43	0.43
			Min.	0.0	0.0	0.0
			Max.	3.1	8.0	3.1
Ipratropium change	Double-blind	Weeks 1-4	n	94	82	44
			Mean	-0.39	-0.34	-0.16
			SE	0.097	0.121	0.099
			Median	-0.07	-0.04	0.00
			Min.	-4.1	-6.1	-2.2
			Max.	1.9	1.3	1.4
		Weeks 5-8	n	90	80	42
			Mean	-0.39	-0.37	-0.20
			SE	0.096	0.134	0.130
			Median	-0.11	-0.04	-0.02
			Min.	-4.2	-6.2	-2.5
			Max.	1.3	2.4	1.6
		Weeks 9-12	n	87	75	40

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Table 7.102

Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS17778257

Treatment: Salmeterol

				A, A	A, T	T, T
-----				-----		
Ipratropium change	Double-blind	Weeks 9-12	Mean	-0.44	-0.54	-0.34
			SE	0.089	0.128	0.128
			Median	-0.18	-0.25	-0.04
			Min.	-2.9	-6.0	-2.3
			Max.	1.2	0.9	1.1
		Weeks 13-16	n	84	72	39
			Mean	-0.48	-0.56	-0.40
			SE	0.103	0.128	0.148
			Median	-0.25	-0.22	-0.07
			Min.	-4.2	-5.4	-2.3
			Max.	1.1	1.0	1.9
		Overall	n	95	83	44
			Mean	-0.41	-0.42	-0.25
			SE	0.087	0.117	0.114
			Median	-0.14	-0.13	-0.02
			Min.	-3.6	-5.9	-2.3
			Max.	1.1	0.9	1.4
	Wash-out	Overall	n	83	70	39
			Mean	-0.25	-0.28	-0.20
			SE	0.112	0.107	0.132
			Median	-0.07	-0.14	0.00
			Min.	-4.6	-3.7	-2.3
			Max.	2.3	1.4	1.7

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Table 7.103
Analysis of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS17778257

				A/A vs. A/T	A/A vs. T/T	A/T vs. T/T
FSC100/50	Double-blind	Weeks 1-4	p-value	0.626	0.294	0.148
			LS Means Diff	-0.05	0.12	0.17
			95% CI for Diff	(-0.24, 0.15)	(-0.10, 0.34)	(-0.06, 0.40)
		Weeks 5-8	p-value	0.816	0.537	0.421
			LS Means Diff	-0.02	0.07	0.10
	Wash-out	Weeks 9-12	95% CI for Diff	(-0.22, 0.18)	(-0.16, 0.30)	(-0.14, 0.33)
			p-value	0.647	0.228	0.412
			LS Means Diff	0.05	0.15	0.10
		Weeks 13-16	95% CI for Diff	(-0.16, 0.25)	(-0.09, 0.39)	(-0.14, 0.34)
			p-value	0.923	0.157	0.182
	Double-blind	Weeks 1-4	LS Means Diff	0.01	0.18	0.17
			95% CI for Diff	(-0.20, 0.23)	(-0.07, 0.44)	(-0.08, 0.43)
		Weeks 5-8	p-value	0.839	0.249	0.192
			LS Means Diff	-0.02	0.12	0.14
		Weeks 9-12	95% CI for Diff	(-0.19, 0.16)	(-0.08, 0.32)	(-0.07, 0.35)
	Wash-out	Weeks 13-16	p-value	0.764	0.146	0.229
			LS Means Diff	0.04	0.20	0.17
			95% CI for Diff	(-0.20, 0.27)	(-0.07, 0.48)	(-0.11, 0.44)
		Overall	p-value			
			LS Means Diff			

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS17778257. Least squares mean differences are calculated as A/A-A/T, A/A-T/T and A/T-T/T.

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Table 7.103
Analysis of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS17778257

				A/A vs. A/T	A/A vs. T/T	A/T vs. T/T
Salmeterol	Double-blind	Weeks 1-4	p-value	0.939	0.380	0.415
			LS Means Diff	-0.01	-0.11	-0.10
			95% CI for Diff	(-0.21, 0.19)	(-0.35, 0.13)	(-0.34, 0.14)
		Weeks 5-8	p-value	0.966	0.600	0.622
			LS Means Diff	-0.00	-0.07	-0.06
	Wash-out	Weeks 9-12	95% CI for Diff	(-0.22, 0.21)	(-0.33, 0.19)	(-0.32, 0.19)
			p-value	0.130	0.616	0.455
			LS Means Diff	0.13	0.05	-0.08
		Weeks 13-16	95% CI for Diff	(-0.04, 0.31)	(-0.16, 0.27)	(-0.29, 0.13)
			p-value	0.144	0.535	0.558
	Double-blind	Weeks 1-4	LS Means Diff	0.14	0.07	-0.07
			95% CI for Diff	(-0.05, 0.32)	(-0.15, 0.29)	(-0.29, 0.16)
		Weeks 5-8	p-value	0.570	0.696	0.393
			LS Means Diff	0.05	-0.04	-0.09
	Wash-out	Weeks 9-12	95% CI for Diff	(-0.12, 0.21)	(-0.24, 0.16)	(-0.29, 0.11)
			p-value	0.810	0.977	0.865
			LS Means Diff	0.03	0.00	-0.03
		Weeks 13-16	95% CI for Diff	(-0.22, 0.28)	(-0.30, 0.31)	(-0.33, 0.28)
			p-value	0.810	0.977	0.865
		Overall	LS Means Diff	0.03	0.00	-0.03

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS17778257. Least squares mean differences are calculated as A/A-A/T, A/A-T/T and A/T-T/T.

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Table 7.104

Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS11168070

Treatment: FSC100/50

				C, C	C, G	G, G
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Subjects in treatment				147	73	23
Ipratropium use	Double-blind	Baseline	n	139	70	23
			Mean	1.15	1.02	0.99
			SE	0.100	0.135	0.213
			Median	1.00	0.57	0.57
			Min.	0.0	0.0	0.0
			Max.	5.9	4.6	4.0
		Weeks 1-4	n	145	71	21
			Mean	0.63	0.54	0.63
			SE	0.063	0.088	0.177
			Median	0.29	0.21	0.39
			Min.	0.0	0.0	0.0
			Max.	2.8	3.3	2.9
		Weeks 5-8	n	141	66	21
			Mean	0.56	0.51	0.49
			SE	0.062	0.090	0.143
			Median	0.19	0.15	0.29
			Min.	0.0	0.0	0.0
			Max.	3.0	3.6	2.0
		Weeks 9-12	n	136	66	19
			Mean	0.61	0.44	0.65
			SE	0.065	0.080	0.178
			Median	0.29	0.14	0.43
			Min.	0.0	0.0	0.0
			Max.	2.9	2.5	2.1
		Weeks 13-16	n	133	66	19
			Mean	0.61	0.46	0.67
			SE	0.067	0.089	0.199

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Table 7.104

Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS11168070

Treatment: FSC100/50

				C, C	C, G	G, G
Ipratropium use	Double-blind	Weeks 13-16	Median	0.21	0.14	0.37
			Min.	0.0	0.0	0.0
			Max.	3.6	3.9	2.9
		Overall	n	145	72	22
			Mean	0.59	0.49	0.57
			SE	0.058	0.076	0.147
			Median	0.25	0.22	0.35
			Min.	0.0	0.0	0.0
			Max.	3.0	2.8	2.0
	Wash-out	Overall	n	131	66	16
			Mean	0.82	0.65	0.35
			SE	0.084	0.109	0.141
			Median	0.50	0.30	0.14
			Min.	0.0	0.0	0.0
			Max.	4.9	4.4	2.0
Ipratropium change	Double-blind	Weeks 1-4	n	138	70	21
			Mean	-0.55	-0.47	-0.42
			SE	0.095	0.103	0.183
			Median	-0.12	-0.17	-0.29
			Min.	-5.9	-4.2	-3.5
			Max.	1.9	0.9	0.8
		Weeks 5-8	n	134	65	21
			Mean	-0.62	-0.58	-0.55
			SE	0.096	0.125	0.223
			Median	-0.29	-0.29	-0.21
			Min.	-5.9	-4.2	-3.7
			Max.	1.2	1.5	0.5
		Weeks 9-12	n	129	64	19
		[REDACTED]				

Table 7.104

Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS11168070

Treatment: FSC100/50

				C, C	C, G	G, G
Ipratropium change	Double-blind	Weeks 9-12	Mean	-0.56	-0.62	-0.41
			SE	0.096	0.141	0.201
			Median	-0.29	-0.29	-0.03
			Min.	-5.0	-4.1	-3.4
			Max.	2.0	1.8	0.6
		Weeks 13-16	n	126	64	19
			Mean	-0.57	-0.60	-0.39
			SE	0.095	0.129	0.209
			Median	-0.29	-0.29	-0.21
			Min.	-5.0	-4.3	-3.6
		Max.	2.0	1.3	0.6	
		Overall	n	138	70	22
			Mean	-0.59	-0.54	-0.44
			SE	0.094	0.112	0.174
			Median	-0.22	-0.28	-0.25
			Min.	-5.9	-4.1	-3.5
		Max.	1.4	1.1	0.3	
		Wash-out	Overall	n	125	64
Mean	-0.42			-0.40	-0.46	
SE	0.087			0.131	0.225	
Median	-0.14			-0.17	-0.29	
Min.	-5.0			-4.0	-2.9	
Max.	1.6			2.0	0.9	

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Table 7.104

Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS11168070

Treatment: Salmeterol

				C, C	C, G	G, G
-----				-----		
Subjects in treatment				136	71	25
Ipratropium use	Double-blind	Baseline	n	130	71	23
			Mean	1.09	1.11	0.92
			SE	0.096	0.159	0.262
			Median	0.79	0.57	0.29
			Min.	0.0	0.0	0.0
			Max.	4.6	6.7	4.7
		Weeks 1-4	n	130	69	25
			Mean	0.85	0.58	0.68
			SE	0.076	0.083	0.178
			Median	0.50	0.36	0.29
			Min.	0.0	0.0	0.0
			Max.	3.1	2.7	3.1
		Weeks 5-8	n	126	67	23
			Mean	0.82	0.61	0.48
			SE	0.079	0.086	0.140
			Median	0.43	0.43	0.14
			Min.	0.0	0.0	0.0
			Max.	4.4	2.8	2.0
		Weeks 9-12	n	119	66	20
			Mean	0.71	0.54	0.46
			SE	0.068	0.079	0.160
			Median	0.44	0.30	0.09
			Min.	0.0	0.0	0.0
			Max.	3.1	2.0	2.0
		Weeks 13-16	n	114	64	20
			Mean	0.65	0.53	0.51
			SE	0.068	0.083	0.158

Table 7.104

Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS11168070

Treatment: Salmeterol

				C, C	C, G	G, G
Ipratropium use	Double-blind	Weeks 13-16	Median	0.34	0.24	0.11
			Min.	0.0	0.0	0.0
			Max.	3.3	2.2	2.0
		Overall	n	131	70	25
			Mean	0.77	0.56	0.58
			SE	0.067	0.072	0.160
			Median	0.55	0.39	0.25
			Min.	0.0	0.0	0.0
			Max.	3.0	2.2	3.0
	Wash-out	Overall	n	111	64	20
			Mean	0.86	0.82	0.63
			SE	0.083	0.154	0.181
			Median	0.62	0.35	0.15
			Min.	0.0	0.0	0.0
			Max.	3.6	8.0	2.0
Ipratropium change	Double-blind	Weeks 1-4	n	128	69	23
			Mean	-0.24	-0.52	-0.19
			SE	0.073	0.144	0.151
			Median	0.00	-0.14	-0.04
			Min.	-3.9	-6.1	-2.2
			Max.	1.4	1.3	1.9
		Weeks 5-8	n	124	67	21
			Mean	-0.27	-0.51	-0.26
			SE	0.082	0.155	0.134
			Median	0.00	-0.05	-0.14
			Min.	-4.2	-6.2	-1.7
			Max.	2.4	2.2	1.2
		Weeks 9-12	n	118	66	18

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Table 7.104

Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS11168070

Treatment: Salmeterol

				C, C	C, G	G, G
-----				-----		
Ipratropium change	Double-blind	Weeks 9-12	Mean	-0.39	-0.60	-0.38
			SE	0.075	0.146	0.119
			Median	-0.20	-0.27	-0.16
			Min.	-3.4	-6.0	-1.6
			Max.	1.2	1.1	0.2
		Weeks 13-16	n	113	64	18
			Mean	-0.45	-0.62	-0.33
			SE	0.085	0.150	0.126
			Median	-0.21	-0.24	-0.18
			Min.	-3.7	-5.4	-1.6
			Max.	1.9	1.1	0.4
		Overall	n	129	70	23
			Mean	-0.31	-0.54	-0.29
			SE	0.070	0.140	0.123
			Median	-0.07	-0.16	-0.04
			Min.	-3.6	-5.9	-1.8
			Max.	1.4	1.1	0.5
	Wash-out	Overall	n	110	64	18
			Mean	-0.21	-0.34	-0.19
			SE	0.086	0.130	0.172
			Median	-0.02	-0.14	-0.14
			Min.	-4.6	-4.1	-1.6
			Max.	2.3	1.4	1.9

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Table 7.105
Analysis of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS11168070

				C/C vs. C/G	C/C vs. G/G	C/G vs. G/G
FSC100/50	Double-blind	Weeks 1-4	p-value	0.714	0.377	0.530
			LS Means Diff	-0.04	-0.14	-0.10
			95% CI for Diff	(-0.23,0.16)	(-0.45,0.17)	(-0.42,0.22)
		Weeks 5-8	p-value	0.825	0.878	0.991
			LS Means Diff	-0.02	-0.02	-0.00
	95% CI for Diff		(-0.22,0.18)	(-0.34,0.29)	(-0.33,0.32)	
	Weeks 9-12	p-value	0.403	0.369	0.173	
		LS Means Diff	0.09	-0.15	-0.24	
		95% CI for Diff	(-0.12,0.29)	(-0.48,0.18)	(-0.58,0.10)	
	Weeks 13-16	p-value	0.440	0.412	0.209	
LS Means Diff		0.08	-0.14	-0.23		
95% CI for Diff		(-0.13,0.30)	(-0.49,0.20)	(-0.58,0.13)		
Wash-out	Overall	p-value	0.928	0.438	0.422	
		LS Means Diff	0.01	-0.11	-0.12	
		95% CI for Diff	(-0.17,0.19)	(-0.39,0.17)	(-0.41,0.17)	
	Overall	p-value	0.627	0.251	0.393	
		LS Means Diff	0.06	0.24	0.18	
95% CI for Diff		(-0.17,0.29)	(-0.17,0.64)	(-0.23,0.59)		

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS11168070. Least squares mean differences are calculated as C/C-C/G, C/C-G/G and C/G-G/G.

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Table 7.105
Analysis of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS11168070

				C/C vs. C/G	C/C vs. G/G	C/G vs. G/G
Salmeterol	Double-blind	Weeks 1-4	p-value	0.019	0.958	0.140
			LS Means Diff	0.24	0.01	-0.23
			95% CI for Diff	(0.04,0.44)	(-0.30,0.31)	(-0.54,0.08)
		Weeks 5-8	p-value	0.235	0.729	0.674
			LS Means Diff	0.13	0.06	-0.07
			95% CI for Diff	(-0.09,0.35)	(-0.27,0.39)	(-0.41,0.27)
		Weeks 9-12	p-value	0.261	0.915	0.430
			LS Means Diff	0.10	-0.02	-0.12
			95% CI for Diff	(-0.08,0.28)	(-0.30,0.27)	(-0.41,0.17)
		Weeks 13-16	p-value	0.389	0.627	0.309
			LS Means Diff	0.08	-0.07	-0.16
			95% CI for Diff	(-0.11,0.27)	(-0.38,0.23)	(-0.46,0.15)
		Overall	p-value	0.080	0.894	0.205
	LS Means Diff		0.15	-0.02	-0.17	
95% CI for Diff	(-0.02,0.32)		(-0.27,0.24)	(-0.43,0.09)		
Wash-out	Overall	p-value	0.271	0.600	0.869	
		LS Means Diff	0.14	0.11	-0.03	
		95% CI for Diff	(-0.11,0.40)	(-0.30,0.51)	(-0.44,0.37)	

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS11168070. Least squares mean differences are calculated as C/C-C/G, C/C-G/G and C/G-G/G.

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Table 7.106

Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS9325122

Treatment: FSC100/50

				C, C	C, T	T, T
-----				-----		
Subjects in treatment				23	65	145
Ipratropium use	Double-blind	Baseline	n	23	62	137
			Mean	0.85	0.96	1.17
			SE	0.169	0.129	0.101
			Median	0.43	0.57	1.00
			Min.	0.0	0.0	0.0
			Max.	2.9	4.3	5.9
		Weeks 1-4	n	21	63	143
			Mean	0.62	0.49	0.64
			SE	0.178	0.082	0.063
			Median	0.37	0.14	0.29
			Min.	0.0	0.0	0.0
			Max.	2.9	2.3	2.8
		Weeks 5-8	n	21	58	139
			Mean	0.49	0.48	0.57
			SE	0.144	0.085	0.063
			Median	0.29	0.14	0.21
			Min.	0.0	0.0	0.0
			Max.	2.0	2.5	3.0
		Weeks 9-12	n	19	58	134
			Mean	0.64	0.46	0.61
			SE	0.178	0.090	0.065
			Median	0.36	0.14	0.29
			Min.	0.0	0.0	0.0
			Max.	2.1	2.5	2.9
		Weeks 13-16	n	19	59	131
			Mean	0.67	0.41	0.60
			SE	0.199	0.080	0.067

Table 7.106

Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS9325122

Treatment: FSC100/50

				C, C	C, T	T, T
Ipratropium use	Double-blind	Weeks 13-16	Median	0.32	0.14	0.21
			Min.	0.0	0.0	0.0
			Max.	2.9	2.3	3.6
		Overall	n	22	64	143
			Mean	0.57	0.47	0.59
			SE	0.147	0.077	0.058
			Median	0.31	0.16	0.25
			Min.	0.0	0.0	0.0
			Max.	2.0	2.2	3.0
	Wash-out	Overall	n	17	59	129
			Mean	0.37	0.57	0.83
			SE	0.130	0.097	0.085
			Median	0.22	0.29	0.57
			Min.	0.0	0.0	0.0
			Max.	2.0	2.6	4.9
Ipratropium change	Double-blind	Weeks 1-4	n	21	62	136
			Mean	-0.28	-0.46	-0.56
			SE	0.107	0.112	0.097
			Median	-0.21	-0.21	-0.18
			Min.	-1.6	-4.2	-5.9
			Max.	0.8	0.9	1.9
		Weeks 5-8	n	21	57	132
			Mean	-0.41	-0.55	-0.63
			SE	0.164	0.130	0.097
			Median	-0.14	-0.29	-0.29
			Min.	-2.9	-4.2	-5.9
			Max.	0.5	1.5	1.2
		Weeks 9-12	n	19	56	127

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Table 7.106

Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS9325122

Treatment: FSC100/50

				C, C	C, T	T, T
-----				-----		
Ipratropium change	Double-blind	Weeks 9-12	Mean	-0.25	-0.54	-0.58
			SE	0.124	0.132	0.095
			Median	0.00	-0.29	-0.29
			Min.	-1.6	-3.6	-5.0
			Max.	0.6	1.8	1.8
		Weeks 13-16	n	19	57	124
			Mean	-0.22	-0.58	-0.60
			SE	0.122	0.131	0.095
			Median	0.00	-0.29	-0.29
			Min.	-1.4	-4.3	-5.0
			Max.	0.6	1.3	1.3
		Overall	n	22	62	136
			Mean	-0.30	-0.51	-0.61
			SE	0.101	0.115	0.095
			Median	-0.17	-0.28	-0.23
			Min.	-1.6	-4.1	-5.9
			Max.	0.3	1.1	1.4
	Wash-out	Overall	n	17	57	123
			Mean	-0.44	-0.41	-0.42
			SE	0.219	0.134	0.088
			Median	-0.29	-0.23	-0.14
			Min.	-2.9	-4.0	-5.0
			Max.	0.9	2.0	1.6

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Table 7.106

Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS9325122

Treatment: Salmeterol

				C, C	C, T	T, T
Subjects in treatment				27	63	129
Ipratropium use	Double-blind	Baseline	n	25	63	124
			Mean	0.95	1.06	1.07
			SE	0.249	0.165	0.096
			Median	0.29	0.57	0.79
			Min.	0.0	0.0	0.0
			Max.	4.7	6.7	4.6
			Weeks 1-4	n	27	61
		Mean		0.63	0.55	0.83
		SE		0.168	0.089	0.076
		Median		0.21	0.29	0.50
		Min.		0.0	0.0	0.0
		Max.		3.1	2.7	3.1
		Weeks 5-8	n	25	60	119
			Mean	0.47	0.60	0.82
			SE	0.129	0.092	0.080
			Median	0.14	0.27	0.43
			Min.	0.0	0.0	0.0
			Max.	2.0	2.8	4.4
		Weeks 9-12	n	23	58	112
			Mean	0.41	0.53	0.71
			SE	0.142	0.084	0.070
Median	0.07		0.27	0.44		
Min.	0.0		0.0	0.0		
Max.	2.0		2.0	3.1		
Weeks 13-16	n	23	57	108		
	Mean	0.45	0.52	0.66		
	SE	0.141	0.087	0.071		

Table 7.106

Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS9325122

Treatment: Salmeterol

				C, C	C, T	T, T
Ipratropium use	Double-blind	Weeks 13-16	Median	0.07	0.22	0.34
			Min.	0.0	0.0	0.0
			Max.	2.0	2.2	3.3
		Overall	n	27	62	124
			Mean	0.54	0.54	0.76
			SE	0.150	0.076	0.066
			Median	0.25	0.30	0.55
			Min.	0.0	0.0	0.0
			Max.	3.0	2.2	3.0
	Wash-out	Overall	n	23	57	105
			Mean	0.62	0.84	0.84
			SE	0.165	0.170	0.086
			Median	0.14	0.42	0.57
			Min.	0.0	0.0	0.0
			Max.	2.0	8.0	3.6
Ipratropium change	Double-blind	Weeks 1-4	n	25	61	122
			Mean	-0.28	-0.50	-0.24
			SE	0.165	0.152	0.074
			Median	-0.07	-0.11	0.00
			Min.	-2.4	-6.1	-3.9
			Max.	1.9	1.3	1.4
		Weeks 5-8	n	23	60	118
			Mean	-0.33	-0.46	-0.27
			SE	0.157	0.155	0.083
			Median	-0.14	-0.09	0.00
			Min.	-2.4	-6.2	-4.2
			Max.	1.2	2.2	2.4
		Weeks 9-12	n	21	58	112

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Table 7.106

Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS9325122

Treatment: Salmeterol

				C, C	C, T	T, T
-----				-----		
Ipratropium change	Double-blind	Weeks 9-12	Mean	-0.46	-0.57	-0.39
			SE	0.142	0.149	0.077
			Median	-0.18	-0.29	-0.20
			Min.	-2.4	-6.0	-3.4
			Max.	0.2	1.1	1.2
		Weeks 13-16	n	21	57	108
			Mean	-0.42	-0.59	-0.42
			SE	0.147	0.154	0.084
			Median	-0.21	-0.29	-0.21
			Min.	-2.4	-5.4	-3.7
			Max.	0.4	1.1	1.9
		Overall	n	25	62	123
			Mean	-0.37	-0.51	-0.31
			SE	0.142	0.143	0.071
			Median	-0.04	-0.14	-0.12
			Min.	-2.4	-5.9	-3.6
			Max.	0.5	1.1	1.4
	Wash-out	Overall	n	21	57	105
			Mean	-0.23	-0.27	-0.20
			SE	0.152	0.133	0.088
			Median	-0.14	-0.03	-0.05
			Min.	-1.6	-4.1	-4.6
			Max.	1.9	1.4	2.3

Table 7.107

Analysis of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS9325122

				C/C vs. C/T	C/C vs. T/T	C/T vs. T/T
FSC100/50	Double-blind	Weeks 1-4	p-value	0.302	0.264	0.951
			LS Means Diff	0.17	0.18	0.01
			95% CI for Diff	(-0.15,0.50)	(-0.13,0.49)	(-0.20,0.21)
		Weeks 5-8	p-value	0.727	0.657	0.909
			LS Means Diff	0.06	0.07	0.01
			95% CI for Diff	(-0.27,0.38)	(-0.24,0.38)	(-0.20,0.22)
		Weeks 9-12	p-value	0.179	0.194	0.866
			LS Means Diff	0.23	0.22	-0.02
			95% CI for Diff	(-0.11,0.58)	(-0.11,0.54)	(-0.23,0.20)
		Weeks 13-16	p-value	0.077	0.181	0.434
			LS Means Diff	0.31	0.22	-0.09
			95% CI for Diff	(-0.03,0.65)	(-0.10,0.55)	(-0.30,0.13)
		Overall	p-value	0.271	0.256	0.984
			LS Means Diff	0.16	0.16	-0.00
			95% CI for Diff	(-0.13,0.45)	(-0.12,0.44)	(-0.19,0.18)
Wash-out	Overall	p-value	0.654	0.300	0.356	
		LS Means Diff	-0.09	-0.20	-0.11	
		95% CI for Diff	(-0.48,0.30)	(-0.58,0.18)	(-0.35,0.13)	

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS9325122. Least squares mean differences are calculated as C/C-C/T, C/C-T/T and C/T-T/T.

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Table 7.107
Analysis of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS9325122

				C/C vs. C/T	C/C vs. T/T	C/T vs. T/T
Salmeterol	Double-blind	Weeks 1-4	p-value	0.261	0.546	0.014
			LS Means Diff	0.17	-0.09	-0.26
			95% CI for Diff	(-0.13, 0.48)	(-0.39, 0.21)	(-0.48, -0.05)
		Weeks 5-8	p-value	0.888	0.513	0.255
			LS Means Diff	0.02	-0.11	-0.13
	Wash-out	Weeks 9-12	95% CI for Diff	(-0.31, 0.35)	(-0.43, 0.21)	(-0.36, 0.09)
			p-value	0.805	0.576	0.239
			LS Means Diff	0.03	-0.08	-0.11
		Weeks 13-16	95% CI for Diff	(-0.24, 0.31)	(-0.35, 0.19)	(-0.30, 0.07)
			p-value	0.532	0.901	0.276
	Double-blind	Weeks 1-4	LS Means Diff	0.09	-0.02	-0.11
			95% CI for Diff	(-0.20, 0.38)	(-0.30, 0.26)	(-0.31, 0.09)
		Weeks 5-8	p-value	0.350	0.716	0.062
			LS Means Diff	0.12	-0.05	-0.17
		Weeks 9-12	95% CI for Diff	(-0.13, 0.37)	(-0.29, 0.20)	(-0.34, 0.01)
	Wash-out	Weeks 13-16	p-value	0.859	0.431	0.384
			LS Means Diff	-0.04	-0.15	-0.12
			95% CI for Diff	(-0.42, 0.35)	(-0.54, 0.23)	(-0.39, 0.15)
		Overall	p-value			
			LS Means Diff			

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and SNP RS9325122. Least squares mean differences are calculated as C/C-C/T, C/C-T/T and C/T-T/T.

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Protocol: SFA100062

Population: ITT Excluding Investigator

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Table 7.108

Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1800888

Treatment: FSC100/50

00100/00

				C, C	C, T		

Subjects in treatment				240	3		
Ipratropium use	Double-blind	Baseline	n	229	3		
			Mean	1.10	0.43		
			SE	0.076	0.297		
			Median	0.86	0.29		
			Min.	0.0	0.0		
			Max.	5.9	1.0		
			Weeks 1-4		n	234	3
			Mean	0.61	0.12		
			SE	0.049	0.086		
			Median	0.29	0.07		
			Min.	0.0	0.0		
			Max.	3.3	0.3		
			Weeks 5-8		n	225	3
			Mean	0.54	0.12		
			SE	0.049	0.048		
			Median	0.21	0.07		
			Min.	0.0	0.1		
			Max.	3.6	0.2		
			Weeks 9-12		n	218	3
			Mean	0.57	0.13		
			SE	0.049	0.131		
Median	0.22	0.00					
Min.	0.0	0.0					
Max.	2.9	0.4					
Weeks 13-16		n	216	2			
Mean	0.57	0.27					
SE	0.053	0.232					

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Table 7.108

Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1800888

Treatment: FSC100/50

				C, C	C, T
-----				-----	
Ipratropium use	Double-blind	Weeks 13-16	Median	0.21	0.27
			Min.	0.0	0.0
			Max.	3.9	0.5
		Overall	n	236	3
			Mean	0.56	0.14
			SE	0.044	0.103
			Median	0.25	0.05
	Wash-out	Overall	Min.	0.0	0.0
			Max.	3.0	0.3
			n	211	2
Ipratropium change	Double-blind	Weeks 1-4	Mean	0.74	0.07
			SE	0.064	0.071
			Median	0.38	0.07
			Min.	0.0	0.0
			Max.	4.9	0.1
		Weeks 5-8	n	226	3
			Mean	-0.51	-0.31
			SE	0.068	0.212
			Median	-0.17	-0.21
			Min.	-5.9	-0.7
			Max.	1.9	0.0
		Weeks 9-12	n	217	3
			Mean	-0.60	-0.31
			SE	0.073	0.252
			Median	-0.29	-0.21
			Min.	-5.9	-0.8
			Max.	1.5	0.1
		Weeks 13-16	n	209	3
			Mean	0.56	0.14
			SE	0.044	0.103

Protocol: SFA100062

Population: ITT Excluding Investigator

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Table 7.108

Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1800888

Treatment: FSC100/50

				C, C	C, T
-----				-----	
Ipratropium change	Double-blind	Weeks 9-12	Mean	-0.57	-0.30
			SE	0.075	0.175
			Median	-0.29	-0.29
			Min.	-5.0	-0.6
			Max.	2.0	0.0
		Weeks 13-16	n	207	2
			Mean	-0.57	-0.23
			SE	0.073	0.268
			Median	-0.29	-0.23
			Min.	-5.0	-0.5
			Max.	2.0	0.0
		Overall	n	227	3
			Mean	-0.56	-0.29
			SE	0.069	0.198
			Median	-0.23	-0.24
			Min.	-5.9	-0.7
			Max.	1.4	0.0
	Wash-out	Overall	n	203	2
			Mean	-0.42	-0.43
			SE	0.070	0.571
			Median	-0.14	-0.43
			Min.	-5.0	-1.0
			Max.	2.0	0.1

Table 7.108

Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1800888

Treatment: Salmeterol

				C, C	C, T

Subjects in treatment				226	6
Ipratropium use	Double-blind	Baseline	n	218	6
			Mean	1.09	0.74
			SE	0.081	0.550
			Median	0.57	0.14
			Min.	0.0	0.0
			Max.	6.7	3.4
		Weeks 1-4	n	218	6
			Mean	0.75	0.72
			SE	0.055	0.492
			Median	0.43	0.16
			Min.	0.0	0.0
			Max.	3.1	3.1
		Weeks 5-8	n	211	5
			Mean	0.72	0.75
			SE	0.055	0.683
			Median	0.39	0.07
			Min.	0.0	0.0
			Max.	4.4	3.5
		Weeks 9-12	n	200	5
			Mean	0.63	0.69
			SE	0.049	0.562
			Median	0.36	0.14
			Min.	0.0	0.0
			Max.	3.1	2.9
		Weeks 13-16	n	193	5
			Mean	0.60	0.53
			SE	0.050	0.460

Table 7.108

Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1800888

Treatment: Salmeterol

				C, C	C, T
Ipratropium use	Double-blind	Weeks 13-16	Median	0.29	0.00
			Min.	0.0	0.0
			Max.	3.3	2.4
	Overall		n	220	6
			Mean	0.69	0.70
			SE	0.048	0.472
			Median	0.40	0.16
			Min.	0.0	0.0
			Max.	3.0	3.0
	Wash-out	Overall	n	190	5
			Mean	0.82	0.90
			SE	0.072	0.574
			Median	0.44	0.57
			Min.	0.0	0.0
			Max.	8.0	3.1
Ipratropium change	Double-blind	Weeks 1-4	n	214	6
			Mean	-0.33	-0.02
			SE	0.066	0.102
			Median	-0.04	0.00
			Min.	-6.1	-0.4
			Max.	1.9	0.3
		Weeks 5-8	n	207	5
			Mean	-0.35	0.01
			SE	0.071	0.069
			Median	-0.07	0.00
			Min.	-6.2	-0.2
			Max.	2.4	0.2
		Weeks 9-12	n	197	5

Table 7.108

Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS1800888

Treatment: Salmeterol

				C, C	C, T
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Ipratropium change	Double-blind	Weeks 9-12	Mean	-0.47	-0.05
			SE	0.067	0.150
			Median	-0.21	0.00
			Min.	-6.0	-0.5
			Max.	1.2	0.4
		Weeks 13-16	n	190	5
			Mean	-0.50	-0.21
			SE	0.072	0.233
			Median	-0.21	0.00
			Min.	-5.4	-1.1
			Max.	1.9	0.3
		Overall	n	216	6
			Mean	-0.39	-0.03
			SE	0.063	0.116
			Median	-0.13	0.02
			Min.	-5.9	-0.5
			Max.	1.4	0.3
Wash-out	Overall	Overall	n	187	5
			Mean	-0.26	0.16
			SE	0.069	0.147
			Median	-0.14	0.14
			Min.	-4.6	-0.3
			Max.	2.3	0.6

Table 7.109

Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS3729943

Treatment: FSC100/50

				C, C	C, G

Subjects in treatment				241	2
Ipratropium use	Double-blind	Baseline	n	230	2
			Mean	1.10	0.64
			SE	0.076	0.643
			Median	0.86	0.64
			Min.	0.0	0.0
			Max.	5.9	1.3
		Weeks 1-4	n	235	2
			Mean	0.61	0.14
			SE	0.049	0.071
			Median	0.29	0.14
			Min.	0.0	0.1
			Max.	3.3	0.2
		Weeks 5-8	n	226	2
			Mean	0.54	0.13
			SE	0.048	0.054
			Median	0.21	0.13
			Min.	0.0	0.1
			Max.	3.6	0.2
		Weeks 9-12	n	219	2
			Mean	0.57	0.02
			SE	0.049	0.018
			Median	0.22	0.02
			Min.	0.0	0.0
			Max.	2.9	0.0
		Weeks 13-16	n	216	2
			Mean	0.57	0.04
			SE	0.052	0.036

Table 7.109

Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS3729943

Treatment: FSC100/50

				C, C	C, G
-----				-----	
Ipratropium use	Double-blind	Weeks 13-16	Median	0.21	0.04
			Min.	0.0	0.0
			Max.	3.9	0.1
	Overall		n	237	2
			Mean	0.56	0.08
			SE	0.044	0.027
			Median	0.25	0.08
			Min.	0.0	0.1
			Max.	3.0	0.1
	Wash-out	Overall	n	211	2
			Mean	0.74	0.62
			SE	0.064	0.310
			Median	0.36	0.62
			Min.	0.0	0.3
			Max.	4.9	0.9
Ipratropium change	Double-blind	Weeks 1-4	n	227	2
			Mean	-0.51	-0.50
			SE	0.068	0.571
			Median	-0.20	-0.50
			Min.	-5.9	-1.1
			Max.	1.9	0.1
		Weeks 5-8	n	218	2
			Mean	-0.60	-0.52
			SE	0.072	0.589
			Median	-0.29	-0.52
			Min.	-5.9	-1.1
			Max.	1.5	0.1
		Weeks 9-12	n	210	2

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Population: ITT Excluding Investigator

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Table 7.109

Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS3729943

Treatment: FSC100/50

				C, C	C, G
-----				-----	
Ipratropium change	Double-blind	Weeks 9-12	Mean	-0.56	-0.63
			SE	0.075	0.625
			Median	-0.29	-0.63
			Min.	-5.0	-1.3
			Max.	2.0	0.0
		Weeks 13-16	n	207	2
			Mean	-0.57	-0.61
			SE	0.073	0.679
			Median	-0.29	-0.61
			Min.	-5.0	-1.3
	Wash-out	Overall	Max.	2.0	0.1
			n	228	2
			Mean	-0.56	-0.56
			SE	0.068	0.616
			Median	-0.23	-0.56
			Min.	-5.9	-1.2
			Max.	1.4	0.1
		Overall	n	203	2
			Mean	-0.42	-0.02
			SE	0.070	0.332
			Median	-0.14	-0.02
			Min.	-5.0	-0.4
			Max.	2.0	0.3

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Table 7.109

Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS3729943

Treatment: Salmeterol

				C, C	C, G
-----				-----	
Subjects in treatment				231	1
Ipratropium use	Double-blind	Baseline	n	223	1
			Mean	1.07	4.00
			SE	0.079	
			Median	0.57	4.00
			Min.	0.0	4.0
			Max.	6.7	4.0
		Weeks 1-4	n	223	1
			Mean	0.74	2.81
			SE	0.055	
			Median	0.43	2.81
			Min.	0.0	2.8
			Max.	3.1	2.8
		Weeks 5-8	n	215	1
			Mean	0.71	2.07
			SE	0.056	
			Median	0.36	2.07
			Min.	0.0	2.1
			Max.	4.4	2.1
		Weeks 9-12	n	204	1
			Mean	0.63	2.07
			SE	0.049	
			Median	0.36	2.07
			Min.	0.0	2.1
			Max.	3.1	2.1
		Weeks 13-16	n	197	1
			Mean	0.60	0.71
			SE	0.050	

Table 7.109

Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS3729943

Treatment: Salmeterol

				C, C	C, G
Ipratropium use	Double-blind	Weeks 13-16	Median	0.29	0.71
			Min.	0.0	0.7
			Max.	3.3	0.7
	Wash-out	Overall	n	225	1
			Mean	0.68	1.91
			SE	0.048	
			Median	0.40	1.91
			Min.	0.0	1.9
			Max.	3.0	1.9
	Double-blind	Weeks 1-4	n	219	1
			Mean	-0.32	-1.19
			SE	0.064	
			Median	-0.04	-1.19
			Min.	-6.1	-1.2
			Max.	1.9	-1.2
Ipratropium change	Wash-out	Overall	n	194	1
			Mean	0.81	2.57
			SE	0.071	
			Median	0.44	2.57
			Min.	0.0	2.6
			Max.	8.0	2.6
	Double-blind	Weeks 5-8	n	211	1
			Mean	-0.34	-1.93
			SE	0.070	
			Median	-0.05	-1.93
			Min.	-6.2	-1.9
			Max.	2.4	-1.9
	Wash-out	Weeks 9-12	n	201	1

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Population: ITT Excluding Investigator

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Table 7.109

Summary of Supplemental Ipratropium Use (puffs/day) - ADRB2 Gene SNP RS3729943

Treatment: Salmeterol

				C, C	C, G
-----				-----	
Ipratropium change	Double-blind	Weeks 9-12	Mean	-0.45	-1.93
			SE	0.066	
			Median	-0.21	-1.93
			Min.	-6.0	-1.9
			Max.	1.2	-1.9
		Weeks 13-16	n	194	1
			Mean	-0.48	-3.29
			SE	0.070	
			Median	-0.21	-3.29
			Min.	-5.4	-3.3
			Max.	1.9	-3.3
	Wash-out	Overall	n	221	1
			Mean	-0.37	-2.09
			SE	0.061	
			Median	-0.12	-2.09
			Min.	-5.9	-2.1
			Max.	1.4	-2.1
	Wash-out	Overall	n	191	1
			Mean	-0.24	-1.43
			SE	0.067	
			Median	-0.07	-1.43
			Min.	-4.6	-1.4
			Max.	2.3	-1.4

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Table 7.110

Summary of Supplemental Ipratropium Use (puffs/day) - Poly-C Repeat Group

Treatment: FSC100/50

				<12 Repeats	>=12 Repeats

Subjects in treatment				102	137
Ipratropium use	Double-blind	Baseline	n	100	128
			Mean	1.04	1.14
			SE	0.107	0.105
			Median	0.71	0.86
			Min.	0.0	0.0
			Max.	5.9	5.0
		Weeks 1-4	n	99	134
			Mean	0.63	0.59
			SE	0.079	0.063
			Median	0.29	0.29
			Min.	0.0	0.0
			Max.	2.9	3.3
		Weeks 5-8	n	97	128
			Mean	0.53	0.55
			SE	0.072	0.066
			Median	0.21	0.21
			Min.	0.0	0.0
			Max.	2.5	3.6
		Weeks 9-12	n	92	126
			Mean	0.63	0.53
			SE	0.080	0.063
			Median	0.29	0.21
			Min.	0.0	0.0
			Max.	2.5	2.9
		Weeks 13-16	n	92	123
			Mean	0.63	0.53

Table 7.110

Summary of Supplemental Ipratropium Use (puffs/day) - Poly-C Repeat Group

Treatment: FSC100/50

CC100/00

				<12 Repeats	>=12 Repeats	
Ipratropium use	Double-blind	Weeks 13-16	SE	0.081	0.070	
			Median	0.29	0.18	
			Min.	0.0	0.0	
			Max.	3.4	3.9	
		Overall	n	100	135	
			Mean	0.58	0.55	
			SE	0.069	0.059	
			Median	0.28	0.24	
			Min.	0.0	0.0	
			Max.	2.3	3.0	
		Wash-out	Overall	n	89	121
				Mean	0.74	0.74
	SE			0.098	0.085	
	Median			0.43	0.36	
	Min.			0.0	0.0	
	Max.			4.9	4.4	
	Ipratropium change	Double-blind	Weeks 1-4	n	97	128
				Mean	-0.44	-0.55
SE				0.098	0.090	
Median				-0.21	-0.21	
Min.				-5.9	-4.9	
Max.				1.9	0.9	
Weeks 5-8			n	95	122	
			Mean	-0.55	-0.62	
			SE	0.098	0.101	
			Median	-0.28	-0.29	
			Min.	-5.9	-5.0	
			Max.	0.8	1.5	

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Table 7.110

Summary of Supplemental Ipratropium Use (puffs/day) - Poly-C Repeat Group

Treatment: FSC100/50

CC100/00

				<12 Repeats	>=12 Repeats
Ipratropium change	Double-blind	Weeks 9-12	n	90	119
			Mean	-0.44	-0.64
			SE	0.090	0.109
			Median	-0.23	-0.29
			Min.	-3.1	-5.0
			Max.	2.0	1.8
		Weeks 13-16	n	90	116
			Mean	-0.42	-0.65
			SE	0.091	0.103
			Median	-0.29	-0.29
			Min.	-3.1	-5.0
			Max.	2.0	1.3
		Overall	n	98	128
			Mean	-0.49	-0.60
			SE	0.094	0.094
			Median	-0.26	-0.23
			Min.	-5.9	-5.0
			Max.	1.4	1.1
	Wash-out	Overall	n	88	114
			Mean	-0.35	-0.44
			SE	0.093	0.096
			Median	-0.24	-0.14
			Min.	-3.1	-5.0
			Max.	1.6	2.0

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Table 7.110

Summary of Supplemental Ipratropium Use (puffs/day) - Poly-C Repeat Group

Treatment: Salmeterol

				<12 Repeats	>=12 Repeats

Subjects in treatment				91	139
Ipratropium use	Double-blind	Baseline	n	86	136
			Mean	1.18	1.01
			SE	0.151	0.090
			Median	0.64	0.57
			Min.	0.0	0.0
			Max.	6.7	4.3
		Weeks 1-4	n	86	135
			Mean	0.83	0.70
			SE	0.096	0.067
			Median	0.48	0.36
			Min.	0.0	0.0
			Max.	3.1	3.0
		Weeks 5-8	n	83	131
			Mean	0.73	0.71
			SE	0.091	0.071
			Median	0.39	0.36
			Min.	0.0	0.0
			Max.	3.5	4.4
		Weeks 9-12	n	80	123
			Mean	0.69	0.59
			SE	0.087	0.059
			Median	0.39	0.36
			Min.	0.0	0.0
			Max.	3.1	2.5
		Weeks 13-16	n	77	120
			Mean	0.67	0.56

Table 7.110

Summary of Supplemental Ipratropium Use (puffs/day) - Poly-C Repeat Group

Treatment: Salmeterol

				<12 Repeats	>=12 Repeats
Ipratropium use	Double-blind	Weeks 13-16	SE	0.085	0.061
			Median	0.36	0.27
			Min.	0.0	0.0
			Max.	3.3	2.3
	Overall		n	87	137
			Mean	0.71	0.66
			SE	0.081	0.060
			Median	0.46	0.36
			Min.	0.0	0.0
			Max.	3.0	3.0
Ipratropium change	Wash-out	Overall	n	76	118
			Mean	0.97	0.74
			SE	0.137	0.077
			Median	0.65	0.43
			Min.	0.0	0.0
			Max.	8.0	3.6
	Double-blind	Weeks 1-4	n	83	134
			Mean	-0.34	-0.32
			SE	0.117	0.077
			Median	-0.04	-0.02
			Min.	-6.1	-4.1
			Max.	1.9	1.4
		Weeks 5-8	n	80	130
			Mean	-0.41	-0.31
			SE	0.126	0.083
			Median	-0.08	-0.04
			Min.	-6.2	-3.8
			Max.	1.3	2.4

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Table 7.110

Summary of Supplemental Ipratropium Use (puffs/day) - Poly-C Repeat Group

Treatment: Salmeterol

			<12 Repeats		>=12 Repeats	
-----			-----		-----	
Ipratropium change	Double-blind	Weeks 9-12	n	77	123	
			Mean	-0.49	-0.44	
			SE	0.121	0.078	
			Median	-0.21	-0.21	
			Min.	-6.0	-3.6	
			Max.	1.2	1.1	
		Weeks 13-16	n	74	120	
			Mean	-0.54	-0.47	
			SE	0.126	0.085	
			Median	-0.21	-0.21	
			Min.	-5.4	-4.2	
			Max.	1.0	1.9	
		Overall	n	84	136	
			Mean	-0.44	-0.35	
			SE	0.112	0.073	
			Median	-0.17	-0.09	
			Min.	-5.9	-3.7	
			Max.	0.8	1.4	
	Wash-out	Overall	n	73	118	
			Mean	-0.18	-0.28	
			SE	0.119	0.081	
			Median	0.00	-0.14	
			Min.	-4.6	-4.1	
			Max.	2.3	1.7	

Table 7.111
Analysis of Supplemental Ipratropium Use (puffs/day) - Poly-C Repeat Group

				<12 vs. ≥12

FSC100/50	Double-blind	Weeks 1-4	p-value	0.461
			LS Means Diff	0.07
			95% CI for Diff	(-0.11,0.24)
		Weeks 5-8	p-value	0.922
			LS Means Diff	0.01
			95% CI for Diff	(-0.17,0.19)
		Weeks 9-12	p-value	0.195
			LS Means Diff	0.12
			95% CI for Diff	(-0.06,0.31)
		Weeks 13-16	p-value	0.144
			LS Means Diff	0.14
			95% CI for Diff	(-0.05,0.34)
	Overall	p-value	0.481	
		LS Means Diff	0.06	
		95% CI for Diff	(-0.10,0.22)	
	Wash-out	Overall	p-value	0.348
			LS Means Diff	0.10
			95% CI for Diff	(-0.11,0.31)

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and Poly-C repeat group. Least squares mean differences are calculated as <12 Repeats - ≥12 Repeats.

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Table 7.111
Analysis of Supplemental Ipratropium Use (puffs/day) - Poly-C Repeat Group

				<12 vs. ≥12

Salmeterol	Double-blind	Weeks 1-4	p-value	0.379
			LS Means Diff	0.08
			95% CI for Diff	(-0.10,0.26)
		Weeks 5-8	p-value	0.961
			LS Means Diff	0.00
			95% CI for Diff	(-0.19,0.20)
		Weeks 9-12	p-value	0.443
			LS Means Diff	0.06
			95% CI for Diff	(-0.10,0.22)
		Weeks 13-16	p-value	0.570
			LS Means Diff	0.05
			95% CI for Diff	(-0.12,0.22)
		Overall	p-value	0.808
			LS Means Diff	0.02
			95% CI for Diff	(-0.13,0.17)
Wash-out	Overall	p-value	0.219	
		LS Means Diff	0.14	
		95% CI for Diff	(-0.09,0.37)	

Note: P-values are from an ANCOVA model with terms for baseline, ethnicity stratum, sex, age and Poly-C repeat group. Least squares mean differences are calculated as <12 Repeats - ≥12 Repeats.

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Table 7.112
Summary of Frequency for Poly-C Genotypes

		Total (N=479)
Genotype	8, 9	83 (17%)
	10, 9	23 (5%)
	10, 11	91 (19%)
	11, 12	68 (14%)
	12, 9	29 (6%)
	13, 8	24 (5%)
	13, 9	125 (26%)
	10, 12	3 (<1%)
	10, 13	1 (<1%)
	10, 14	4 (<1%)
	11, 13	16 (3%)
	11, 14	3 (<1%)
	12, 8	4 (<1%)
	14, 9	4 (<1%)
	7, 8	1 (<1%)

Table 7.113
Summary of Pre-dose FEV1 (L) by Treatment Group

			FSC100/50 (N=268)	Salmeterol (N=266)
FEV1 (L)	Screening	n	268	266
		Mean	2.71	2.74
		SE	0.038	0.042
		Median	2.71	2.69
		Min.	1.38	1.20
		Max.	4.49	4.97
	Visit 7 (Week 4)	n	258	247
		Mean	3.03	3.03
		SE	0.047	0.050
		Median	2.97	2.94
		Min.	1.36	1.22
		Max.	5.98	5.35
	Visit 8 (Week 8)	n	248	232
		Mean	3.03	2.99
		SE	0.048	0.049
		Median	2.98	2.88
		Min.	1.20	1.24
		Max.	5.68	5.36
	Visit 9 (Week 12)	n	241	220
		Mean	3.04	2.99
		SE	0.050	0.049
		Median	2.94	2.95
		Min.	1.22	1.20
		Max.	5.75	4.99

Table 7.113
Summary of Pre-dose FEV1 (L) by Treatment Group

			FSC100/50 (N=268)	Salmeterol (N=266)
FEV1 (L)	Visit 10 (Week 16)	n	239	214
		Mean	3.03	2.98
		SE	0.049	0.052
		Median	2.97	2.91
		Min.	1.15	1.22
		Max.	5.33	5.15
	Endpoint	n	258	247
		Mean	3.03	2.99
		SE	0.047	0.051
		Median	2.99	2.90
		Min.	1.15	1.22
		Max.	5.33	5.36
	Change from screening	Visit 7 (Week 4)	n	258
			Mean	0.33
			SE	0.021
			Median	0.28
			Min.	-0.49
			Max.	1.67
	Visit 8 (Week 8)	n	248	232
		Mean	0.34	0.27
		SE	0.021	0.023
		Median	0.30	0.21
		Min.	-0.37	-0.64
		Max.	1.37	1.60

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Table 7.113
Summary of Pre-dose FEV1 (L) by Treatment Group

			FSC100/50 (N=268)	Salmeterol (N=266)
Change from screening	Visit 9 (Week 12)	n	241	220
		Mean	0.34	0.27
		SE	0.022	0.022
		Median	0.29	0.21
		Min.	-0.33	-0.69
		Max.	1.56	1.71
	Visit 10 (Week 16)	n	239	214
		Mean	0.33	0.25
		SE	0.023	0.026
		Median	0.27	0.21
		Min.	-0.44	-0.76
		Max.	1.65	2.51
	Endpoint	n	258	247
		Mean	0.33	0.25
		SE	0.023	0.024
		Median	0.26	0.21
		Min.	-0.44	-0.76
		Max.	1.65	2.51

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Table 7.114
Analysis of Pre-Dose FEV1 (L) by Treatment Group

		Endpoint vs. Screen	
FSC100/50	Endpoint	p-value	<0.001
		Mean Diff	0.33
		95% CI for Diff	(0.29, 0.38)
Salmeterol	Endpoint	p-value	<0.001
		Mean Diff	0.25
		95% CI for Diff	(0.20, 0.30)

Note: P-values are from paired t-tests.
Mean differences are calculated as Endpoint FEV1-Screening FEV1.

Table 7.115
Summary of AM PEF (L/min) (Open-Label Albuterol Failure Population)

				Arg/Arg (N=37)	Arg/Gly (N=43)	Gly/Gly (N=28)
AM PEF (L/min)	Albuterol	Week 1	n	24	25	12
			Mean	352.8	362.2	321.4
			SE	20.00	15.38	27.65
			Median	359.8	339.5	334.8
			Min.	67	249	143
			Max.	550	537	539
		Week 2	n	24	25	12
			Mean	352.3	360.7	322.3
			SE	21.34	17.54	25.62
			Median	366.7	336.4	324.9
			Min.	45	230	155
			Max.	567	562	533
		Week 3	n	22	25	12
			Mean	374.1	355.7	320.6
			SE	20.07	17.73	25.97
			Median	373.1	332.1	326.3
			Min.	138	184	139
			Max.	563	531	536
		Week 4	n	22	23	12
			Mean	362.8	355.3	324.6
			SE	19.72	20.46	25.03
			Median	370.2	373.9	317.3
			Min.	102	185	164
			Max.	570	501	542

Table 7.115
Summary of AM PEF (L/min) (Open-Label Albuterol Failure Population)

				Arg/Arg (N=37)	Arg/Gly (N=43)	Gly/Gly (N=28)
AM PEF (L/min)	Albuterol	Week 5	n	10	11	7
			Mean	359.4	392.5	327.6
			SE	35.12	25.15	41.30
			Median	357.6	401.0	312.4
			Min.	177	260	170
			Max.	562	523	535
		Week 6	n	8	7	5
			Mean	333.3	366.1	359.0
			SE	37.78	29.29	42.35
			Median	342.9	404.0	318.3
			Min.	131	259	298
			Max.	496	442	524
		Week 7	n	7	5	4
			Mean	362.1	384.6	297.6
			SE	35.43	32.11	25.64
			Median	369.3	414.9	297.1
			Min.	222	256	236
			Max.	496	422	360
		Week 8	n	6	4	4
			Mean	343.2	433.6	290.8
			SE	34.39	22.31	26.14
			Median	322.3	414.1	278.3
			Min.	255	406	246
			Max.	491	500	361

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Table 7.115
Summary of AM PEF (L/min) (Open-Label Albuterol Failure Population)

				Arg/Arg (N=37)	Arg/Gly (N=43)	Gly/Gly (N=28)
-----		-----		-----		
AM PEF (L/min)	Albuterol	Weeks 1-4	n	24	25	12
			Mean	354.5	358.5	322.2
			SE	20.99	17.02	25.87
			Median	371.1	346.7	327.0
			Min.	57	213	150
			Max.	563	533	538
		Weeks 5-8	n	10	12	7
			Mean	360.1	391.4	324.5
			SE	36.54	22.23	41.56
			Median	370.5	407.5	304.5
			Min.	154	259	170
			Max.	563	523	530
		Overall	n	24	26	12
			Mean	353.4	361.5	320.5
			SE	21.26	16.43	25.50
			Median	370.7	363.3	317.4
			Min.	57	213	152
			Max.	563	533	535

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Table 7.116
Summary of Pre-dose FEV1 (L) (Open-Label Albuterol Failure Population)

			Arg/Arg (N=37)	Arg/Gly (N=43)	Gly/Gly (N=28)
FEV1 (L)	Visit 2 (Week -16)	n	35	38	18
		Mean	2.73	2.64	2.49
		SE	0.114	0.104	0.177
		Median	2.55	2.58	2.27
		Min.	1.84	1.78	1.47
		Max.	4.33	4.41	4.80
	Visit 3 (Week -12)	n	19	18	9
		Mean	2.77	2.52	2.43
		SE	0.163	0.146	0.345
		Median	2.73	2.63	2.14
		Min.	1.65	1.59	1.33
		Max.	4.10	3.69	4.96

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Table 7.117
Summary of Percent of Symptom-Free Days (Open-Label Albuterol Failure Population)

				Arg/Arg (N=37)	Arg/Gly (N=43)	Gly/Gly (N=28)
-----		-----		-----		-----
% Symptom-free days	Albuterol	Week 1	n	24	22	12
			Mean	14.6	24.8	13.1
			SE	5.51	7.70	8.52
			Median	0.0	0.0	0.0
			Min.	0	0	0
			Max.	71	100	100
		Week 2	n	24	23	12
			Mean	14.9	21.1	11.9
			SE	5.73	6.71	8.22
			Median	0.0	0.0	0.0
			Min.	0	0	0
			Max.	100	100	86
		Week 3	n	22	23	12
			Mean	15.6	21.1	8.3
			SE	6.71	6.21	8.33
			Median	0.0	0.0	0.0
			Min.	0	0	0
			Max.	100	86	100
		Week 4	n	22	20	12
			Mean	18.5	22.3	8.3
			SE	7.11	8.12	8.33
			Median	0.0	0.0	0.0
			Min.	0	0	0
			Max.	100	100	100
		Week 5	n	10	10	7
			Mean	14.3	34.3	14.3
			SE	7.97	12.45	14.29
			Median	0.0	21.4	0.0
			Min.	0	0	0

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Table 7.117
Summary of Percent of Symptom-Free Days (Open-Label Albuterol Failure Population)

				Arg/Arg (N=37)	Arg/Gly (N=43)	Gly/Gly (N=28)
-----		-----				
% Symptom-free days	Albuterol	Week 5	Max.	71	100	100
		Week 6	n	8	7	5
			Mean	23.2	36.7	17.1
			SE	12.64	14.90	17.14
			Median	0.0	42.9	0.0
			Min.	0	0	0
			Max.	86	100	86
		Week 7	n	7	4	4
			Mean	11.9	50.0	0.0
			SE	11.90	25.08	0.00
			Median	0.0	50.0	0.0
			Min.	0	0	0
			Max.	83	100	0
		Week 8	n	6	4	4
			Mean	11.9	75.0	0.0
			SE	11.90	25.00	0.00
			Median	0.0	100.0	0.0
			Min.	0	0	0
			Max.	71	100	0
		Weeks 1-4	n	24	23	12
			Mean	16.9	21.6	10.4
			SE	5.92	6.54	8.03
			Median	0.0	0.0	0.0
			Min.	0	0	0
			Max.	93	96	96
		Weeks 5-8	n	10	11	7
			Mean	13.5	34.3	13.3
			SE	7.15	12.04	13.27

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Table 7.117
Summary of Percent of Symptom-Free Days (Open-Label Albuterol Failure Population)

			Arg/Arg (N=37)	Arg/Gly (N=43)	Gly/Gly (N=28)
% Symptom-free days	Albuterol	Weeks 5-8	Median	0.0	11.1
			Min.	0	0
			Max.	60	100
		Overall	n	24	24
			Mean	18.3	24.3
			SE	5.86	6.82
			Median	0.0	1.7
			Min.	0	0
			Max.	93	98
					95

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Table 7.118
Summary of Albuterol Use (puffs/day) (Open-Label Albuterol Failure Population)

				Arg/Arg (N=37)	Arg/Gly (N=43)	Gly/Gly (N=28)
Albuterol use (puffs/day)	Albuterol	Week 1	n	24	23	12
			Mean	2.0	2.2	2.8
			SE	0.34	0.34	0.67
			Median	1.8	2.0	2.8
			Min.	0	0	0
			Max.	6	6	7
		Week 2	n	24	22	12
			Mean	1.9	2.5	3.0
			SE	0.42	0.42	0.67
			Median	1.4	2.1	3.4
			Min.	0	0	0
			Max.	7	7	8
		Week 3	n	22	22	12
			Mean	1.9	2.9	3.0
			SE	0.39	0.50	0.68
			Median	1.4	2.0	2.9
			Min.	0	0	0
			Max.	6	8	8
		Week 4	n	22	19	12
			Mean	2.0	2.6	2.9
			SE	0.45	0.52	0.71
			Median	1.7	2.0	2.9
			Min.	0	0	0
			Max.	6	7	8

Table 7.118
Summary of Albuterol Use (puffs/day) (Open-Label Albuterol Failure Population)

				Arg/Arg (N=37)	Arg/Gly (N=43)	Gly/Gly (N=28)
Albuterol use (puffs/day)	Albuterol	Week 5	n	10	10	7
			Mean	1.9	1.3	2.6
			SE	0.60	0.42	1.04
			Median	1.2	1.2	2.3
			Min.	0	0	0
			Max.	5	4	8
		Week 6	n	8	7	5
			Mean	2.8	1.6	3.1
			SE	1.12	0.58	1.51
			Median	1.5	1.1	2.3
			Min.	0	0	0
			Max.	9	4	8
		Week 7	n	7	4	4
			Mean	1.9	0.8	4.4
			SE	0.79	0.60	1.83
			Median	1.9	0.3	4.0
			Min.	0	0	0
			Max.	6	3	9
		Week 8	n	6	4	4
			Mean	3.8	0.1	5.5
			SE	1.70	0.08	1.25
			Median	2.4	0.0	5.1
			Min.	0	0	3
			Max.	11	0	9

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Table 7.118
Summary of Albuterol Use (puffs/day) (Open-Label Albuterol Failure Population)

				Arg/Arg (N=37)	Arg/Gly (N=43)	Gly/Gly (N=28)
Albuterol use (puffs/day)	Albuterol	Weeks 1-4	n	24	23	12
			Mean	1.9	2.5	2.9
			SE	0.37	0.37	0.67
			Median	1.5	1.9	3.0
			Min.	0	0	0
			Max.	5	7	8
		Weeks 5-8	n	10	11	7
			Mean	2.5	1.3	3.0
			SE	0.74	0.38	1.10
			Median	1.9	1.0	2.3
			Min.	0	0	0
			Max.	5	4	9
		Overall	n	24	24	12
			Mean	1.9	2.4	2.9
			SE	0.37	0.37	0.67
			Median	1.5	1.8	2.9
			Min.	0	0	0
			Max.	5	7	8

Table 7.119
Summary of AM PEF (L/min) (Open-Label Ipratropium Failure Population)

				Arg/Arg (N=27)	Arg/Gly (N=62)	Gly/Gly (N=41)
-----		-----		-----		
AM PEF (L/min)	Albuterol	Week 1	n	23	62	40
			Mean	352.0	363.7	366.2
			SE	17.79	13.52	11.02
			Median	349.8	338.9	371.9
			Min.	239	179	264
			Max.	538	691	599
		Week 2	n	23	62	39
			Mean	357.9	360.3	363.7
			SE	17.23	13.95	11.86
			Median	343.1	342.8	372.6
			Min.	270	174	239
			Max.	568	746	595
		Week 3	n	23	62	39
			Mean	353.1	360.3	370.1
			SE	18.50	13.44	12.62
			Median	338.9	351.4	372.0
			Min.	239	156	259
			Max.	555	721	600
		Week 4	n	23	62	39
			Mean	354.6	361.5	375.6
			SE	17.91	12.90	12.44
			Median	337.9	347.1	385.4
			Min.	250	185	263
			Max.	573	723	597

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Table 7.119
Summary of AM PEF (L/min) (Open-Label Ipratropium Failure Population)

				Arg/Arg (N=27)	Arg/Gly (N=62)	Gly/Gly (N=41)
AM PEF (L/min)	Albuterol	Week 5	n	22	62	37
			Mean	356.4	359.1	382.7
			SE	19.69	12.44	12.63
			Median	337.9	339.0	374.1
			Min.	223	181	260
			Max.	587	659	560
		Week 6	n	23	62	38
			Mean	355.7	361.1	374.4
			SE	19.65	12.29	12.57
			Median	325.6	351.1	370.3
			Min.	225	154	266
			Max.	594	666	557
		Week 7	n	23	62	38
			Mean	350.0	366.2	371.1
			SE	20.79	12.82	13.42
			Median	331.0	349.5	360.3
			Min.	223	158	230
			Max.	584	682	542
		Week 8	n	23	61	38
			Mean	334.7	365.5	375.6
			SE	22.05	13.98	12.43
			Median	299.6	347.2	370.8
			Min.	123	136	263
			Max.	581	683	545

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Table 7.119
Summary of AM PEF (L/min) (Open-Label Ipratropium Failure Population)

				Arg/Arg (N=27)	Arg/Gly (N=62)	Gly/Gly (N=41)
AM PEF (L/min)	Albuterol	Weeks 1-4	n	23	62	40
			Mean	354.5	361.3	367.8
			SE	17.63	13.25	11.12
			Median	341.6	345.1	374.1
			Min.	250	193	262
			Max.	558	720	598
		Weeks 5-8	n	23	62	38
			Mean	348.6	363.0	375.5
			SE	19.95	12.59	12.42
			Median	306.5	346.4	364.8
			Min.	230	160	265
			Max.	586	672	541
		Overall	n	23	62	40
			Mean	351.6	362.2	371.8
			SE	18.63	12.78	11.24
			Median	326.3	347.7	372.8
			Min.	240	177	265
			Max.	572	687	570
	Ipratropium	Week 1	n	16	54	35
			Mean	317.1	368.2	371.8
			SE	20.58	14.98	12.42
			Median	308.3	347.6	383.4
			Min.	170	177	254
			Max.	458	690	577

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Table 7.119
Summary of AM PEF (L/min) (Open-Label Ipratropium Failure Population)

				Arg/Arg (N=27)	Arg/Gly (N=62)	Gly/Gly (N=41)
AM PEF (L/min)	Ipratropium	Week 2	n	16	55	33
			Mean	319.5	372.6	371.5
			SE	22.20	14.67	13.85
			Median	313.2	361.4	379.4
			Min.	145	190	219
			Max.	477	687	601
		Week 3	n	16	55	31
			Mean	312.0	370.7	379.1
			SE	25.04	15.75	14.65
			Median	313.6	348.3	385.6
			Min.	71	184	242
			Max.	476	752	602
		Week 4	n	15	49	31
			Mean	313.1	375.0	376.1
			SE	21.62	19.01	14.80
			Median	317.3	355.0	377.6
			Min.	133	195	259
			Max.	441	881	612
		Week 5	n	6	40	15
			Mean	360.6	358.7	374.3
			SE	39.07	14.10	18.68
			Median	327.1	363.9	369.3
			Min.	272	206	269
			Max.	492	569	504

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Table 7.119
Summary of AM PEF (L/min) (Open-Label Ipratropium Failure Population)

				Arg/Arg (N=27)	Arg/Gly (N=62)	Gly/Gly (N=41)
AM PEF (L/min)	Ipratropium	Week 6	n	5	36	11
			Mean	338.3	349.0	378.5
			SE	41.83	14.88	23.08
			Median	301.9	345.8	395.7
			Min.	272	188	240
			Max.	502	554	483
		Week 7	n	5	34	11
			Mean	336.0	350.7	380.6
			SE	33.40	16.13	22.10
			Median	312.3	348.6	393.1
			Min.	273	207	271
			Max.	464	545	479
		Week 8	n	5	26	8
			Mean	344.1	361.0	374.8
			SE	40.28	19.01	25.56
			Median	311.3	357.0	392.9
			Min.	270	208	284
			Max.	500	556	466
		Weeks 1-4	n	16	55	35
			Mean	314.8	371.2	368.7
			SE	21.68	15.40	13.25
			Median	317.4	358.2	372.9
			Min.	130	187	251
			Max.	458	731	598

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Table 7.119
Summary of AM PEF (L/min) (Open-Label Ipratropium Failure Population)

				Arg/Arg (N=27)	Arg/Gly (N=62)	Gly/Gly (N=41)
AM PEF (L/min)	Ipratropium	Weeks 5-8	n	6	40	15
			Mean	360.9	353.9	364.4
			SE	38.22	13.74	17.90
			Median	320.3	360.4	373.5
			Min.	272	211	272
			Max.	490	552	477
		Overall	n	16	55	35
	Mean		316.3	368.9	368.0	
	SE		22.20	15.17	13.10	
	Median		317.5	356.6	373.2	
	Min.		130	184	251	
	Max.		474	730	598	

Table 7.120
Summary of Pre-Dose FEV1 (L) (Open-Label Ipratropium Failure Population)

		Arg/Arg (N=27)	Arg/Gly (N=62)	Gly/Gly (N=41)
FEV1 (L)	Visit 2 (Week -16)	n	27	62
		Mean	2.66	2.87
		SE	0.125	0.089
		Median	2.67	2.72
		Min.	1.49	1.68
		Max.	4.09	4.86
	Visit 3 (Week -12)	n	26	62
		Mean	2.68	2.88
		SE	0.128	0.095
		Median	2.65	2.70
		Min.	1.45	1.58
		Max.	3.93	4.81
	Visit 4 (Week -8)	n	24	62
		Mean	2.76	2.84
		SE	0.154	0.086
		Median	2.62	2.74
		Min.	1.52	1.76
		Max.	4.23	4.68
	Visit 5 (Week -4)	n	13	45
		Mean	2.53	2.90
		SE	0.173	0.101
		Median	2.59	2.71
		Min.	1.56	1.73
		Max.	3.35	4.84

Table 7.121
Summary of Percent of Symptom-Free Days (Open-Label Ipratropium Failure Population)

				Arg/Arg (N=27)	Arg/Gly (N=62)	Gly/Gly (N=41)
% Symptom-free days	Albuterol	Week 1	n	22	62	40
			Mean	29.2	19.6	18.9
			SE	8.33	3.70	4.99
			Median	0.0	0.0	0.0
			Min.	0	0	0
			Max.	100	100	100
		Week 2	n	22	62	39
			Mean	26.8	18.0	24.4
			SE	7.58	3.63	5.30
			Median	0.0	0.0	0.0
			Min.	0	0	0
			Max.	100	86	100
		Week 3	n	22	62	39
			Mean	28.6	21.2	28.6
			SE	8.14	3.73	5.84
			Median	0.0	0.0	0.0
			Min.	0	0	0
			Max.	86	86	100
		Week 4	n	22	62	39
			Mean	31.2	25.4	29.5
			SE	9.05	4.43	6.29
			Median	0.0	0.0	0.0
			Min.	0	0	0
			Max.	100	100	100
		Week 5	n	22	62	36
			Mean	34.5	24.4	29.8
			SE	9.13	4.32	6.88
			Median	0.0	0.0	0.0
			Min.	0	0	0

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Table 7.121
Summary of Percent of Symptom-Free Days (Open-Label Ipratropium Failure Population)

				Arg/Arg (N=27)	Arg/Gly (N=62)	Gly/Gly (N=41)
-----		-----				
% Symptom-free days	Albuterol	Week 5	Max.	100	100	100
		Week 6	n	23	62	38
			Mean	31.7	22.5	23.7
			SE	8.84	3.85	5.63
			Median	0.0	0.0	0.0
			Min.	0	0	0
			Max.	100	100	100
		Week 7	n	23	62	37
			Mean	28.0	22.6	26.8
			SE	8.01	4.07	5.84
			Median	0.0	0.0	0.0
			Min.	0	0	0
			Max.	100	100	100
		Week 8	n	23	61	38
			Mean	31.2	22.5	21.9
			SE	8.73	4.19	5.46
			Median	0.0	0.0	0.0
			Min.	0	0	0
			Max.	100	100	100
		Weeks 1-4	n	22	62	40
			Mean	29.0	21.0	24.9
			SE	8.03	3.56	5.25
			Median	2.1	3.7	0.0
			Min.	0	0	0
			Max.	96	89	100
		Weeks 5-8	n	23	62	38
			Mean	30.9	23.2	25.3
			SE	8.36	3.69	5.45

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Table 7.121
Summary of Percent of Symptom-Free Days (Open-Label Ipratropium Failure Population)

			Arg/Arg (N=27)	Arg/Gly (N=62)	Gly/Gly (N=41)
% Symptom-free days	Albuterol	Weeks 5-8	Median	0.0	9.4
			Min.	0	0
			Max.	100	100
		Overall	n	23	62
			Mean	31.3	22.1
			SE	8.19	3.50
			Median	3.9	6.2
			Min.	0	0
			Max.	95	93
	Ipratropium	Week 1	n	16	54
			Mean	27.4	26.2
			SE	10.71	5.22
			Median	0.0	0.0
			Min.	0	0
			Max.	100	100
		Week 2	n	15	54
			Mean	29.5	30.2
			SE	11.37	4.92
			Median	0.0	7.1
			Min.	0	0
			Max.	100	100
		Week 3	n	16	55
			Mean	23.2	25.6
			SE	10.17	5.05
			Median	0.0	0.0
			Min.	0	0
			Max.	100	100
		Week 4	n	15	49
					30

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Table 7.121
Summary of Percent of Symptom-Free Days (Open-Label Ipratropium Failure Population)

				Arg/Arg (N=27)	Arg/Gly (N=62)	Gly/Gly (N=41)
-----		-----				
% Symptom-free days	Ipratropium	Week 4	Mean	26.7	23.7	27.1
			SE	10.97	5.18	7.39
			Median	0.0	0.0	0.0
			Min.	0	0	0
			Max.	100	100	100
		Week 5	n	6	39	16
			Mean	40.5	21.1	36.9
			SE	18.60	5.52	9.76
			Median	35.7	0.0	29.8
			Min.	0	0	0
			Max.	100	100	100
		Week 6	n	4	35	12
			Mean	25.0	22.2	31.0
			SE	25.00	5.50	11.90
			Median	0.0	0.0	0.0
			Min.	0	0	0
			Max.	100	100	100
		Week 7	n	5	33	11
			Mean	26.3	22.1	29.9
			SE	16.20	5.84	12.99
			Median	0.0	0.0	0.0
			Min.	0	0	0
			Max.	71	100	100
		Week 8	n	5	25	7
			Mean	36.0	15.2	41.2
			SE	22.27	5.05	17.94
			Median	0.0	0.0	16.7
			Min.	0	0	0
			Max.	100	75	100

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Table 7.121
Summary of Percent of Symptom-Free Days (Open-Label Ipratropium Failure Population)

				Arg/Arg (N=27)	Arg/Gly (N=62)	Gly/Gly (N=41)
-----		-----		-----		
% Symptom-free days	Ipratropium	Weeks 1-4	n	16	55	34
			Mean	25.8	26.3	28.4
			SE	10.14	4.63	6.39
			Median	0.0	7.1	1.8
			Min.	0	0	0
			Max.	100	96	100
		Weeks 5-8	n	6	39	16
			Mean	39.7	20.9	33.8
			SE	18.03	4.80	9.31
			Median	35.3	0.0	23.7
			Min.	0	0	0
			Max.	93	100	100
		Overall	n	16	55	34
			Mean	25.3	26.4	27.7
			SE	9.92	4.49	6.11
			Median	0.0	6.4	1.8
			Min.	0	0	0
			Max.	100	97	100

Table 7.122
Summary of Albuterol Use (puffs/day) (Open-Label Ipratropium Failure Population)

				Arg/Arg (N=27)	Arg/Gly (N=62)	Gly/Gly (N=41)
Albuterol use (puffs/day)	Albuterol	Week 1	n	23	62	40
			Mean	2.4	2.1	1.7
			SE	0.53	0.24	0.28
			Median	1.0	1.7	0.9
			Min.	0	0	0
			Max.	9	7	7
		Week 2	n	23	62	39
			Mean	2.5	2.2	1.8
			SE	0.47	0.26	0.30
			Median	1.7	1.9	1.1
			Min.	0	0	0
			Max.	7	8	7
		Week 3	n	23	62	39
			Mean	2.5	2.0	1.6
			SE	0.53	0.22	0.27
			Median	1.4	1.4	1.1
			Min.	0	0	0
			Max.	8	6	7
		Week 4	n	23	62	39
			Mean	2.5	2.0	1.5
			SE	0.50	0.24	0.28
			Median	1.6	1.5	1.0
			Min.	0	0	0
			Max.	7	7	6

Table 7.122
Summary of Albuterol Use (puffs/day) (Open-Label Ipratropium Failure Population)

				Arg/Arg (N=27)	Arg/Gly (N=62)	Gly/Gly (N=41)
-----	-----	-----	-----	-----	-----	-----
Albuterol use (puffs/day)	Albuterol	Week 5	n	22	62	36
			Mean	2.4	1.9	1.7
			SE	0.51	0.22	0.32
			Median	1.8	1.3	1.0
			Min.	0	0	0
			Max.	8	7	7
		Week 6	n	23	62	37
			Mean	2.5	1.9	1.7
			SE	0.55	0.22	0.29
			Median	1.4	1.6	1.1
			Min.	0	0	0
			Max.	8	7	7
		Week 7	n	23	62	36
			Mean	2.3	1.8	1.7
			SE	0.45	0.22	0.33
			Median	1.7	1.3	0.9
			Min.	0	0	0
			Max.	9	7	8
		Week 8	n	23	61	37
			Mean	2.4	1.8	2.0
			SE	0.49	0.24	0.37
			Median	1.7	1.4	1.4
			Min.	0	0	0
			Max.	9	7	11

Table 7.122
Summary of Albuterol Use (puffs/day) (Open-Label Ipratropium Failure Population)

				Arg/Arg (N=27)	Arg/Gly (N=62)	Gly/Gly (N=41)
Albuterol use (puffs/day)	Albuterol	Weeks 1-4	n	23	62	40
			Mean	2.5	2.1	1.7
			SE	0.50	0.23	0.26
			Median	1.7	1.4	1.1
			Min.	0	0	0
			Max.	7	7	7
		Weeks 5-8	n	23	62	38
			Mean	2.4	1.9	1.8
			SE	0.47	0.22	0.30
			Median	2.0	1.4	1.3
			Min.	0	0	0
			Max.	8	7	8
		Overall	n	23	62	40
			Mean	2.4	2.0	1.7
			SE	0.47	0.22	0.27
			Median	1.9	1.5	1.2
			Min.	0	0	0
			Max.	8	7	8
	Ipratropium	Week 1	n	16	55	32
			Mean	1.3	1.4	1.2
			SE	0.45	0.19	0.22
			Median	0.9	1.1	0.9
			Min.	0	0	0
			Max.	6	7	4

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Table 7.122
Summary of Albuterol Use (puffs/day) (Open-Label Ipratropium Failure Population)

				Arg/Arg (N=27)	Arg/Gly (N=62)	Gly/Gly (N=41)
-----	-----	-----	-----	-----	-----	-----
Albuterol use (puffs/day)	Ipratropium	Week 2	n	16	53	32
			Mean	1.5	1.2	0.8
			SE	0.46	0.22	0.19
			Median	1.0	0.6	0.3
			Min.	0	0	0
			Max.	7	7	4
		Week 3	n	16	55	29
			Mean	2.0	1.3	1.1
			SE	0.59	0.22	0.24
			Median	1.1	0.9	0.6
			Min.	0	0	0
			Max.	9	8	5
		Week 4	n	15	48	28
			Mean	1.8	1.5	1.1
			SE	0.57	0.26	0.26
			Median	1.4	1.0	0.8
			Min.	0	0	0
			Max.	8	9	5
		Week 5	n	6	39	16
			Mean	0.8	1.2	0.6
			SE	0.43	0.22	0.22
			Median	0.3	0.7	0.4
			Min.	0	0	0
			Max.	3	6	3

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Table 7.122
Summary of Albuterol Use (puffs/day) (Open-Label Ipratropium Failure Population)

				Arg/Arg (N=27)	Arg/Gly (N=62)	Gly/Gly (N=41)
-----	-----	-----	-----	-----	-----	-----
Albuterol use (puffs/day)	Ipratropium	Week 6	n	5	36	12
			Mean	0.3	1.3	0.7
			SE	0.28	0.25	0.21
			Median	0.0	0.9	0.5
			Min.	0	0	0
			Max.	1	7	2
		Week 7	n	5	34	12
			Mean	0.8	1.4	0.8
			SE	0.53	0.27	0.18
			Median	0.3	0.9	0.9
			Min.	0	0	0
			Max.	3	6	2
		Week 8	n	5	25	8
			Mean	0.7	1.4	0.5
			SE	0.44	0.29	0.19
			Median	0.1	1.0	0.4
			Min.	0	0	0
			Max.	2	6	1
		Weeks 1-4	n	16	55	34
			Mean	1.6	1.4	1.1
			SE	0.49	0.21	0.21
			Median	1.2	0.9	0.8
			Min.	0	0	0
			Max.	7	7	4

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Table 7.122
Summary of Albuterol Use (puffs/day) (Open-Label Ipratropium Failure Population)

				Arg/Arg (N=27)	Arg/Gly (N=62)	Gly/Gly (N=41)
-----				-----		
Albuterol use (puffs/day)	Ipratropium	Weeks 5-8	n	6	39	16
			Mean	0.6	1.3	0.6
			SE	0.36	0.22	0.17
			Median	0.3	0.7	0.6
			Min.	0	0	0
			Max.	2	6	3
		Overall	n	16	55	34
			Mean	1.6	1.3	1.1
			SE	0.48	0.20	0.20
			Median	1.1	0.9	0.7
			Min.	0	0	0
			Max.	7	7	4

Table 7.123
Summary of Ipratropium Use (puffs/day) (Open-Label Ipratropium Failure Population)

				Arg/Arg (N=27)	Arg/Gly (N=62)	Gly/Gly (N=41)
Ipratropium use	Ipratropium	Week 1	n	16	54	33
			Mean	1.9	1.4	1.3
			SE	0.42	0.17	0.20
			Median	1.5	1.1	1.1
			Min.	0	0	0
			Max.	4	5	4
		Week 2	n	16	54	33
			Mean	2.1	1.4	1.1
			SE	0.49	0.18	0.22
			Median	1.4	1.1	0.5
			Min.	0	0	0
			Max.	5	6	4
		Week 3	n	16	54	30
			Mean	2.2	1.4	1.4
			SE	0.56	0.20	0.25
			Median	1.7	0.9	0.9
			Min.	0	0	0
			Max.	7	7	4
		Week 4	n	15	48	28
			Mean	2.5	1.3	1.6
			SE	0.65	0.18	0.30
			Median	2.0	1.1	1.0
			Min.	0	0	0
			Max.	6	6	5

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Table 7.123
Summary of Ipratropium Use (puffs/day) (Open-Label Ipratropium Failure Population)

				Arg/Arg (N=27)	Arg/Gly (N=62)	Gly/Gly (N=41)
Ipratropium use	Ipratropium	Week 5	n	6	39	16
			Mean	2.3	1.3	0.8
			SE	1.07	0.19	0.24
			Median	1.5	1.0	0.5
			Min.	0	0	0
			Max.	6	5	3
		Week 6	n	5	36	12
			Mean	2.6	1.3	1.1
			SE	1.19	0.18	0.30
			Median	2.6	1.1	0.7
			Min.	0	0	0
			Max.	6	5	3
		Week 7	n	5	34	12
			Mean	3.2	1.4	1.3
			SE	1.33	0.24	0.29
			Median	2.1	1.0	1.1
			Min.	1	0	0
			Max.	7	6	3
		Week 8	n	5	25	8
			Mean	2.7	1.3	0.9
			SE	1.26	0.21	0.35
			Median	2.0	1.0	0.4
			Min.	0	0	0
			Max.	6	5	2

Table 7.123
Summary of Ipratropium Use (puffs/day) (Open-Label Ipratropium Failure Population)

				Arg/Arg (N=27)	Arg/Gly (N=62)	Gly/Gly (N=41)

Ipratropium use	Ipratropium	Weeks 1-4	n	16	54	34
			Mean	2.1	1.4	1.3
			SE	0.51	0.17	0.21
			Median	1.5	1.1	0.7
			Min.	0	0	0
			Max.	5	5	4
		Weeks 5-8	n	6	39	16
			Mean	2.4	1.3	0.9
			SE	1.08	0.18	0.24
			Median	1.4	1.0	0.7
			Min.	0	0	0
			Max.	6	5	3
		Overall	n	16	55	34
			Mean	2.2	1.4	1.3
			SE	0.53	0.15	0.21
			Median	1.5	1.1	0.8
			Min.	0	0	0
			Max.	5	5	4

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Table 8.1
Summary of Exposure to Study Drug (days)

Treatment: FSC100/50

		Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Subjects in treatment group		89	92	91	272
Double-blind treatment	n	88	92	88	268
	Mean	108.9	108.2	108.9	108.7
	SD	21.26	18.85	19.83	19.91
	Median	112.0	112.0	112.0	112.0
	Min.	17	6	3	3
Max.		149	154	146	154

Table 8.1
Summary of Exposure to Study Drug (days)

Treatment: Salmeterol

		Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
-----		-----			
Subjects in treatment group		90	90	92	272
Double-blind treatment	n	85	87	89	261
	Mean	104.7	103.1	104.2	104.0
	SD	22.94	26.91	26.72	25.53
	Median	112.0	112.0	112.0	112.0
	Min.	26	7	4	4
Max.		123	120	133	133

Trt	Arg16Gly genotype	Inv.	Subject	Treatment Start Date	Treatment Stop Date	Exposure (days)
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.						

Table 8.3
Summary of All Adverse Events During Open-Label Albuterol Period (ITT Population)

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Subjects in treatment group	89	92	91	272
Any event	43 (48%)	30 (33%)	41 (45%)	114 (42%)
Nervous system disorders				
Any event	17 (19%)	10 (11%)	13 (14%)	40 (15%)
Headache	16 (18%)	9 (10%)	10 (11%)	35 (13%)
Dizziness	0	1 (1%)	1 (1%)	2 (<1%)
Migraine	0	1 (1%)	1 (1%)	2 (<1%)
Sciatica	1 (1%)	0	1 (1%)	2 (<1%)
Hypoaesthesia	0	0	1 (1%)	1 (<1%)
Tremor	0	0	1 (1%)	1 (<1%)
Infections and infestations				
Any event	11 (12%)	10 (11%)	10 (11%)	31 (11%)
Nasopharyngitis	5 (6%)	5 (5%)	3 (3%)	13 (5%)
Influenza	1 (1%)	1 (1%)	1 (1%)	3 (1%)
Viral infection	1 (1%)	1 (1%)	1 (1%)	3 (1%)
Sinusitis	1 (1%)	1 (1%)	0	2 (<1%)
Tooth abscess	0	1 (1%)	1 (1%)	2 (<1%)
Gastroenteritis	0	1 (1%)	0	1 (<1%)
Gastroenteritis viral	0	0	1 (1%)	1 (<1%)
Herpes simplex	1 (1%)	0	0	1 (<1%)
Herpes zoster	0	0	1 (1%)	1 (<1%)
Localised infection	1 (1%)	0	0	1 (<1%)
Respiratory tract infection	1 (1%)	0	0	1 (<1%)
Rhinitis	0	0	1 (1%)	1 (<1%)
Upper respiratory tract infection	0	0	1 (1%)	1 (<1%)
Vulvovaginal mycotic infection	1 (1%)	0	0	1 (<1%)

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Table 8.3
Summary of All Adverse Events During Open-Label Albuterol Period (ITT Population)

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Respiratory, thoracic and mediastinal disorders				
Any event	13 (15%)	5 (5%)	14 (15%)	32 (12%)
Pharyngolaryngeal pain	6 (7%)	3 (3%)	4 (4%)	13 (5%)
Cough	2 (2%)	3 (3%)	3 (3%)	8 (3%)
Nasal congestion	1 (1%)	0	3 (3%)	4 (1%)
Rhinitis seasonal	1 (1%)	0	2 (2%)	3 (1%)
Sinus congestion	2 (2%)	0	0	2 (<1%)
Paranasal sinus hypersecretion	0	0	1 (1%)	1 (<1%)
Pleurisy	1 (1%)	0	0	1 (<1%)
Productive cough	1 (1%)	0	0	1 (<1%)
Respiratory tract congestion	1 (1%)	0	0	1 (<1%)
Rhinitis perennial	1 (1%)	0	0	1 (<1%)
Rhinorrhoea	0	1 (1%)	0	1 (<1%)
Throat irritation	1 (1%)	0	0	1 (<1%)
Vasomotor rhinitis	0	0	1 (1%)	1 (<1%)
Wheezing	0	0	1 (1%)	1 (<1%)
Gastrointestinal disorders				
Any event	6 (7%)	6 (7%)	10 (11%)	22 (8%)
Nausea	1 (1%)	0	4 (4%)	5 (2%)
Stomach discomfort	1 (1%)	3 (3%)	1 (1%)	5 (2%)
Abdominal pain upper	1 (1%)	1 (1%)	1 (1%)	3 (1%)
Toothache	1 (1%)	2 (2%)	0	3 (1%)
Diarrhoea	0	1 (1%)	1 (1%)	2 (<1%)
Dyspepsia	0	0	2 (2%)	2 (<1%)
Abdominal pain	1 (1%)	0	0	1 (<1%)
Abdominal pain lower	0	0	1 (1%)	1 (<1%)
Flatulence	1 (1%)	0	0	1 (<1%)
Musculoskeletal and connective tissue disorders				
Any event	8 (9%)	4 (4%)	7 (8%)	19 (7%)
Myalgia	2 (2%)	1 (1%)	4 (4%)	7 (3%)

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Table 8.3
Summary of All Adverse Events During Open-Label Albuterol Period (ITT Population)

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Back pain	1 (1%)	3 (3%)	2 (2%)	6 (2%)
Musculoskeletal chest pain	2 (2%)	0	0	2 (<1%)
Neck pain	0	1 (1%)	1 (1%)	2 (<1%)
Pain in extremity	1 (1%)	1 (1%)	0	2 (<1%)
Arthralgia	0	0	1 (1%)	1 (<1%)
Costochondritis	1 (1%)	0	0	1 (<1%)
Joint swelling	1 (1%)	0	0	1 (<1%)
Muscle spasms	0	1 (1%)	0	1 (<1%)
Musculoskeletal stiffness	0	0	1 (1%)	1 (<1%)
Injury, poisoning and procedural complications				
Any event	1 (1%)	2 (2%)	2 (2%)	5 (2%)
Joint sprain	0	0	1 (1%)	1 (<1%)
Meniscus lesion	0	0	1 (1%)	1 (<1%)
Muscle strain	0	1 (1%)	0	1 (<1%)
Patella fracture	0	1 (1%)	0	1 (<1%)
Procedural pain	0	0	1 (1%)	1 (<1%)
Whiplash injury	1 (1%)	0	0	1 (<1%)
General disorders and administration site conditions				
Any event	3 (3%)	2 (2%)	3 (3%)	8 (3%)
Pyrexia	2 (2%)	1 (1%)	0	3 (1%)
Pain	0	1 (1%)	1 (1%)	2 (<1%)
Asthenia	0	0	1 (1%)	1 (<1%)
Chest discomfort	0	0	1 (1%)	1 (<1%)
Ill-defined disorder	1 (1%)	0	0	1 (<1%)
Skin and subcutaneous tissue disorders				
Any event	2 (2%)	0	2 (2%)	4 (1%)
Angioneurotic oedema	1 (1%)	0	0	1 (<1%)
Eczema nummular	0	0	1 (1%)	1 (<1%)

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Table 8.3
Summary of All Adverse Events During Open-Label Albuterol Period (ITT Population)

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Pruritus	1 (1%)	0	0	1 (<1%)
Rash	0	0	1 (1%)	1 (<1%)
Psychiatric disorders				
Any event	3 (3%)	0	0	3 (1%)
Insomnia	3 (3%)	0	0	3 (1%)
Reproductive system and breast disorders				
Any event	1 (1%)	2 (2%)	1 (1%)	4 (1%)
Dysmenorrhoea	1 (1%)	2 (2%)	1 (1%)	4 (1%)
Ear and labyrinth disorders				
Any event	2 (2%)	1 (1%)	0	3 (1%)
Ear pain	2 (2%)	1 (1%)	0	3 (1%)
Eye disorders				
Any event	1 (1%)	1 (1%)	1 (1%)	3 (1%)
Conjunctivitis	1 (1%)	0	0	1 (<1%)
Dry eye	0	0	1 (1%)	1 (<1%)
Lacrimation increased	0	1 (1%)	0	1 (<1%)
Immune system disorders				
Any event	1 (1%)	0	1 (1%)	2 (<1%)
Hypersensitivity	0	0	1 (1%)	1 (<1%)
Multiple allergies	1 (1%)	0	0	1 (<1%)
Vascular disorders				
Any event	0	1 (1%)	0	1 (<1%)
Hypertension	0	1 (1%)	0	1 (<1%)

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Table 8.3
Summary of All Adverse Events During Open-Label Albuterol Period (ITT Population)

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Any event	1 (1%)	0	0	1 (<1%)
Uterine leiomyoma	1 (1%)	0	0	1 (<1%)

Table 8.3
Summary of All Adverse Events During Open-Label Albuterol Period (ITT Population)

Treatment: Salmeterol

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Subjects in treatment group	90	90	92	272
Any event	33 (37%)	38 (42%)	36 (39%)	107 (39%)
Nervous system disorders				
Any event	12 (13%)	17 (19%)	17 (18%)	46 (17%)
Headache	11 (12%)	15 (17%)	17 (18%)	43 (16%)
Presyncope	0	1 (1%)	0	1 (<1%)
Sinus headache	0	1 (1%)	0	1 (<1%)
Tremor	1 (1%)	0	0	1 (<1%)
Infections and infestations				
Any event	12 (13%)	10 (11%)	9 (10%)	31 (11%)
Nasopharyngitis	4 (4%)	4 (4%)	2 (2%)	10 (4%)
Influenza	2 (2%)	2 (2%)	1 (1%)	5 (2%)
Upper respiratory tract infection	4 (4%)	0	1 (1%)	5 (2%)
Viral infection	1 (1%)	1 (1%)	2 (2%)	4 (1%)
Bronchitis	1 (1%)	0	0	1 (<1%)
Cellulitis	0	0	1 (1%)	1 (<1%)
Ear infection	1 (1%)	0	0	1 (<1%)
Gastroenteritis	0	1 (1%)	0	1 (<1%)
Impetigo	0	0	1 (1%)	1 (<1%)
Malaria	1 (1%)	0	0	1 (<1%)
Rhinitis	1 (1%)	0	0	1 (<1%)
Sinusitis	0	1 (1%)	0	1 (<1%)
Skin infection	0	0	1 (1%)	1 (<1%)
Urinary tract infection	0	1 (1%)	0	1 (<1%)
Vaginal infection	0	0	1 (1%)	1 (<1%)
Respiratory, thoracic and mediastinal disorders				
Any event	7 (8%)	7 (8%)	7 (8%)	21 (8%)

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Table 8.3
Summary of All Adverse Events During Open-Label Albuterol Period (ITT Population)

Treatment: Salmeterol

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Pharyngolaryngeal pain	2 (2%)	5 (6%)	5 (5%)	12 (4%)
Nasal congestion	1 (1%)	2 (2%)	1 (1%)	4 (1%)
Cough	2 (2%)	0	1 (1%)	3 (1%)
Throat irritation	1 (1%)	1 (1%)	0	2 (<1%)
Asthma	1 (1%)	0	0	1 (<1%)
Dry throat	0	0	1 (1%)	1 (<1%)
Dyspnoea	1 (1%)	0	0	1 (<1%)
Hyperventilation	1 (1%)	0	0	1 (<1%)
Postnasal drip	0	0	1 (1%)	1 (<1%)
Rhinorrhoea	1 (1%)	0	0	1 (<1%)
Gastrointestinal disorders				
Any event	8 (9%)	9 (10%)	8 (9%)	25 (9%)
Abdominal pain upper	4 (4%)	2 (2%)	2 (2%)	8 (3%)
Toothache	1 (1%)	3 (3%)	0	4 (1%)
Vomiting	0	1 (1%)	3 (3%)	4 (1%)
Nausea	2 (2%)	0	1 (1%)	3 (1%)
Stomach discomfort	2 (2%)	1 (1%)	0	3 (1%)
Abdominal pain	0	1 (1%)	1 (1%)	2 (<1%)
Diarrhoea	1 (1%)	0	1 (1%)	2 (<1%)
Diarrhoea haemorrhagic	0	0	1 (1%)	1 (<1%)
Dry mouth	0	1 (1%)	0	1 (<1%)
Flatulence	0	0	1 (1%)	1 (<1%)
Food poisoning	0	0	1 (1%)	1 (<1%)
Gastritis	0	1 (1%)	0	1 (<1%)
Tooth disorder	0	0	1 (1%)	1 (<1%)
Musculoskeletal and connective tissue disorders				
Any event	3 (3%)	7 (8%)	5 (5%)	15 (6%)
Back pain	1 (1%)	4 (4%)	1 (1%)	6 (2%)
Myalgia	1 (1%)	1 (1%)	2 (2%)	4 (1%)
Neck pain	1 (1%)	0	1 (1%)	2 (<1%)

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Table 8.3
Summary of All Adverse Events During Open-Label Albuterol Period (ITT Population)

Treatment: Salmeterol

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Arthritis	0	1 (1%)	0	1 (<1%)
Exostosis	0	1 (1%)	0	1 (<1%)
Flank pain	0	1 (1%)	0	1 (<1%)
Joint swelling	0	0	1 (1%)	1 (<1%)
Muscle spasms	0	1 (1%)	0	1 (<1%)
Musculoskeletal stiffness	0	0	1 (1%)	1 (<1%)
Pain in extremity	0	0	1 (1%)	1 (<1%)
Injury, poisoning and procedural complications				
Any event	3 (3%)	5 (6%)	3 (3%)	11 (4%)
Foot fracture	0	1 (1%)	1 (1%)	2 (<1%)
Joint sprain	0	2 (2%)	0	2 (<1%)
Ankle fracture	0	1 (1%)	0	1 (<1%)
Back injury	0	1 (1%)	0	1 (<1%)
Clavicle fracture	0	0	1 (1%)	1 (<1%)
Excoriation	1 (1%)	0	0	1 (<1%)
Hand fracture	1 (1%)	0	0	1 (<1%)
Muscle strain	1 (1%)	0	0	1 (<1%)
Procedural pain	0	0	1 (1%)	1 (<1%)
General disorders and administration site conditions				
Any event	2 (2%)	2 (2%)	3 (3%)	7 (3%)
Pyrexia	1 (1%)	1 (1%)	1 (1%)	3 (1%)
Fatigue	1 (1%)	1 (1%)	0	2 (<1%)
Chest discomfort	0	0	1 (1%)	1 (<1%)
Influenza like illness	0	0	1 (1%)	1 (<1%)
Skin and subcutaneous tissue disorders				
Any event	1 (1%)	1 (1%)	2 (2%)	4 (1%)
Dermatitis contact	0	0	1 (1%)	1 (<1%)
Onychalgia	0	1 (1%)	0	1 (<1%)

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Table 8.3
Summary of All Adverse Events During Open-Label Albuterol Period (ITT Population)

Treatment: Salmeterol

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Pruritus allergic	0	0	1 (1%)	1 (<1%)
Urticaria	1 (1%)	0	0	1 (<1%)
Psychiatric disorders				
Any event	1 (1%)	2 (2%)	0	3 (1%)
Insomnia	0	2 (2%)	0	2 (<1%)
Depression	1 (1%)	0	0	1 (<1%)
Reproductive system and breast disorders				
Any event	0	2 (2%)	0	2 (<1%)
Dysmenorrhoea	0	2 (2%)	0	2 (<1%)
Ovarian cyst	0	1 (1%)	0	1 (<1%)
Pelvic pain	0	1 (1%)	0	1 (<1%)
Renal and urinary disorders				
Any event	0	2 (2%)	1 (1%)	3 (1%)
Micturition urgency	0	1 (1%)	0	1 (<1%)
Nephrolithiasis	0	0	1 (1%)	1 (<1%)
Stress urinary incontinence	0	1 (1%)	0	1 (<1%)
Vascular disorders				
Any event	0	0	1 (1%)	1 (<1%)
Hypertension	0	0	1 (1%)	1 (<1%)

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Table 8.4
Summary of All Adverse Events During Open-Label Ipratropium Period (ITT Population)

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Subjects in treatment group	89	92	91	272
Any event	26 (29%)	32 (35%)	41 (45%)	99 (36%)
Nervous system disorders				
Any event	11 (12%)	11 (12%)	15 (16%)	37 (14%)
Headache	11 (12%)	11 (12%)	13 (14%)	35 (13%)
Dizziness	1 (1%)	1 (1%)	0	2 (<1%)
Sinus headache	0	0	2 (2%)	2 (<1%)
Tension headache	0	0	1 (1%)	1 (<1%)
Tremor	0	1 (1%)	0	1 (<1%)
Infections and infestations				
Any event	7 (8%)	4 (4%)	10 (11%)	21 (8%)
Influenza	1 (1%)	0	5 (5%)	6 (2%)
Nasopharyngitis	2 (2%)	1 (1%)	1 (1%)	4 (1%)
Upper respiratory tract infection	1 (1%)	1 (1%)	1 (1%)	3 (1%)
Bronchitis	2 (2%)	0	0	2 (<1%)
Vulvovaginal mycotic infection	1 (1%)	1 (1%)	0	2 (<1%)
Gastroenteritis	1 (1%)	0	0	1 (<1%)
Gastroenteritis viral	0	0	1 (1%)	1 (<1%)
Lower respiratory tract infection	0	0	1 (1%)	1 (<1%)
Oophoritis	0	0	1 (1%)	1 (<1%)
Sinusitis	0	1 (1%)	0	1 (<1%)
Respiratory, thoracic and mediastinal disorders				
Any event	9 (10%)	5 (5%)	7 (8%)	21 (8%)
Pharyngolaryngeal pain	3 (3%)	3 (3%)	3 (3%)	9 (3%)
Cough	3 (3%)	1 (1%)	3 (3%)	7 (3%)
Nasal congestion	0	1 (1%)	2 (2%)	3 (1%)
Asthma	1 (1%)	0	0	1 (<1%)

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Table 8.4
Summary of All Adverse Events During Open-Label Ipratropium Period (ITT Population)

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Dyspnoea	1 (1%)	0	0	1 (<1%)
Rhinitis allergic	0	0	1 (1%)	1 (<1%)
Rhinorrhoea	0	0	1 (1%)	1 (<1%)
Sinus congestion	1 (1%)	0	0	1 (<1%)
Wheezing	1 (1%)	0	0	1 (<1%)
Gastrointestinal disorders				
Any event	5 (6%)	8 (9%)	11 (12%)	24 (9%)
Toothache	1 (1%)	3 (3%)	6 (7%)	10 (4%)
Abdominal pain	1 (1%)	1 (1%)	1 (1%)	3 (1%)
Abdominal pain upper	2 (2%)	0	1 (1%)	3 (1%)
Dyspepsia	1 (1%)	1 (1%)	1 (1%)	3 (1%)
Nausea	1 (1%)	1 (1%)	1 (1%)	3 (1%)
Diarrhoea	1 (1%)	1 (1%)	0	2 (<1%)
Constipation	0	1 (1%)	0	1 (<1%)
Stomach discomfort	0	0	1 (1%)	1 (<1%)
Vomiting	0	0	1 (1%)	1 (<1%)
Musculoskeletal and connective tissue disorders				
Any event	4 (4%)	5 (5%)	5 (5%)	14 (5%)
Back pain	2 (2%)	1 (1%)	2 (2%)	5 (2%)
Arthralgia	1 (1%)	1 (1%)	0	2 (<1%)
Musculoskeletal pain	0	1 (1%)	1 (1%)	2 (<1%)
Musculoskeletal stiffness	0	1 (1%)	1 (1%)	2 (<1%)
Myalgia	1 (1%)	0	1 (1%)	2 (<1%)
Muscle tightness	0	1 (1%)	0	1 (<1%)
Neck pain	0	1 (1%)	0	1 (<1%)
Pain in extremity	0	0	1 (1%)	1 (<1%)
Injury, poisoning and procedural complications				
Any event	1 (1%)	3 (3%)	4 (4%)	8 (3%)
Back injury	0	0	2 (2%)	2 (<1%)

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Table 8.4
Summary of All Adverse Events During Open-Label Ipratropium Period (ITT Population)

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Procedural pain	1 (1%)	1 (1%)	0	2 (<1%)
Arthropod bite	0	1 (1%)	0	1 (<1%)
Arthropod sting	0	0	1 (1%)	1 (<1%)
Contusion	0	0	1 (1%)	1 (<1%)
Corneal abrasion	0	0	1 (1%)	1 (<1%)
Joint dislocation	0	1 (1%)	0	1 (<1%)
Joint injury	0	0	1 (1%)	1 (<1%)
General disorders and administration site conditions				
Any event	0	2 (2%)	4 (4%)	6 (2%)
Pain	0	1 (1%)	1 (1%)	2 (<1%)
Pyrexia	0	1 (1%)	1 (1%)	2 (<1%)
Chest pain	0	1 (1%)	0	1 (<1%)
Ill-defined disorder	0	0	1 (1%)	1 (<1%)
Non-cardiac chest pain	0	0	1 (1%)	1 (<1%)
Reproductive system and breast disorders				
Any event	1 (1%)	3 (3%)	2 (2%)	6 (2%)
Dysmenorrhoea	0	3 (3%)	1 (1%)	4 (1%)
Endometriosis	1 (1%)	0	0	1 (<1%)
Ovarian cyst	0	0	1 (1%)	1 (<1%)
Polycystic ovaries	1 (1%)	0	0	1 (<1%)
Psychiatric disorders				
Any event	0	1 (1%)	1 (1%)	2 (<1%)
Insomnia	0	1 (1%)	1 (1%)	2 (<1%)
Skin and subcutaneous tissue disorders				
Any event	0	0	2 (2%)	2 (<1%)
Dermatitis allergic	0	0	1 (1%)	1 (<1%)
Pruritus	0	0	1 (1%)	1 (<1%)

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Table 8.4
Summary of All Adverse Events During Open-Label Ipratropium Period (ITT Population)

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Immune system disorders				
Any event	1 (1%)	1 (1%)	0	2 (<1%)
Multiple allergies	1 (1%)	0	0	1 (<1%)
Seasonal allergy	0	1 (1%)	0	1 (<1%)
Ear and labyrinth disorders				
Any event	0	1 (1%)	0	1 (<1%)
Ear pain	0	1 (1%)	0	1 (<1%)
Endocrine disorders				
Any event	0	0	1 (1%)	1 (<1%)
Hypothyroidism	0	0	1 (1%)	1 (<1%)

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Table 8.4
Summary of All Adverse Events During Open-Label Ipratropium Period (ITT Population)

Treatment: Salmeterol

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Subjects in treatment group	90	90	92	272
Any event	22 (24%)	24 (27%)	36 (39%)	82 (30%)
Nervous system disorders				
Any event	7 (8%)	10 (11%)	12 (13%)	29 (11%)
Headache	6 (7%)	9 (10%)	11 (12%)	26 (10%)
Sinus headache	1 (1%)	0	2 (2%)	3 (1%)
Dizziness	1 (1%)	0	0	1 (<1%)
Migraine	0	1 (1%)	0	1 (<1%)
Infections and infestations				
Any event	6 (7%)	5 (6%)	12 (13%)	23 (8%)
Nasopharyngitis	2 (2%)	1 (1%)	4 (4%)	7 (3%)
Sinusitis	0	0	3 (3%)	3 (1%)
Influenza	0	1 (1%)	1 (1%)	2 (<1%)
Pharyngitis	0	1 (1%)	1 (1%)	2 (<1%)
Upper respiratory tract infection	2 (2%)	0	0	2 (<1%)
Viral infection	1 (1%)	0	1 (1%)	2 (<1%)
Cystitis	0	1 (1%)	0	1 (<1%)
Ear infection	1 (1%)	0	0	1 (<1%)
Herpes simplex	0	0	1 (1%)	1 (<1%)
Nail infection	0	1 (1%)	0	1 (<1%)
Pyelonephritis	0	0	1 (1%)	1 (<1%)
Viral upper respiratory tract infection	0	0	1 (1%)	1 (<1%)
Respiratory, thoracic and mediastinal disorders				
Any event	8 (9%)	5 (6%)	7 (8%)	20 (7%)
Pharyngolaryngeal pain	2 (2%)	3 (3%)	4 (4%)	9 (3%)
Cough	2 (2%)	1 (1%)	2 (2%)	5 (2%)
Choking sensation	0	0	1 (1%)	1 (<1%)

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Table 8.4
Summary of All Adverse Events During Open-Label Ipratropium Period (ITT Population)

Treatment: Salmeterol

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Dyspnoea	1 (1%)	0	0	1 (<1%)
Epistaxis	0	0	1 (1%)	1 (<1%)
Nasal congestion	0	0	1 (1%)	1 (<1%)
Rhinitis allergic	1 (1%)	0	0	1 (<1%)
Rhinorrhoea	1 (1%)	0	0	1 (<1%)
Throat irritation	0	1 (1%)	0	1 (<1%)
Wheezing	1 (1%)	0	0	1 (<1%)
Gastrointestinal disorders				
Any event	5 (6%)	5 (6%)	5 (5%)	15 (6%)
Toothache	1 (1%)	3 (3%)	2 (2%)	6 (2%)
Stomach discomfort	2 (2%)	0	0	2 (<1%)
Abdominal distension	1 (1%)	0	0	1 (<1%)
Aphthous stomatitis	0	1 (1%)	0	1 (<1%)
Diarrhoea	0	0	1 (1%)	1 (<1%)
Dyspepsia	0	0	1 (1%)	1 (<1%)
Gastrooesophageal reflux disease	1 (1%)	0	0	1 (<1%)
Nausea	0	0	1 (1%)	1 (<1%)
Vomiting	0	1 (1%)	0	1 (<1%)
Musculoskeletal and connective tissue disorders				
Any event	2 (2%)	5 (6%)	2 (2%)	9 (3%)
Back pain	2 (2%)	2 (2%)	1 (1%)	5 (2%)
Arthralgia	0	1 (1%)	1 (1%)	2 (<1%)
Muscle spasms	1 (1%)	0	0	1 (<1%)
Myalgia	0	1 (1%)	0	1 (<1%)
Neck pain	0	1 (1%)	0	1 (<1%)
Injury, poisoning and procedural complications				
Any event	0	0	3 (3%)	3 (1%)
Joint sprain	0	0	2 (2%)	2 (<1%)
Lower limb fracture	0	0	1 (1%)	1 (<1%)

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Table 8.4
Summary of All Adverse Events During Open-Label Ipratropium Period (ITT Population)

Treatment: Salmeterol

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)

General disorders and administration site conditions				
Any event	1 (1%)	2 (2%)	0	3 (1%)
Pyrexia	1 (1%)	2 (2%)	0	3 (1%)
Ill-defined disorder	1 (1%)	0	0	1 (<1%)
Pain	0	1 (1%)	0	1 (<1%)
Reproductive system and breast disorders				
Any event	1 (1%)	0	1 (1%)	2 (<1%)
Dysmenorrhoea	1 (1%)	0	1 (1%)	2 (<1%)
Psychiatric disorders				
Any event	0	2 (2%)	1 (1%)	3 (1%)
Anxiety	0	1 (1%)	0	1 (<1%)
Depression	0	0	1 (1%)	1 (<1%)
Insomnia	0	1 (1%)	0	1 (<1%)
Skin and subcutaneous tissue disorders				
Any event	2 (2%)	0	1 (1%)	3 (1%)
Acne	1 (1%)	0	0	1 (<1%)
Dermatitis contact	0	0	1 (1%)	1 (<1%)
Photosensitivity reaction	1 (1%)	0	0	1 (<1%)
Immune system disorders				
Any event	1 (1%)	0	1 (1%)	2 (<1%)
Hypersensitivity	1 (1%)	0	1 (1%)	2 (<1%)
Ear and labyrinth disorders				
Any event	1 (1%)	0	0	1 (<1%)
Ear pain	1 (1%)	0	0	1 (<1%)

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Table 8.4
Summary of All Adverse Events During Open-Label Ipratropium Period (ITT Population)

Treatment: Salmeterol

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)

Eye disorders				
Any event	0	0	2 (2%)	2 (<1%)
Eye allergy	0	0	1 (1%)	1 (<1%)
Eye pruritus	0	0	1 (1%)	1 (<1%)

Table 8.5
Summary of All Adverse Events During Double-Blind Treatment (ITT Population)

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Subjects in treatment group	89	92	91	272
Any event	43 (48%)	44 (48%)	45 (49%)	132 (49%)
Infections and infestations				
Any event	16 (18%)	17 (18%)	26 (29%)	59 (22%)
Nasopharyngitis	3 (3%)	6 (7%)	12 (13%)	21 (8%)
Upper respiratory tract infection	1 (1%)	3 (3%)	4 (4%)	8 (3%)
Influenza	1 (1%)	0	5 (5%)	6 (2%)
Sinusitis	2 (2%)	3 (3%)	1 (1%)	6 (2%)
Bronchitis	1 (1%)	1 (1%)	1 (1%)	3 (1%)
Lower respiratory tract infection	0	1 (1%)	2 (2%)	3 (1%)
Pharyngitis streptococcal	1 (1%)	2 (2%)	0	3 (1%)
Pharyngitis	2 (2%)	0	0	2 (<1%)
Pneumonia	0	0	2 (2%)	2 (<1%)
Viral infection	1 (1%)	1 (1%)	0	2 (<1%)
Acute sinusitis	1 (1%)	0	0	1 (<1%)
Arthritis infective	0	0	1 (1%)	1 (<1%)
Candidiasis	0	1 (1%)	0	1 (<1%)
Cystitis	1 (1%)	0	0	1 (<1%)
Gingival infection	0	1 (1%)	0	1 (<1%)
Herpes zoster	0	0	1 (1%)	1 (<1%)
Malaria	0	0	1 (1%)	1 (<1%)
Otitis media	1 (1%)	0	0	1 (<1%)
Respiratory tract infection	1 (1%)	0	0	1 (<1%)
Tooth abscess	1 (1%)	0	0	1 (<1%)
Tooth infection	1 (1%)	0	0	1 (<1%)
Urinary tract infection	1 (1%)	0	0	1 (<1%)
Vulvovaginal mycotic infection	1 (1%)	0	0	1 (<1%)

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Table 8.5
Summary of All Adverse Events During Double-Blind Treatment (ITT Population)

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Nervous system disorders				
Any event	10 (11%)	20 (22%)	12 (13%)	42 (15%)
Headache	8 (9%)	19 (21%)	9 (10%)	36 (13%)
Migraine	0	1 (1%)	2 (2%)	3 (1%)
Aphonia	1 (1%)	0	0	1 (<1%)
Dizziness	0	1 (1%)	0	1 (<1%)
Sciatica	0	0	1 (1%)	1 (<1%)
Tension headache	1 (1%)	0	0	1 (<1%)
Respiratory, thoracic and mediastinal disorders				
Any event	9 (10%)	11 (12%)	8 (9%)	28 (10%)
Pharyngolaryngeal pain	5 (6%)	4 (4%)	2 (2%)	11 (4%)
Cough	1 (1%)	6 (7%)	1 (1%)	8 (3%)
Nasal congestion	1 (1%)	1 (1%)	3 (3%)	5 (2%)
Sinus congestion	2 (2%)	0	1 (1%)	3 (1%)
Upper respiratory tract congestion	1 (1%)	1 (1%)	0	2 (<1%)
Dry throat	1 (1%)	0	0	1 (<1%)
Respiratory tract congestion	0	1 (1%)	0	1 (<1%)
Rhinitis allergic	0	0	1 (1%)	1 (<1%)
Rhinorrhoea	0	1 (1%)	0	1 (<1%)
Throat irritation	0	0	1 (1%)	1 (<1%)
Musculoskeletal and connective tissue disorders				
Any event	6 (7%)	8 (9%)	7 (8%)	21 (8%)
Back pain	2 (2%)	2 (2%)	2 (2%)	6 (2%)
Arthralgia	1 (1%)	3 (3%)	1 (1%)	5 (2%)
Myalgia	1 (1%)	1 (1%)	2 (2%)	4 (1%)
Pain in extremity	1 (1%)	1 (1%)	1 (1%)	3 (1%)
Musculoskeletal stiffness	0	0	2 (2%)	2 (<1%)
Arthritis	0	0	1 (1%)	1 (<1%)
Neck pain	0	1 (1%)	0	1 (<1%)
Tendon pain	0	1 (1%)	0	1 (<1%)

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Table 8.5
Summary of All Adverse Events During Double-Blind Treatment (ITT Population)

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Tendonitis	1 (1%)	0	0	1 (<1%)
Gastrointestinal disorders				
Any event	5 (6%)	12 (13%)	3 (3%)	20 (7%)
Toothache	0	4 (4%)	0	4 (1%)
Abdominal pain upper	0	2 (2%)	1 (1%)	3 (1%)
Diarrhoea	1 (1%)	0	2 (2%)	3 (1%)
Dyspepsia	0	3 (3%)	0	3 (1%)
Stomach discomfort	2 (2%)	1 (1%)	0	3 (1%)
Gastrooesophageal reflux disease	1 (1%)	1 (1%)	0	2 (<1%)
Vomiting	0	1 (1%)	1 (1%)	2 (<1%)
Abdominal pain	0	1 (1%)	0	1 (<1%)
Nausea	0	0	1 (1%)	1 (<1%)
Oral pain	1 (1%)	0	0	1 (<1%)
General disorders and administration site conditions				
Any event	6 (7%)	2 (2%)	3 (3%)	11 (4%)
Pyrexia	3 (3%)	0	2 (2%)	5 (2%)
Pain	0	1 (1%)	1 (1%)	2 (<1%)
Chest discomfort	0	1 (1%)	0	1 (<1%)
Fatigue	1 (1%)	0	0	1 (<1%)
Influenza like illness	1 (1%)	0	0	1 (<1%)
Non-cardiac chest pain	1 (1%)	0	0	1 (<1%)
Ulcer	1 (1%)	0	0	1 (<1%)
Injury, poisoning and procedural complications				
Any event	5 (6%)	4 (4%)	3 (3%)	12 (4%)
Joint sprain	0	2 (2%)	0	2 (<1%)
Procedural pain	1 (1%)	0	1 (1%)	2 (<1%)
Tendon rupture	1 (1%)	1 (1%)	0	2 (<1%)
Contusion	0	0	1 (1%)	1 (<1%)

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Table 8.5
Summary of All Adverse Events During Double-Blind Treatment (ITT Population)

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Fractured coccyx	1 (1%)	0	0	1 (<1%)
Muscle strain	0	0	1 (1%)	1 (<1%)
Patella fracture	0	1 (1%)	0	1 (<1%)
Tooth fracture	1 (1%)	0	0	1 (<1%)
Upper limb fracture	1 (1%)	0	0	1 (<1%)
Psychiatric disorders				
Any event	3 (3%)	1 (1%)	1 (1%)	5 (2%)
Insomnia	3 (3%)	1 (1%)	1 (1%)	5 (2%)
Reproductive system and breast disorders				
Any event	0	4 (4%)	1 (1%)	5 (2%)
Dysmenorrhoea	0	3 (3%)	1 (1%)	4 (1%)
Polymenorrhoea	0	1 (1%)	0	1 (<1%)
Ear and labyrinth disorders				
Any event	1 (1%)	0	3 (3%)	4 (1%)
Ear pain	0	0	1 (1%)	1 (<1%)
Middle ear effusion	0	0	1 (1%)	1 (<1%)
Motion sickness	1 (1%)	0	0	1 (<1%)
Tinnitus	0	0	1 (1%)	1 (<1%)
Skin and subcutaneous tissue disorders				
Any event	0	1 (1%)	0	1 (<1%)
Photodermatitis	0	1 (1%)	0	1 (<1%)
Vascular disorders				
Any event	1 (1%)	1 (1%)	1 (1%)	3 (1%)
Hypertension	0	1 (1%)	1 (1%)	2 (<1%)
Vasculitis	1 (1%)	0	0	1 (<1%)

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Table 8.5
Summary of All Adverse Events During Double-Blind Treatment (ITT Population)

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Cardiac disorders				
Any event	0	0	1 (1%)	1 (<1%)
Palpitations	0	0	1 (1%)	1 (<1%)
Eye disorders				
Any event	0	0	1 (1%)	1 (<1%)
Vision blurred	0	0	1 (1%)	1 (<1%)
Immune system disorders				
Any event	0	0	2 (2%)	2 (<1%)
Multiple allergies	0	0	2 (2%)	2 (<1%)
Hypersensitivity	0	0	1 (1%)	1 (<1%)
Blood and lymphatic system disorders				
Any event	0	0	1 (1%)	1 (<1%)
Anaemia	0	0	1 (1%)	1 (<1%)
Surgical and medical procedures				
Any event	1 (1%)	0	0	1 (<1%)
Breast lump removal	1 (1%)	0	0	1 (<1%)

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Table 8.5
Summary of All Adverse Events During Double-Blind Treatment (ITT Population)

Treatment: Salmeterol

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Subjects in treatment group	90	90	92	272
Any event	39 (43%)	37 (41%)	44 (48%)	120 (44%)
Infections and infestations				
Any event	26 (29%)	15 (17%)	20 (22%)	61 (22%)
Nasopharyngitis	6 (7%)	3 (3%)	9 (10%)	18 (7%)
Upper respiratory tract infection	7 (8%)	2 (2%)	3 (3%)	12 (4%)
Sinusitis	6 (7%)	0	2 (2%)	8 (3%)
Bronchitis	3 (3%)	0	1 (1%)	4 (1%)
Influenza	1 (1%)	1 (1%)	1 (1%)	3 (1%)
Pharyngitis	1 (1%)	2 (2%)	0	3 (1%)
Viral infection	1 (1%)	0	2 (2%)	3 (1%)
Gastroenteritis viral	1 (1%)	1 (1%)	0	2 (<1%)
Lower respiratory tract infection	1 (1%)	0	1 (1%)	2 (<1%)
Tonsillitis	0	0	2 (2%)	2 (<1%)
Tooth infection	0	1 (1%)	1 (1%)	2 (<1%)
Viral upper respiratory tract infection	0	2 (2%)	0	2 (<1%)
Acute sinusitis	1 (1%)	0	0	1 (<1%)
Ear infection	1 (1%)	0	0	1 (<1%)
Kidney infection	0	1 (1%)	0	1 (<1%)
Lyme disease	0	1 (1%)	0	1 (<1%)
Onychomycosis	0	1 (1%)	0	1 (<1%)
Pneumonia	0	1 (1%)	0	1 (<1%)
Respiratory tract infection	1 (1%)	0	0	1 (<1%)
Tooth abscess	0	0	1 (1%)	1 (<1%)
Urethritis	0	1 (1%)	0	1 (<1%)
Urinary tract infection	0	0	1 (1%)	1 (<1%)
Nervous system disorders				
Any event	7 (8%)	12 (13%)	15 (16%)	34 (13%)

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Table 8.5
Summary of All Adverse Events During Double-Blind Treatment (ITT Population)

Treatment: Salmeterol

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Headache	6 (7%)	12 (13%)	12 (13%)	30 (11%)
Sinus headache	1 (1%)	0	2 (2%)	3 (1%)
Tremor	0	0	2 (2%)	2 (<1%)
Respiratory, thoracic and mediastinal disorders				
Any event	7 (8%)	6 (7%)	8 (9%)	21 (8%)
Pharyngolaryngeal pain	1 (1%)	3 (3%)	3 (3%)	7 (3%)
Cough	0	1 (1%)	3 (3%)	4 (1%)
Nasal congestion	1 (1%)	0	2 (2%)	3 (1%)
Asthma	0	1 (1%)	1 (1%)	2 (<1%)
Dry throat	0	0	1 (1%)	1 (<1%)
Dyspnoea	1 (1%)	0	0	1 (<1%)
Epistaxis	0	1 (1%)	0	1 (<1%)
Rhinitis allergic	1 (1%)	0	0	1 (<1%)
Rhinorrhoea	1 (1%)	0	0	1 (<1%)
Sinus congestion	0	1 (1%)	0	1 (<1%)
Snoring	1 (1%)	0	0	1 (<1%)
Throat irritation	1 (1%)	0	0	1 (<1%)
Musculoskeletal and connective tissue disorders				
Any event	4 (4%)	6 (7%)	8 (9%)	18 (7%)
Back pain	0	1 (1%)	6 (7%)	7 (3%)
Arthralgia	0	1 (1%)	2 (2%)	3 (1%)
Musculoskeletal pain	1 (1%)	2 (2%)	0	3 (1%)
Myalgia	1 (1%)	1 (1%)	0	2 (<1%)
Muscle spasms	1 (1%)	0	0	1 (<1%)
Musculoskeletal chest pain	0	1 (1%)	0	1 (<1%)
Pain in extremity	0	1 (1%)	0	1 (<1%)
Tendonitis	1 (1%)	0	0	1 (<1%)
Gastrointestinal disorders				
Any event	3 (3%)	6 (7%)	3 (3%)	12 (4%)

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Table 8.5
Summary of All Adverse Events During Double-Blind Treatment (ITT Population)

Treatment: Salmeterol

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Abdominal pain upper	0	2 (2%)	0	2 (<1%)
Diarrhoea	1 (1%)	1 (1%)	0	2 (<1%)
Dyspepsia	0	1 (1%)	1 (1%)	2 (<1%)
Vomiting	2 (2%)	0	0	2 (<1%)
Aphthous stomatitis	0	0	1 (1%)	1 (<1%)
Gastrooesophageal reflux disease	0	1 (1%)	0	1 (<1%)
Nausea	0	0	1 (1%)	1 (<1%)
Toothache	0	1 (1%)	0	1 (<1%)
General disorders and administration site conditions				
Any event	0	2 (2%)	5 (5%)	7 (3%)
Pain	0	1 (1%)	3 (3%)	4 (1%)
Pyrexia	0	2 (2%)	0	2 (<1%)
Chest discomfort	0	0	1 (1%)	1 (<1%)
Feeling jittery	0	0	1 (1%)	1 (<1%)
Oedema peripheral	0	0	1 (1%)	1 (<1%)
Injury, poisoning and procedural complications				
Any event	2 (2%)	3 (3%)	1 (1%)	6 (2%)
Back injury	0	0	1 (1%)	1 (<1%)
Fall	0	1 (1%)	0	1 (<1%)
Limb injury	1 (1%)	0	0	1 (<1%)
Muscle strain	1 (1%)	0	0	1 (<1%)
Procedural pain	0	1 (1%)	0	1 (<1%)
Skin laceration	0	1 (1%)	0	1 (<1%)
Psychiatric disorders				
Any event	0	2 (2%)	1 (1%)	3 (1%)
Insomnia	0	0	1 (1%)	1 (<1%)
Nervousness	0	1 (1%)	0	1 (<1%)
Panic attack	0	1 (1%)	0	1 (<1%)

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Table 8.5
Summary of All Adverse Events During Double-Blind Treatment (ITT Population)

Treatment: Salmeterol

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Restlessness	0	0	1 (1%)	1 (<1%)
Reproductive system and breast disorders				
Any event	1 (1%)	2 (2%)	0	3 (1%)
Dysmenorrhoea	1 (1%)	1 (1%)	0	2 (<1%)
Menorrhagia	1 (1%)	0	0	1 (<1%)
Ovarian cyst ruptured	0	1 (1%)	0	1 (<1%)
Ear and labyrinth disorders				
Any event	1 (1%)	0	1 (1%)	2 (<1%)
Motion sickness	1 (1%)	0	0	1 (<1%)
Vertigo	0	0	1 (1%)	1 (<1%)
Skin and subcutaneous tissue disorders				
Any event	0	1 (1%)	2 (2%)	3 (1%)
Rash	0	1 (1%)	2 (2%)	3 (1%)
Vascular disorders				
Any event	0	0	1 (1%)	1 (<1%)
Haematoma	0	0	1 (1%)	1 (<1%)
Cardiac disorders				
Any event	0	1 (1%)	1 (1%)	2 (<1%)
Palpitations	0	1 (1%)	1 (1%)	2 (<1%)
Eye disorders				
Any event	2 (2%)	0	0	2 (<1%)
Conjunctivitis	1 (1%)	0	0	1 (<1%)
Conjunctivitis allergic	1 (1%)	0	0	1 (<1%)
Investigations				
Any event	0	1 (1%)	0	1 (<1%)

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Table 8.5
Summary of All Adverse Events During Double-Blind Treatment (ITT Population)

Treatment: Salmeterol

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Heart rate irregular	0	1 (1%)	0	1 (<1%)
Renal and urinary disorders				
Any event	0	0	1 (1%)	1 (<1%)
Nephrolithiasis	0	0	1 (1%)	1 (<1%)

Table 8.6
Summary of Most Common (>3%) Adverse Events During Double-Blind Treatment (ITT Population)

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Subjects in treatment group	89	92	91	272
Any event	43 (48%)	44 (48%)	45 (49%)	132 (49%)
Headache	8 (9%)	19 (21%)	9 (10%)	36 (13%)
Nasopharyngitis	3 (3%)	6 (7%)	12 (13%)	21 (8%)
Upper respiratory tract infection	1 (1%)	3 (3%)	4 (4%)	8 (3%)
Pharyngolaryngeal pain	5 (6%)	4 (4%)	2 (2%)	11 (4%)
Cough	1 (1%)	6 (7%)	1 (1%)	8 (3%)
Influenza	1 (1%)	0	5 (5%)	6 (2%)
Toothache	0	4 (4%)	0	4 (1%)

Table 8.6
Summary of Most Common (>3%) Adverse Events During Double-Blind Treatment (ITT Population)

Treatment: Salmeterol

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Subjects in treatment group	90	90	92	272
Any event	39 (43%)	37 (41%)	44 (48%)	120 (44%)
Headache	6 (7%)	12 (13%)	12 (13%)	30 (11%)
Nasopharyngitis	6 (7%)	3 (3%)	9 (10%)	18 (7%)
Upper respiratory tract infection	7 (8%)	2 (2%)	3 (3%)	12 (4%)
Sinusitis	6 (7%)	0	2 (2%)	8 (3%)
Back pain	0	1 (1%)	6 (7%)	7 (3%)

Table 8.7
Summary of All Adverse Events Post Double-Blind Treatment (ITT Population)

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Subjects in treatment group	89	92	91	272
Any event	6 (7%)	14 (15%)	10 (11%)	30 (11%)
Infections and infestations				
Any event	2 (2%)	4 (4%)	2 (2%)	8 (3%)
Nasopharyngitis	1 (1%)	2 (2%)	0	3 (1%)
Upper respiratory tract infection	1 (1%)	0	1 (1%)	2 (<1%)
Ear infection	0	0	1 (1%)	1 (<1%)
Pharyngitis	0	1 (1%)	0	1 (<1%)
Pharyngitis bacterial	0	1 (1%)	0	1 (<1%)
Viral infection	0	0	1 (1%)	1 (<1%)
Respiratory, thoracic and mediastinal disorders				
Any event	1 (1%)	6 (7%)	4 (4%)	11 (4%)
Cough	1 (1%)	2 (2%)	2 (2%)	5 (2%)
Pharyngolaryngeal pain	0	1 (1%)	2 (2%)	3 (1%)
Nasal congestion	1 (1%)	1 (1%)	0	2 (<1%)
Nasal oedema	0	1 (1%)	0	1 (<1%)
Paranasal sinus hypersecretion	0	0	1 (1%)	1 (<1%)
Rhinitis allergic	0	1 (1%)	0	1 (<1%)
Sinus congestion	0	0	1 (1%)	1 (<1%)
Nervous system disorders				
Any event	0	6 (7%)	1 (1%)	7 (3%)
Headache	0	6 (7%)	0	6 (2%)
Dizziness	0	1 (1%)	0	1 (<1%)
Tension headache	0	0	1 (1%)	1 (<1%)

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Table 8.7
Summary of All Adverse Events Post Double-Blind Treatment (ITT Population)

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Gastrointestinal disorders				
Any event	0	1 (1%)	0	1 (<1%)
Abdominal pain upper	0	1 (1%)	0	1 (<1%)
Musculoskeletal and connective tissue disorders				
Any event	0	0	3 (3%)	3 (1%)
Back pain	0	0	2 (2%)	2 (<1%)
Musculoskeletal stiffness	0	0	1 (1%)	1 (<1%)
Neck pain	0	0	1 (1%)	1 (<1%)
Skin and subcutaneous tissue disorders				
Any event	1 (1%)	0	0	1 (<1%)
Dry skin	1 (1%)	0	0	1 (<1%)
General disorders and administration site conditions				
Any event	1 (1%)	0	1 (1%)	2 (<1%)
Chest discomfort	0	0	1 (1%)	1 (<1%)
Pain	1 (1%)	0	0	1 (<1%)
Reproductive system and breast disorders				
Any event	0	1 (1%)	0	1 (<1%)
Dysmenorrhoea	0	1 (1%)	0	1 (<1%)
Ear and labyrinth disorders				
Any event	0	0	1 (1%)	1 (<1%)
Ear pain	0	0	1 (1%)	1 (<1%)
Eye disorders				
Any event	0	1 (1%)	0	1 (<1%)
Conjunctivitis	0	1 (1%)	0	1 (<1%)

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Table 8.7
Summary of All Adverse Events Post Double-Blind Treatment (ITT Population)

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Psychiatric disorders				
Any event	0	1 (1%)	0	1 (<1%)
Insomnia	0	1 (1%)	0	1 (<1%)
Surgical and medical procedures				
Any event	1 (1%)	0	0	1 (<1%)
Sinus operation	1 (1%)	0	0	1 (<1%)

Table 8.7
Summary of All Adverse Events Post Double-Blind Treatment (ITT Population)

Treatment: Salmeterol

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Subjects in treatment group	90	90	92	272
Any event	7 (8%)	14 (16%)	7 (8%)	28 (10%)
Infections and infestations				
Any event	3 (3%)	2 (2%)	4 (4%)	9 (3%)
Nasopharyngitis	2 (2%)	1 (1%)	2 (2%)	5 (2%)
Gastroenteritis viral	0	0	1 (1%)	1 (<1%)
Influenza	0	0	1 (1%)	1 (<1%)
Pharyngitis	0	1 (1%)	0	1 (<1%)
Upper respiratory tract infection	1 (1%)	0	0	1 (<1%)
Respiratory, thoracic and mediastinal disorders				
Any event	1 (1%)	3 (3%)	0	4 (1%)
Epistaxis	1 (1%)	0	0	1 (<1%)
Nasal oedema	0	1 (1%)	0	1 (<1%)
Pharyngolaryngeal pain	0	1 (1%)	0	1 (<1%)
Sinus congestion	0	1 (1%)	0	1 (<1%)
Nervous system disorders				
Any event	3 (3%)	1 (1%)	2 (2%)	6 (2%)
Headache	3 (3%)	1 (1%)	2 (2%)	6 (2%)
Gastrointestinal disorders				
Any event	0	4 (4%)	0	4 (1%)
Abdominal pain	0	1 (1%)	0	1 (<1%)
Aphthous stomatitis	0	1 (1%)	0	1 (<1%)
Diarrhoea	0	1 (1%)	0	1 (<1%)
Stomach discomfort	0	1 (1%)	0	1 (<1%)
Toothache	0	1 (1%)	0	1 (<1%)

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Table 8.7
Summary of All Adverse Events Post Double-Blind Treatment (ITT Population)

Treatment: Salmeterol

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Musculoskeletal and connective tissue disorders				
Any event	0	1 (1%)	1 (1%)	2 (<1%)
Back pain	0	0	1 (1%)	1 (<1%)
Pain in extremity	0	1 (1%)	0	1 (<1%)
Skin and subcutaneous tissue disorders				
Any event	0	2 (2%)	0	2 (<1%)
Acrodermatitis	0	1 (1%)	0	1 (<1%)
Erythema	0	1 (1%)	0	1 (<1%)
Reproductive system and breast disorders				
Any event	0	1 (1%)	0	1 (<1%)
Dysmenorrhoea	0	1 (1%)	0	1 (<1%)
Cardiac disorders				
Any event	0	1 (1%)	0	1 (<1%)
Palpitations	0	1 (1%)	0	1 (<1%)
Injury, poisoning and procedural complications				
Any event	0	1 (1%)	0	1 (<1%)
Skin laceration	0	1 (1%)	0	1 (<1%)
Investigations				
Any event	0	1 (1%)	0	1 (<1%)
Blood pressure increased	0	1 (1%)	0	1 (<1%)

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Table 8.8
Listing of All Adverse Events (ITT Population)

Treatment: FSC100/50
Arg16Gly Genotype: Arg/Arg

Inv./ Subj	Age(y)/ Sex/ Race		Preferred Term/ VERBATIM TEXT	Outcome/ Onset Date/ Date of Resolution/ Duration	Study Day/ Day within Period	Frequency/ Severity/ Serious/ Withdrawal	Action Taken/ Relation to Study Drug
	Study period						

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.

Table 8.9
Listing of Subject Numbers for Individual Adverse Events (ITT Population)

Treatment: FSC100/50

System Organ Class Preferred Term	Arg16Gly genotype	No. with Event	Subject Numbers

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.

Table 8.10
Relationship of Adverse Event System Organ Class, Preferred Term and Verbatim Text

System Organ Class	Preferred Term	Verbatim Text
Blood and lymphatic system disorders	Anaemia	ANEMIA
Cardiac disorders	Angina pectoris Palpitations	CARDIAC CHEST PAIN HEART PALPITATIONS PALPATATIONS PALPITATIONS RARE PALPITATIONS
	Tachycardia	TACHYCARDIA
Ear and labyrinth disorders	Ear discomfort Ear pain	R EAR PRESSURE BILAT EARACHE BILATERAL EAR ACHE EARACHE EARACHE- RIGHT LEFT INNER EAR PAIN R EAR PAIN RIGHT EAR PAIN
	Middle ear effusion Motion sickness	FLUID IN EARS BILATERAL AIR SICKNESS AIRSICKNESS MOTION SICKNESS SEASICKNESS
	Tinnitus Vertigo	RINGING IN EARS VERTIGO
Endocrine disorders	Hypothyroidism	HYPOTHYROIDISM
Eye disorders	Conjunctivitis	CONJUNCTIVITIS CONJUNCTIVITIS L EYE MILD CONJUNCTIVITIS
	Conjunctivitis allergic Dry eye Eye allergy	ALLERGIC CONJUNCTIVITIS BOTH EYES DRY EYES ALLERGY (OCULAR)

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Table 8.10
Relationship of Adverse Event System Organ Class, Preferred Term and Verbatim Text

System Organ Class	Preferred Term	Verbatim Text
Eye disorders	Eye pruritus Lacrimation increased Vision blurred	OCCASIONAL ITCHY EYES WATERY EYES BLURRED VISION
Gastrointestinal disorders	Abdominal discomfort Abdominal distension Abdominal pain Abdominal pain lower Abdominal pain upper Aphthous stomatitis Constipation Diarrhoea Diarrhoea haemorrhagic Dry mouth Dyspepsia Flatulence Food poisoning	GI DISTRESS ABDOMINAL BLOATING ABDOMINAL CRAMPING ABDOMINAL CRAMPS ABDOMINAL PAIN INTERMITTENT ABDOMINAL PAIN PAIN R ABD SEVERE ABDOMINAL PAIN RIGHT LOWER ABDOMINAL PAIN EPIGASTRALGIA EPIGASTRALGYA EPIGASTRIC PAINS STOMACH ACHE STOMACH CRAMPS STOMACH PAIN STOMACHACHE STOMACHE ACHE APHTHOUS ULCER ON UVULA CANKER SORE CANKER SORES CONSTIPATION DIARRHEA BLOODY DIARRHEA DRY MOUTH DISPEPSIA HEARTBURN INDIGESTION GAS STOMACH PAIN (GAS) FOOD POISONING

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Table 8.10
Relationship of Adverse Event System Organ Class, Preferred Term and Verbatim Text

System Organ Class	Preferred Term	Verbatim Text
Gastrointestinal disorders	Gastritis	GASTRITIS
		ACID REFLUX
	Gastrooesophageal reflux disease	CHEST PAIN-SEVERE ACID REFLUX
		GASTRIC REFLUX
	Gingival bleeding	GERD
		SUSPECTED ACID REFLUX
		BLEEDING GUMS
		THROBBING IN LOWER LIPS
		SWELLING IN LOWER LIPS
	Lip pain	NAUSEA
		NAUSEAS
	Lip swelling	NAUSEOUS
		SORE MOUTH
	Nausea	NERVOUS STOMACHE
		STOMACH UPSET
	Oral pain	UPSET STOMACH
		UPSET STOMACHE
General disorders and administration site conditions	Stomach discomfort	WHITE BUMPS ON TONGUE
		TOOTHACHE (LOST FILLING)
	Tongue disorder	DENTAL PAIN
		PAIN TOOTH
	Tooth disorder	TOOTH ACHE
		TOOTH PAIN
	Toothache	TOOTHACHE
		WISDOM TEETH PAIN
	Vomiting	VOMITING
		VOMITTING
	Asthenia	VOMMITTING
		WEAK
	Chest discomfort	WEAKNESS
		CHEST TIGHTNESS
		TIGHT CHEST

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Table 8.10
Relationship of Adverse Event System Organ Class, Preferred Term and Verbatim Text

System Organ Class	Preferred Term	Verbatim Text
General disorders and administration site conditions	Chest pain	CHEST PAIN
		UNKNOWN CHEST PAIN
	Cyst	CYST RIGHT WRIST
	Fatigue	FATIGUE
		TIRED
	Feeling jittery	JITTERY FEELING
	Ill-defined disorder	CONGESTION (UNKNOWN)
	Influenza like illness	FLU LIKE SYMPTOMS
		FLU-LIKE SYMPTOMS
	Non-cardiac chest pain	NON CARDIAC CHEST PAIN (TWINGE)
		INTERMITTANT
		RESPIRATORY CHEST DISCOMFORT
		EXERCISE
	Oedema peripheral	BILATERAL LEG SWELLING
		LEFT SWOLLEN SHIN
	Pain	ACHINESS
		ACHY
		BODY ACHE
		BODY ACHES
		BODYACHES
		PAIN
		SORENESS (GENERALIZED)
	Pyrexia	FEVER
	Sensation of blood flow	PULSING IN LOWER LIPS
	Ulcer	UNKNOWN ULCER
Immune system disorders	Drug hypersensitivity	ALLERGIC REACTION TO SMZTMP MEDICATION
	Hypersensitivity	ALLERGIC REACTION (LOCAL R ARM)
		ALLERGY FLARE
		COUGH (INCREASED ALLERGY SYMPTOMS)
		COUGH INCREASED ALLERGY SYMPTOMS
		INCREASED ALLERGY SYMPTOMS

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Table 8.10
Relationship of Adverse Event System Organ Class, Preferred Term and Verbatim Text

System Organ Class	Preferred Term	Verbatim Text
Immune system disorders	Hypersensitivity	INCREASED ALLERGY SYMPTOMS NASAL CONGESTION ITCHY THROAT INCREASED ALLERGY SYMPTOMS NASAL CONGESTION INCREASED ALLERGY SYMPTOMS SORE THROAT INCREASED ALLERGY SYMPTOMS
	Multiple allergies	ALLERGIES
	Seasonal allergy	SINUS CONGESTION (ALLERGIES) SEASONAL ALLERGY FLARE
Infections and infestations	Acute sinusitis	ACUTE SINUSITIS
	Arthritis infective	LEFT KNEE INFECTION
	Bronchitis	BRONCHIAL INFECTION BRONCHITIS
	Candidiasis	POSSIBLE THRUSH
	Cellulitis	CELLULITIS R ARM
	Cystitis	BLADDER INFECTION CYSTITIS
	Ear infection	EAR INFECTION LT EAR INFECTION OTITIS
	Furuncle	BOIL
	Gastroenteritis	GASTROENTERITIS
	Gastroenteritis viral	STOMACH FLU STOMACH VIRUS STOMACHE FLU VIRAL GASTROENTERITIS
	Gastrointestinal infection	GI INFECTION
	Gingival infection	GUM INFECTION
	Herpes simplex	COLD SORE
	Herpes zoster	HERPES ZOSTER ZOSTER HERPES

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Table 8.10
Relationship of Adverse Event System Organ Class, Preferred Term and Verbatim Text

System Organ Class	Preferred Term	Verbatim Text
Infections and infestations	Impetigo	IMPETIGO
	Influenza	FLU
		FLU SYMPTOMS
		INFLUENZA
	Kidney infection	KIDNEY INFECTION
	Laryngitis	LARYNGITIS
	Localised infection	RIGHT FOOT INFECTION
	Lower respiratory tract infection	CHEST COLD
		LOWER RESPIRATORY INFECTION
	Lyme disease	LYMES DISEASE
	Malaria	MALARIA
	Nail infection	CUTICLE INFECTION
	Nasopharyngitis	COLD
		COLD & SINUS
		COLD HEAD COLD
		COLD SYMPTOMS
		COLDS
		COMMON COLD
		HEAD COLD
		HEADCOLD
		POSSIBLE COLD SYMPTOMS
		SINUS COLD
		SINUS HEAD COLD
		SLIGHT HEAD COLD
	Onychomycosis	TOENAIL FUNGAL INFECTION
	Oophoritis	INFLAMMED OVARY
	Otitis externa	BILATERAL OTITIS EXTERNA
	Otitis media	L OTITIS MEDIA
		OTITIS MEDIA
	Pharyngitis	PHARYNGITIS
	Pharyngitis bacterial	BACTERIAL INFECTION "THROAT"
	Pharyngitis streptococcal	STREP PHARYNGITIS
		STREP THROAT
		STREPTOCOCCAL PHARYNGITIS

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Table 8.10
Relationship of Adverse Event System Organ Class, Preferred Term and Verbatim Text

System Organ Class	Preferred Term	Verbatim Text
Infections and infestations	Pneumonia	PNEMONIA PNEUMONIA
	Pyelonephritis	PYELONEPHRITH PYELONEPHRITIS
	Respiratory tract infection	RESPIRATORY TRACT INFECTION SUSPECTED RESPIRATORY TRACT INFECTION
	Respiratory tract infection viral	VIRAL RESPIRATORY ILLNESS
	Rhinitis	RHINITIS
	Sinusitis	SINUS INFECTION SINUSITIS SINUSTIS
	Skin infection	SKIN INFECTION
	Staphylococcal infection	COMMUNITY ACQUIRED METHICILLIN RESISTANT SKIN LESIONS LEGS
	Tonsillitis	TONSILITIS TONSILLITIS
	Tooth abscess	ABCESS TOOTH EXTREME TOOTH PAIN [ABSCCESS] TOOTH ABCESS TOOTH ABSCCESS
	Tooth infection	DENTAL INFECTION ROOT CANAL INFECTION TOOTH INFECTION
	Upper respiratory tract infection	POSSIBLE UPPER RESPIRATORY INFECTION SUSPECTED URI UPPER RESPIRATORY INFEC UPPER RESPIRATORY INFECT UPPER RESPIRATORY INFECTION UPPER RESPIRATORY TRACT INFECTION URI
	Urethritis	URETHRITIS
	Urinary tract infection	URINARY TRACT INFECTION

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Table 8.10
Relationship of Adverse Event System Organ Class, Preferred Term and Verbatim Text

System Organ Class	Preferred Term	Verbatim Text
Infections and infestations	Urinary tract infection	UTI
	Vaginal infection	VAGINITIS
	Viral infection	VIRAL ILLNESS
		VIRAL SYNDROME
	Viral upper respiratory tract infection	UPPER RESPIRATORY INFECTION VIRAL
Injury, poisoning and procedural complications		VIRAL UPPER RESPIRATORY INFECTION
		VIRAL URI
	Vulvovaginal mycotic infection	SUSPECT VAGINAL YEAST INFECTION
		VAGINAL YEAST INFECTION
	Ankle fracture	FRACTURED ANKLE
	Arthropod bite	ITCHING POST INSECT BITE
		MOSQUITO BITES
	Arthropod sting	BEE STING
		INSECT STING
	Back injury	BACK INJURY
		BACK STRAIN
		LUMBAR STRAIN
	Clavicle fracture	BROKEN LEFT COLLAR BONE
	Contusion	CONTUSION R ARM
		CONTUSION RIB (PAIN)
		HAND CONTUSION
		L HAND BRUISED
	Corneal abrasion	SCRATCHED CORNEA
	Excoriation	FINGER ABRASION
	Fall	FALL
	Foot fracture	BROKEN TOE
		FRACTURED L FOOT
	Fractured coccyx	BROKEN TAILBONE
	Hand fracture	LEFT THUMB FRACTURE
	Joint dislocation	DISLOCATED SHOULDER
	Joint injury	WRIST INJURY

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Table 8.10
Relationship of Adverse Event System Organ Class, Preferred Term and Verbatim Text

System Organ Class	Preferred Term	Verbatim Text
Injury, poisoning and procedural complications	Joint sprain	RIGHT ANKLE SPRAIN
		SPRAIN ANKLE
	Limb injury	SPRAINED ANKLE
		SPRAINED LEFT ANKLE
		SPRAINED LEFT KNEE
		FOOT INJURY
		RIGHT KNEE FRACTURE
		TORN MENISCUS LEFT KNEE
		MUSCLE STRAIN
		MUSCLE STRAIN ARM & SHOULDER
		PULLED MUSCLE
		STRAINED R UPPER LEG QUADARANT
	Lower limb fracture	FRACTURED (L) PATELLA
		PAIN FROM FRACTURED PATELLA
	Meniscus lesion	ELBOW PAIN POST SURGERY
		ORAL PAIN WITH TEETH EXTRACTION
	Muscle strain	PAIN FROM EAR PIERCING
		PAIN FROM TOOTH EXTRACTION
		PAIN-POST CERVICAL EXAM
		PAIN-POST WISDOM TOOTH EXTRACTION
		POST LEFT KNEE MENISCUS REPAIR
		SURGERY PAIN
		TOOTH EXTRACTION PAIN
		SMOKE INHALATION
		AUTO ACCIDENT
		LACERATION R ARM
		R INDEX KNUCKLE LACERATION
		THUMB LACERATION LEFT
	Patella fracture	TENDON INJURY
		ACHILLES TENDON TEAR
	Procedural pain	BROKEN TOOTH
		BROKEN ARM
	Respiratory fume inhalation disorder	WHIPLASH
	Road traffic accident	
	Skin laceration	
	Tendon injury	
	Tendon rupture	
	Tooth fracture	
	Upper limb fracture	
	Whiplash injury	

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Table 8.10
Relationship of Adverse Event System Organ Class, Preferred Term and Verbatim Text

System Organ Class	Preferred Term	Verbatim Text
Injury, poisoning and procedural complications	Wrist fracture	FRACTURED WRIST
Investigations	Blood pressure increased Heart rate irregular	ELEVATED BLOOD PRESSURE IRREGULAR HEART BEAT
Musculoskeletal and connective tissue disorders	Arthralgia	ANKLE PAIN KNEE ACHE KNEE PAIN KNEE PAIN-RIGHT LEFT (PAIN IN HIP) LEFT ELBOW PAIN PAIN IN ELBOW RIGHT KNEE PAIN RIGHT SHOULDER JOINT PAIN
	Arthritis	ARTHRITIS WORSENING ARTHRITIS
	Back pain	BACK ACHE BACK PAIN BACKACHE LOW BACKACHE LOWER BACK PAIN LUMBALGIA SEVERE BACK PAIN
	Bone pain	BONES ACHE
	Bursitis	BRUSITIS
	Costochondritis	COSTO CHONDRITIS
	Exostosis	HEEL SPUR
	Flank pain	FLANK PAIN
	Intervertebral disc protrusion	LEFT C6-C7 CERVICAL DISK HERNIATION
	Joint swelling	LEFT ANKLE SWOLLEN RIGHT ANKLE SWELLING

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Table 8.10
Relationship of Adverse Event System Organ Class, Preferred Term and Verbatim Text

System Organ Class	Preferred Term	Verbatim Text
Musculoskeletal and connective tissue disorders	Joint swelling	SWOLLEN ANKLE
	Muscle spasms	BACK SPASMS CERVICAL SPASM CRAMPS LEG CRAMPS MUSCLE CRAMPS-BACK MUSCLE TENSION
	Muscle tightness	CHEST DISCOMFORT (SORENESS AND PAIN)
	Musculoskeletal chest pain	CHEST PAIN (MUSCULOSKELETAL) CHEST WALL TENDERNESS LEFT RIB PAIN MUSCLE PAIN-R-RIB CAGE LEFT SHOULDER PAIN SHOULDER PAIN
	Musculoskeletal pain	STIFF NECK STIFFNESS NECK & SHOULDER TENSE SHOULDERS
	Musculoskeletal stiffness	GENERAL MUSCLE PAIN MUSCLE ACHE MUSCLE ACHE-BILATERAL LEGS MUSCLE ACHES MUSCLE PAIN MUSCLE PAIN RIGHT ARM MUSCLE SORENESS MUSCULAR LEG ACHE MYALGIA MYALGIAS
	Myalgia	SORE BACK MUSCLES SORE MUSCLES SORE MUSCLES (DUE TO SPORTS)
	Neck pain	LEFT NECK PAIN NECK PAIN

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Table 8.10
Relationship of Adverse Event System Organ Class, Preferred Term and Verbatim Text

System Organ Class	Preferred Term	Verbatim Text
Musculoskeletal and connective tissue disorders	Neck pain	NECKACHE
	Pain in extremity	SORE NECK
		ACHILLES PAIN
		ARM PAIN
		FOOT PAIN
		HEEL PAIN
		LEFT ARM PAIN
		LEG ACHES
		LEG PAIN
		PAIN R LEG
PAIN RIGHT HAND		
R ARM PAIN		
R FOOT PAIN		
Tendon pain Tendonitis	ACHILLES TENDON PAIN	
	L ELBOW TENDONITIS	
	RIGHT KNEE TENDONITIS	
	TENDINITIS (LT FOOT)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Fibromatosis	PLANTAR FIBROMATOSIS
	Uterine leiomyoma	FIBROIDS IN UTERUS
Nervous system disorders	Aphonia Cervicobrachial syndrome Dizziness	VOICE LOSS
		CERVICAL RADICULOPATHY
		DIZZINESS
		DIZZY
		HEADACHE/DIZZY
		LIGHTHEADED
	Headache	HEADACHE
		HEADACHE DUE TO MENSTRUAL CYCLE
		HEADACHE/DIZZY
		HEADACHES

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Table 8.10
Relationship of Adverse Event System Organ Class, Preferred Term and Verbatim Text

System Organ Class	Preferred Term	Verbatim Text
Nervous system disorders	Headache	INTERMITTENT HEADACHES INTERMITTENT HEADACHE
	Hypoaesthesia	NUMBNESS ON LEFT SIDE OF THE BODY
	Migraine	MIGRAINE MIGRAINE HEADACHE MIGRAINES POSSIBLE MIGRAINE
	Neuropathy peripheral	INFLAMED NERVE RIGHT LEG
	Paraesthesia	PARESTHESIAS IN BOTH HANDS
	Presyncope	NEAR-SYNCOPE
	Sciatica	RIGHT SIATIC PAIN SCIATIC PAIN SCIATICA
	Sinus headache	SINUS HEADACHE SINUS WORSENING HEADACHE
	Syncope	SYNCOPE
	Tension headache	HEADACHE MOST PROBABLE TENSION TENSION HEADACHE
Pregnancy, puerperium and perinatal conditions	Tremor	FINGER TREMOR INTENSE SHAKING SHAKINESS SHAKY
	Abortion spontaneous	SPONTANEOUS ABORTION
Psychiatric disorders	Anxiety	ANXIETY
	Anxiety disorder	ANXIETY DISORDER
	Depression	DEPRESSION
	Emotional distress	MENTAL STRESS
	Insomnia	INSOMNIA INSOMNIA (SLEEP AIDE) SLEEPLESSNESS
	Nervousness	NERVOUSNESS

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Table 8.10
Relationship of Adverse Event System Organ Class, Preferred Term and Verbatim Text

System Organ Class	Preferred Term	Verbatim Text
Psychiatric disorders	Nervousness Panic attack Restlessness	SHAKY FEELING PANIC ATTACKS RESTLESSNESS
Renal and urinary disorders	Micturition urgency Nephrolithiasis Pollakiuria Stress urinary incontinence	URINARY URGENCY KIDNEY STONE FREQUENT URINATION STRESS INCONTINENCE
Reproductive system and breast disorders	Dysmenorrhoea	DYSMENORRHEA DYSPMENORRHEA MENSTRUAL CRAMPS MENSTRUAL PAIN MENSTRUAL PERIOD (CRAMPS) ENDOMETRIOSIS INCREASED MENSTRUAL BLEEDING OVARIAN CYST OVARIAN CYSTS RUPTURE R OVARIAN CYST PELVIC PAIN POLYCYSTIC OVARIAN SYNDROME FREQUENT MENSTRAL PERIOD
Respiratory, thoracic and mediastinal disorders	Asthma	ASTHMA EXACERBATION MILD ASTHMA EXACERBATION SEVERE ASTHMA EXACERBATION CHOKING SENSATION COUGH COUGHING DRY COUGH INCREASED COUGH NON PRODUCTIVE COUGH
	Choking sensation Cough	

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Table 8.10
Relationship of Adverse Event System Organ Class, Preferred Term and Verbatim Text

System Organ Class	Preferred Term	Verbatim Text
Respiratory, thoracic and mediastinal disorders	Cough	NON-PRODUCTIVE COUGH
	Dry throat	DRY THROAT
	Dysphonia	DYSPHONY
	Dyspnoea	SHORTNESS OF BREATH
		SOB
		TROUBLE BREATHING
	Epistaxis	BLOODY NOSE
		EPISTAXIS
		NOSE BLEED
	Hyperventilation	HYPERVENTILATION
	Nasal congestion	CONGESTION
		INCREASED NASAL CONGESTION
		NASAL BLOCKAGE
		NASAL CONGESTED
		NASAL CONGESTION
		STUFFY HEAD
		STUFFY NOSE
	Nasal oedema	NASAL TURBINATE SWELLING
	Paranasal sinus hypersecretion	DISCHARGE FROM SINUSES
	Pharyngolaryngeal pain	INTERMITTANT SORE THROAT
		SORE THROAT
		SORE THROUGH
	Pleurisy	PLEURISY
	Postnasal drip	POST NASAL DRIP
	Productive cough	ESPUTO/SPUTUM
		PRODUCTIVE COUGH
	Respiratory failure	RESPIRATORY FAILURE
	Respiratory tract congestion	CHEST CONGESTION NOS
		CONGESTION
		RESPIRATORY CHEST CONGESTION
	Rhinitis allergic	ACUTE ALLERGIC RHINITIS
		ALLERGIC RHINITIS
		WORSENING OF ALLERGIC RHINITIS

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Table 8.10
Relationship of Adverse Event System Organ Class, Preferred Term and Verbatim Text

System Organ Class	Preferred Term	Verbatim Text
Respiratory, thoracic and mediastinal disorders	Rhinitis allergic	WORSENING OF AR
	Rhinitis perennial	PERENNIAL ALLERGIC RHINITIS WORSENING OF PERENNIAL ALLERGIC RHINITIS
	Rhinitis seasonal	EXACERBATION OF SEASONAL ALLERGIC RHINITIS SEASONAL ALLERGIC RHINITIS WORSENING OF SEASONAL ALLERGIC RHINITIS
	Rhinorrhoea	CLEAR NASAL DRAINAGE (DISCHARGE) CLEAR NASAL DRAINAGE DISCHARGE NASAL DISCHARGE RHINORRHEA RUNNY NOSE
	Sinus congestion	SINUS CONGESTION
	Sneezing	SNEEZING
	Snoring	EXCESSIVE SNORING
	Throat irritation	BURNING SENSATION IN THROAT IRRITATION IN THROAT ITCHY THROAT SCRATCHY THROAT THROAT IRRITATION THROAT ITCHING
	Upper respiratory tract congestion	UPPER RESPIRATORY CHEST CONGESTION
	Vasomotor rhinitis	VASOMOTOR RHINITIS
Skin and subcutaneous tissue disorders	Wheezing	WHEEZING
	Acne	ACNE
	Acrodermatitis	MILD DERMATITIS ON HANDS
	Angioneurotic oedema	ANGIOEDEMA
	Dermatitis allergic	ALLERGIC REACTION "RASH"
	Dermatitis atopic	ATOPIC DERMATITIS

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Table 8.10
Relationship of Adverse Event System Organ Class, Preferred Term and Verbatim Text

System Organ Class	Preferred Term	Verbatim Text
Skin and subcutaneous tissue disorders	Dermatitis contact	POISON IVY
		POISON OAK
	Dry skin	DRY SKIN
	Eczema nummular	NUMMLAR ECZEMA
	Erythema	ERYTHEMA OF UVULA
	Onychalgia	PAIN RIGHT 3RD FINGER NAILBED
	Photodermatosis	SUN RASH
	Photosensitivity reaction	SENSITIVITY TO LIGHT
	Pruritus	ITCHING
		ITICHING
	Pruritus allergic	PRURITIS
	Rash	PRURITUS ALLERGIC
		RASH
		RASH (FOREARMS)
Surgical and medical procedures		RASH ON STOMACH
		RASH-UPPER ANKLE
Vascular disorders		HIVES
		URTICARIA
	Breast lump removal	LUMPECTOMY L BREAST
	Sinus operation	SINUS SURGERY
	Haematoma	RIGHT KNEE HEMATOMA
	Hypertension	HIGH BLOOD PRESSURE
		HYPERTENSION
	Vasculitis	WORSENING OF HYPERTENSION
		WORSENING OF VASCULITIS

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Table 8.11
Summary of Drug-Related Adverse Events During Double-Blind Treatment (ITT Population)

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Subjects in treatment group	89	92	91	272
Any event	6 (7%)	5 (5%)	2 (2%)	13 (5%)
Nervous system disorders				
Any event	1 (1%)	2 (2%)	1 (1%)	4 (1%)
Headache	0	1 (1%)	1 (1%)	2 (<1%)
Aphonia	1 (1%)	0	0	1 (<1%)
Migraine	0	1 (1%)	0	1 (<1%)
Infections and infestations				
Any event	2 (2%)	2 (2%)	1 (1%)	5 (2%)
Upper respiratory tract infection	1 (1%)	1 (1%)	0	2 (<1%)
Candidiasis	0	1 (1%)	0	1 (<1%)
Herpes zoster	0	0	1 (1%)	1 (<1%)
Nasopharyngitis	0	0	1 (1%)	1 (<1%)
Pharyngitis	1 (1%)	0	0	1 (<1%)
Sinusitis	1 (1%)	0	0	1 (<1%)
Respiratory, thoracic and mediastinal disorders				
Any event	3 (3%)	0	1 (1%)	4 (1%)
Cough	1 (1%)	0	1 (1%)	2 (<1%)
Dry throat	1 (1%)	0	0	1 (<1%)
Pharyngolaryngeal pain	1 (1%)	0	0	1 (<1%)
Sinus congestion	1 (1%)	0	0	1 (<1%)
Gastrointestinal disorders				
Any event	2 (2%)	2 (2%)	0	4 (1%)
Abdominal pain	0	1 (1%)	0	1 (<1%)
Abdominal pain upper	0	1 (1%)	0	1 (<1%)
Oral pain	1 (1%)	0	0	1 (<1%)

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Table 8.11
Summary of Drug-Related Adverse Events During Double-Blind Treatment (ITT Population)

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)

Stomach discomfort	1 (1%)	0	0	1 (<1%)
Ear and labyrinth disorders				
Any event	0	0	1 (1%)	1 (<1%)
Ear pain	0	0	1 (1%)	1 (<1%)
Musculoskeletal and connective tissue disorders				
Any event	1 (1%)	0	1 (1%)	2 (<1%)
Musculoskeletal stiffness	0	0	1 (1%)	1 (<1%)
Myalgia	1 (1%)	0	0	1 (<1%)

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Table 8.11
Summary of Drug-Related Adverse Events During Double-Blind Treatment (ITT Population)

Treatment: Salmeterol

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Subjects in treatment group	90	90	92	272
Any event	1 (1%)	4 (4%)	5 (5%)	10 (4%)
Nervous system disorders				
Any event	0	2 (2%)	3 (3%)	5 (2%)
Headache	0	2 (2%)	1 (1%)	3 (1%)
Tremor	0	0	2 (2%)	2 (<1%)
Sinus headache	0	0	1 (1%)	1 (<1%)
Infections and infestations				
Any event	0	1 (1%)	1 (1%)	2 (<1%)
Sinusitis	0	0	1 (1%)	1 (<1%)
Viral upper respiratory tract infection	0	1 (1%)	0	1 (<1%)
Respiratory, thoracic and mediastinal disorders				
Any event	1 (1%)	1 (1%)	1 (1%)	3 (1%)
Pharyngolaryngeal pain	0	1 (1%)	1 (1%)	2 (<1%)
Throat irritation	1 (1%)	0	0	1 (<1%)
Ear and labyrinth disorders				
Any event	0	0	1 (1%)	1 (<1%)
Vertigo	0	0	1 (1%)	1 (<1%)
Psychiatric disorders				
Any event	0	1 (1%)	1 (1%)	2 (<1%)
Insomnia	0	0	1 (1%)	1 (<1%)
Panic attack	0	1 (1%)	0	1 (<1%)
Restlessness	0	0	1 (1%)	1 (<1%)

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Table 8.11
Summary of Drug-Related Adverse Events During Double-Blind Treatment (ITT Population)

Treatment: Salmeterol

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Cardiac disorders				
Any event	0	1 (1%)	0	1 (<1%)
Palpitations	0	1 (1%)	0	1 (<1%)
General disorders and administration site conditions				
Any event	0	0	1 (1%)	1 (<1%)
Feeling jittery	0	0	1 (1%)	1 (<1%)
Investigations				
Any event	0	1 (1%)	0	1 (<1%)
Heart rate irregular	0	1 (1%)	0	1 (<1%)

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Table 8.12
Summary of Serious Adverse Events During Double-Blind Treatment (ITT Population)

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Subjects in treatment group	89	92	91	272
Any event	0	0	0	0

Table 8.12
Summary of Serious Adverse Events During Double-Blind Treatment (ITT Population)

Treatment: Salmeterol

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Subjects in treatment group	90	90	92	272
Any event	0	2 (2%)	0	2 (<1%)
Respiratory, thoracic and mediastinal disorders				
Any event	0	1 (1%)	0	1 (<1%)
Asthma	0	1 (1%)	0	1 (<1%)
Reproductive system and breast disorders				
Any event	0	1 (1%)	0	1 (<1%)
Ovarian cyst ruptured	0	1 (1%)	0	1 (<1%)

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Table 8.13
Listing of Fatal Adverse Events (Total Population)

Treatment: Salmeterol
Arg16Gly Genotype: Arg/Gly

Inv./ Subj	Age(y)/ Sex/ Race	Study period	Preferred Term/ VERBATIM TEXT	Outcome/ Onset Date/ Date of Resolution/ Duration	Study Day/ Day within Period	Maximum Intensity/ Serious/ Withdrawal	Action Taken/ Relation to Study Drug

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.

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Table 8.14
Listing of Non-Fatal Serious Adverse Events (Total Population)

Treatment:
Arg16Gly Genotype:

Inv./ Subj	Age(y)/ Sex/ Race	Study period	Preferred Term/ VERBATIM TEXT	Outcome/ Onset Date/ Date of Resolution/ Duration	Study Day/ Day within Period	Maximum Intensity/ Serious/ Withdrawal	Action Taken/ Relation to Study Drug

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.

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Table 8.15

Summary of Adverse Events Leading to Study Withdrawal During Double-Blind Treatment (ITT Population)

Treatment: FSC100/50

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Subjects in treatment group	89	92	91	272
Any event	2 (2%)	2 (2%)	1 (1%)	5 (2%)
Infections and infestations				
Any event	1 (1%)	1 (1%)	0	2 (<1%)
Bronchitis	1 (1%)	0	0	1 (<1%)
Upper respiratory tract infection	0	1 (1%)	0	1 (<1%)
Respiratory, thoracic and mediastinal disorders				
Any event	0	1 (1%)	0	1 (<1%)
Cough	0	1 (1%)	0	1 (<1%)
Vascular disorders				
Any event	1 (1%)	0	1 (1%)	2 (<1%)
Hypertension	0	0	1 (1%)	1 (<1%)
Vasculitis	1 (1%)	0	0	1 (<1%)
Gastrointestinal disorders				
Any event	0	1 (1%)	0	1 (<1%)
Gastrooesophageal reflux disease	0	1 (1%)	0	1 (<1%)

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Table 8.15

Summary of Adverse Events Leading to Study Withdrawal During Double-Blind Treatment (ITT Population)

Treatment: Salmeterol

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Subjects in treatment group	90	90	92	272
Any event	1 (1%)	6 (7%)	3 (3%)	10 (4%)
Infections and infestations				
Any event	0	2 (2%)	2 (2%)	4 (1%)
Upper respiratory tract infection	0	1 (1%)	1 (1%)	2 (<1%)
Gastroenteritis viral	0	1 (1%)	0	1 (<1%)
Nasopharyngitis	0	0	1 (1%)	1 (<1%)
Pneumonia	0	1 (1%)	0	1 (<1%)
Respiratory, thoracic and mediastinal disorders				
Any event	1 (1%)	2 (2%)	0	3 (1%)
Asthma	0	1 (1%)	0	1 (<1%)
Cough	0	1 (1%)	0	1 (<1%)
Throat irritation	1 (1%)	0	0	1 (<1%)
Psychiatric disorders				
Any event	0	1 (1%)	1 (1%)	2 (<1%)
Insomnia	0	0	1 (1%)	1 (<1%)
Panic attack	0	1 (1%)	0	1 (<1%)
Restlessness	0	0	1 (1%)	1 (<1%)
Cardiac disorders				
Any event	0	1 (1%)	0	1 (<1%)
Palpitations	0	1 (1%)	0	1 (<1%)
General disorders and administration site conditions				
Any event	0	1 (1%)	0	1 (<1%)
Pain	0	1 (1%)	0	1 (<1%)

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Table 8.15

Summary of Adverse Events Leading to Study Withdrawal During Double-Blind Treatment (ITT Population)

Treatment: Salmeterol

	Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Pyrexia	0	1 (1%)	0	1 (<1%)
Investigations				
Any event	0	1 (1%)	0	1 (<1%)
Heart rate irregular	0	1 (1%)	0	1 (<1%)
Nervous system disorders				
Any event	0	0	1 (1%)	1 (<1%)
Tremor	0	0	1 (1%)	1 (<1%)
Skin and subcutaneous tissue disorders				
Any event	0	1 (1%)	0	1 (<1%)
Rash	0	1 (1%)	0	1 (<1%)

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Table 8.16
Listing of Adverse Events Leading to Study Withdrawal During Double-Blind Treatment (ITT Population)

Treatment: FSC100/50
Arg16Gly Genotype: Arg/Arg

Inv./ Subj	Age(y)/ Sex/ Race	Study period	Preferred Term/ VERBATIM TEXT	Outcome/ Onset Date/ Date of Resolution/ Duration	Study Day/ Day within Period	Frequency/ Severity/ Serious/ Withdrawal	Action Taken/ Relation to Study Drug

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.

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Table 8.17
Summary of Adverse Events (Open-Label Failure Population)

System Organ Class Preferred Term	Arg/Arg (N=64)	Arg/Gly (N=105)	Gly/Gly (N=69)
Any event	27 (42%)	53 (50%)	30 (43%)
Infections and infestations			
Any event	17 (27%)	24 (23%)	13 (19%)
Nasopharyngitis	2 (3%)	7 (7%)	2 (3%)
Sinusitis	3 (5%)	5 (5%)	1 (1%)
Upper respiratory tract infection	2 (3%)	4 (4%)	3 (4%)
Influenza	2 (3%)	1 (<1%)	1 (1%)
Viral upper respiratory tract infection	2 (3%)	0	2 (3%)
Gastroenteritis	1 (2%)	0	1 (1%)
Gastroenteritis viral	1 (2%)	1 (<1%)	0
Tonsillitis	1 (2%)	1 (<1%)	0
Tooth abscess	1 (2%)	1 (<1%)	0
Urinary tract infection	0	1 (<1%)	1 (1%)
Bronchitis	1 (2%)	0	0
Ear infection	0	0	1 (1%)
Furuncle	1 (2%)	0	0
Kidney infection	0	0	1 (1%)
Laryngitis	0	0	1 (1%)
Otitis media	0	1 (<1%)	0
Pharyngitis	1 (2%)	0	0
Pharyngitis streptococcal	0	1 (<1%)	0
Pneumonia	1 (2%)	0	0
Pyelonephritis	0	1 (<1%)	0
Respiratory tract infection	0	0	1 (1%)
Respiratory tract infection viral	0	0	1 (1%)
Staphylococcal infection	0	1 (<1%)	0
Vulvovaginal mycotic infection	0	0	1 (1%)
Nervous system disorders			
Any event	7 (11%)	20 (19%)	11 (16%)
Headache	5 (8%)	17 (16%)	10 (14%)
Dizziness	1 (2%)	3 (3%)	0

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Table 8.17
Summary of Adverse Events (Open-Label Failure Population)

System Organ Class Preferred Term	Arg/Arg (N=64)	Arg/Gly (N=105)	Gly/Gly (N=69)
Migraine	0	2 (2%)	0
Paraesthesia	1 (2%)	0	0
Sinus headache	0	0	1 (1%)
Syncope	0	1 (<1%)	0
Tension headache	1 (2%)	0	0
Respiratory, thoracic and mediastinal disorders			
Any event	10 (16%)	9 (9%)	8 (12%)
Pharyngolaryngeal pain	6 (9%)	3 (3%)	4 (6%)
Cough	3 (5%)	2 (2%)	0
Nasal congestion	2 (3%)	1 (<1%)	1 (1%)
Rhinitis allergic	0	1 (<1%)	3 (4%)
Rhinorrhoea	1 (2%)	2 (2%)	1 (1%)
Sinus congestion	0	1 (<1%)	1 (1%)
Asthma	1 (2%)	0	0
Dysphonia	0	1 (<1%)	0
Dyspnoea	1 (2%)	0	0
Epistaxis	1 (2%)	0	0
Postnasal drip	0	1 (<1%)	0
Productive cough	0	1 (<1%)	0
Respiratory tract congestion	1 (2%)	0	0
Sneezing	0	1 (<1%)	0
Throat irritation	1 (2%)	0	0
Gastrointestinal disorders			
Any event	5 (8%)	10 (10%)	7 (10%)
Abdominal pain upper	1 (2%)	2 (2%)	2 (3%)
Nausea	3 (5%)	1 (<1%)	1 (1%)
Toothache	0	5 (5%)	0
Abdominal pain	2 (3%)	1 (<1%)	0
Diarrhoea	3 (5%)	0	0
Dyspepsia	0	1 (<1%)	1 (1%)
Abdominal discomfort	1 (2%)	0	0

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Table 8.17
Summary of Adverse Events (Open-Label Failure Population)

System Organ Class Preferred Term	Arg/Arg (N=64)	Arg/Gly (N=105)	Gly/Gly (N=69)
Dry mouth	1 (2%)	0	0
Gastrooesophageal reflux disease	0	0	1 (1%)
Gingival bleeding	0	0	1 (1%)
Lip pain	0	1 (<1%)	0
Lip swelling	0	1 (<1%)	0
Stomach discomfort	1 (2%)	0	0
Tongue disorder	0	0	1 (1%)
Vomiting	1 (2%)	0	0
Musculoskeletal and connective tissue disorders			
Any event	2 (3%)	8 (8%)	6 (9%)
Back pain	1 (2%)	2 (2%)	1 (1%)
Arthralgia	0	1 (<1%)	1 (1%)
Musculoskeletal chest pain	0	1 (<1%)	1 (1%)
Musculoskeletal pain	0	1 (<1%)	1 (1%)
Myalgia	1 (2%)	1 (<1%)	0
Neck pain	0	1 (<1%)	1 (1%)
Bone pain	0	1 (<1%)	0
Bursitis	1 (2%)	0	0
Joint swelling	0	0	1 (1%)
Muscle spasms	1 (2%)	0	0
Pain in extremity	0	1 (<1%)	0
Tendonitis	0	0	1 (1%)
General disorders and administration site conditions			
Any event	3 (5%)	7 (7%)	1 (1%)
Fatigue	1 (2%)	2 (2%)	0
Influenza like illness	0	2 (2%)	0
Pain	1 (2%)	1 (<1%)	0
Pyrexia	0	1 (<1%)	1 (1%)
Asthenia	1 (2%)	0	0
Chest discomfort	0	1 (<1%)	0
Ill-defined disorder	1 (2%)	0	0

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Table 8.17
Summary of Adverse Events (Open-Label Failure Population)

System Organ Class Preferred Term	Arg/Arg (N=64)	Arg/Gly (N=105)	Gly/Gly (N=69)
Oedema peripheral	1 (2%)	0	0
Sensation of blood flow	0	1 (<1%)	0
Injury, poisoning and procedural complications			
Any event	2 (3%)	3 (3%)	3 (4%)
Contusion	0	1 (<1%)	1 (1%)
Arthropod bite	1 (2%)	0	0
Arthropod sting	0	0	1 (1%)
Muscle strain	1 (2%)	0	0
Procedural pain	0	1 (<1%)	0
Respiratory fume inhalation disorder	0	1 (<1%)	0
Skin laceration	0	1 (<1%)	0
Tendon injury	0	0	1 (1%)
Wrist fracture	0	0	1 (1%)
Ear and labyrinth disorders			
Any event	1 (2%)	3 (3%)	1 (1%)
Ear pain	1 (2%)	1 (<1%)	1 (1%)
Ear discomfort	0	1 (<1%)	0
Motion sickness	0	1 (<1%)	0
Cardiac disorders			
Any event	1 (2%)	1 (<1%)	1 (1%)
Angina pectoris	0	0	1 (1%)
Palpitations	1 (2%)	0	0
Tachycardia	0	1 (<1%)	0
Psychiatric disorders			
Any event	1 (2%)	2 (2%)	0
Insomnia	1 (2%)	2 (2%)	0
Emotional distress	0	1 (<1%)	0
Nervousness	1 (2%)	0	0

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Table 8.17
Summary of Adverse Events (Open-Label Failure Population)

System Organ Class Preferred Term	Arg/Arg (N=64)	Arg/Gly (N=105)	Gly/Gly (N=69)

Skin and subcutaneous tissue disorders			
Any event	1 (2%)	2 (2%)	0
Dermatitis atopic	0	1 (<1%)	0
Rash	0	1 (<1%)	0
Urticaria	1 (2%)	0	0
Immune system disorders			
Any event	1 (2%)	0	1 (1%)
Drug hypersensitivity	1 (2%)	0	0
Hypersensitivity	0	0	1 (1%)
Renal and urinary disorders			
Any event	1 (2%)	0	1 (1%)
Nephrolithiasis	0	0	1 (1%)
Pollakiuria	1 (2%)	0	0
Reproductive system and breast disorders			
Any event	0	2 (2%)	0
Dysmenorrhoea	0	1 (<1%)	0
Pelvic pain	0	1 (<1%)	0
Investigations			
Any event	0	1 (<1%)	0
Blood pressure increased	0	1 (<1%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Any event	0	0	1 (1%)
Fibromatosis	0	0	1 (1%)
Pregnancy, puerperium and perinatal conditions			
Any event	1 (2%)	0	0
Abortion spontaneous	1 (2%)	0	0

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Table 8.18
Listing of Positive Pregnancy Tests

Inv.	Subj.	Trt	Arg16Gly genotype	Subject became pregnant?	Exposed to double-blind study drug?

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.

Table 8.19
Summary of Asthma Exacerbations During Double-Blind Period (ITT Population)

Treatment: FSC100/50

		Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Subjects in treatment group		89	92	91	272
Number of Subjects with an Exacerbation		0	0	1 (1%)	1 (<1%)
Number of Exacerbations		0	0	1	1
Primary Cause	Cold air/Cold weather	0	0	1 (100%)	1 (100%)
	Other NSAIDS	0	0	0	0
	Withholding or reducing asthma meds.	0	0	0	0
	Unknown etiology	0	0	0	0
	Lack of efficacy	0	0	0	0
	Lower respiratory infection	0	0	0	0
	Tobacco smoke	0	0	0	0
	Upper respiratory infection	0	0	0	0
	Air pollution	0	0	0	0
	Allergy	0	0	0	0
	Exercise	0	0	0	0
	Stress/Emotions	0	0	0	0
	Beta-blockers	0	0	0	0
	Aspirin	0	0	0	0
	Other	0	0	0	0
Outcome	Resolved	0	0	1 (100%)	1 (100%)
	Fatal	0	0	0	0
	Not resolved	0	0	0	0
Severity	Mild	0	0	0	0
	Moderate	0	0	0	0
	Severe	0	0	1 (100%)	1 (100%)

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Table 8.19
Summary of Asthma Exacerbations During Double-Blind Period (ITT Population)

Treatment: Salmeterol

		Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Subjects in treatment group		90	90	92	272
Number of Subjects with an Exacerbation		3 (3%)	3 (3%)	4 (4%)	10 (4%)
Number of Exacerbations		3	3	4	10
Primary Cause	Cold air/Cold weather	0	0	2 (50%)	2 (20%)
	Other NSAIDS	0	0	0	0
	Withholding or reducing asthma meds.	0	0	0	0
	Unknown etiology	1 (33%)	1 (33%)	0	2 (20%)
	Lack of efficacy	0	0	0	0
	Lower respiratory infection	0	0	0	0
	Tobacco smoke	0	0	0	0
	Upper respiratory infection	2 (67%)	1 (33%)	1 (25%)	4 (40%)
	Air pollution	0	0	0	0
	Allergy	0	0	0	0
	Exercise	0	0	0	0
	Stress/Emotions	0	0	0	0
	Beta-blockers	0	0	0	0
	Aspirin	0	0	0	0
	Other	0	0	1 (25%)	1 (10%)
	Missing	0	1 (33%)	0	1 (10%)
Outcome	Resolved	3 (100%)	2 (67%)	3 (75%)	8 (80%)
	Fatal	0	1 (33%)	0	1 (10%)
	Not resolved	0	0	1 (25%)	1 (10%)
Severity	Mild	0	0	2 (50%)	2 (20%)
	Moderate	3 (100%)	2 (67%)	1 (25%)	6 (60%)
	Severe	0	1 (33%)	1 (25%)	2 (20%)

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Table 8.20
Summary of Asthma Exacerbations During Open-Label Periods (ITT Population)

Treatment: FSC100/50

		Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Subjects in treatment group		89	92	91	272
Number of Subjects with an Exacerbation		5 (6%)	0	2 (2%)	7 (3%)
Number of Exacerbations		5	0	2	7
Primary Cause	Cold air/Cold weather	0	0	0	0
	Other NSAIDS	0	0	0	0
	Withholding or reducing asthma meds.	0	0	0	0
	Unknown etiology	1 (20%)	0	0	1 (14%)
	Lack of efficacy	0	0	0	0
	Lower respiratory infection	0	0	0	0
	Tobacco smoke	0	0	0	0
	Upper respiratory infection	2 (40%)	0	1 (50%)	3 (43%)
	Air pollution	0	0	0	0
	Allergy	0	0	1 (50%)	1 (14%)
	Exercise	0	0	0	0
	Stress/Emotions	0	0	0	0
	Beta-blockers	0	0	0	0
	Aspirin	0	0	0	0
	Other	2 (40%)	0	0	2 (29%)
Outcome	Resolved	5 (100%)	0	2 (100%)	7 (100%)
	Fatal	0	0	0	0
	Not resolved	0	0	0	0
Severity	Mild	0	0	0	0
	Moderate	5 (100%)	0	2 (100%)	7 (100%)
	Severe	0	0	0	0

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Table 8.20
Summary of Asthma Exacerbations During Open-Label Periods (ITT Population)

Treatment: Salmeterol

		Arg/Arg (N=179)	Arg/Gly (N=182)	Gly/Gly (N=183)	Total (N=544)
Subjects in treatment group		90	90	92	272
Number of Subjects with an Exacerbation		5 (6%)	0	0	5 (2%)
Number of Exacerbations		5	0	0	5
Primary Cause					
	Cold air/Cold weather	0	0	0	0
	Other NSAIDS	0	0	0	0
	Withholding or reducing asthma meds.	0	0	0	0
	Unknown etiology	1 (20%)	0	0	1 (20%)
	Lack of efficacy	0	0	0	0
	Lower respiratory infection	0	0	0	0
	Tobacco smoke	0	0	0	0
	Upper respiratory infection	2 (40%)	0	0	2 (40%)
	Air pollution	0	0	0	0
	Allergy	1 (20%)	0	0	1 (20%)
	Exercise	1 (20%)	0	0	1 (20%)
	Stress/Emotions	0	0	0	0
	Beta-blockers	0	0	0	0
	Aspirin	0	0	0	0
	Other	0	0	0	0
Outcome					
	Resolved	5 (100%)	0	0	5 (100%)
	Fatal	0	0	0	0
	Not resolved	0	0	0	0
Severity					
	Mild	1 (20%)	0	0	1 (20%)
	Moderate	4 (80%)	0	0	4 (80%)
	Severe	0	0	0	0

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Table 8.21
Listing of Asthma Exacerbations

Treatment: FSC100/50
Arg16Gly Genotype: Arg/Arg

Inv.	Subj.	Stratum	Period	Onset date/ Resolution Date	Study day/ Day within period	Outcome	Severity	Primary cause of exacerbation

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.

This subject withdrew from the study and therefore, did not enter the wash-out period.

Protocol: SFA100062
Population: Intent-to-Treat

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Table 8.22
Listing of Asthma Exacerbation Medications

Treatment: FSC100/50
Arg16Gly Genotype: Arg/Arg

Inv.	Subj.	Period	Study day/ Day within period	Medication	Dose/ Unit/ Freq/ Route	Start/ Stop/ Ongoing?

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.

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Note: Study period is missing for the subject who experienced an exacerbation during the double-blind treatment period and started exacerbation medications post double-blind treatment.

Table 8.23
Summary of Asthma Exacerbations (Open-Label Failure Population)

		Arg/Arg (N=64)	Arg/Gly (N=105)	Gly/Gly (N=69)	Total (N=238)
Number of Subjects with an Exacerbation		8 (13%)	10 (10%)	5 (7%)	23 (10%)
Number of Exacerbations		8	10	5	23
Primary Cause	Missing	0	0	0	0
	Cold air/Cold weather	0	1 (10%)	0	1 (4%)
	Other NSAIDS	0	0	0	0
	Withholding or reducing asthma meds.	0	0	1 (20%)	1 (4%)
	Unknown etiology	2 (25%)	3 (30%)	0	5 (22%)
	Lack of efficacy	0	0	1 (20%)	1 (4%)
	Lower respiratory infection	1 (13%)	1 (10%)	0	2 (9%)
	Tobacco smoke	0	0	0	0
	Upper respiratory infection	4 (50%)	2 (20%)	1 (20%)	7 (30%)
	Air pollution	0	0	1 (20%)	1 (4%)
	Allergy	1 (13%)	3 (30%)	1 (20%)	5 (22%)
	Exercise	0	0	0	0
	Stress/Emotions	0	0	0	0
	Beta-blockers	0	0	0	0
	Aspirin	0	0	0	0
	Other	0	0	0	0
Outcome	Resolved	7 (88%)	10 (100%)	5 (100%)	22 (96%)
	Not resolved	1 (13%)	0	0	1 (4%)
Severity	Mild	1 (13%)	3 (30%)	1 (20%)	5 (22%)
	Moderate	6 (75%)	6 (60%)	4 (80%)	16 (70%)
	Severe	1 (13%)	1 (10%)	0	2 (9%)

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Synopsis

Identifier: RM2007/00065/00 **Study Number:** SFA100062

Title: A Randomized, Parallel Group, Double-Blind, Comparative Trial Assessing Lung Function and Other Measures of Asthma Control in Adults and Adolescents, at least 12 Years of Age, with Asthma, Who Have Either a B16-Arg/Arg, a B16-Gly/Gly or a B16-Arg/Gly Genotype and are Treated With Fluticasone Propionate/Salmeterol DISKUS™ Combination Product 100/50mcg or Salmeterol DISKUS 50mcg BID

Investigator(s): This was a multi-center study

Study center(s): This Phase IV study was conducted at 63 sites in the US, two sites in Peru, and two sites in Kenya.

Publication(s): None at the time of this report.

Study Period: 25 October 2004 – 21 January 2007

Phase of Development: IV

Objectives: The primary objective of this study was to evaluate lung function as assessed by AM PEF AUC relative to baseline [AUC(bl)] in subjects who have the B16 Arg/Arg genotype compared with that of subjects who have the B16 Gly/Gly genotype over 16 weeks of treatment with FSC DISKUS 100/50mcg BID.

The secondary objective of this study was to evaluate lung function as assessed by AM PEF AUC(bl) and other measures in other *ADRB2* genotypes in the SM and FSC treatment groups over 16 weeks of treatment.

Other objectives included:

- Evaluation by genotype of lung function as assessed by AM PEF AUC(bl) and other measures during the last four weeks of open-label treatment with *prn* albuterol versus that during the last four weeks of open-label treatment with *prn* ipratropium bromide
- Evaluation of maximum albuterol dose response (MADR) by genotype
- Evaluation of lung function as assessed by AM PEF AUC(bl) in other *ADRB2* haplotype pairs in the SM and FSC treatment groups over 16 weeks of treatment
- Evaluation of assay sensitivity
- Evaluation of screen failures to address concerns regarding possible selection bias in the two prevalent genotypes.

Methodology: This was a multi-center, randomized, double-blind, parallel group, active comparator controlled design. Five hundred forty four (544) randomized subjects

provided data on 272 subjects per treatment group for fluticasone propionate/salmeterol combination (SFC) DISKUS 100/50 BID and salmeterol (SM) DISKUS 50mcg BID. Ninety (90) subjects per genotype (3) per blinded treatment arm (2) were targeted for randomization in order to complete at least 82 evaluable subjects per genotype per treatment arm. An evaluable subject was defined as a subject who completed at least 2 weeks of double-blind treatment, as documented in the patient diary card.

Subjects with the Arg/Arg genotype (which occurs at a frequency of about 15% in the general population) were compared to subjects with the Gly/Gly genotype (which occurs with approximately a 35% frequency) and to subjects with the Gly/Arg genotype (which occurs with approximately a 50% frequency).

The population frequency for the B16Arg/Arg genotype varies according to race/ethnicity. In the US, Hispanics and African Americans have higher frequencies for the Arg 16 alleles compared with the Caucasian group. In order to optimize enrolment of a representative sample of beta-receptor haplotypes, study sites were selected based on site demographics. In order to ensure that racial/ethnic groups were equally represented across treatment arms, randomization to treatment groups was stratified by genotype and race.

An additional eleven SNPs in the 5' and coding region and a poly-C repeat in the 3' region were genotyped across the *ADRB2*. Because of impact of study design on haplotype estimation, haplotypes will be reported in a subsequent exploratory analysis.

Disposition of Subjects

Disposition of subjects during the double-blind period and the washout period is presented as follows.

Disposition of Subjects in the ITT Population during the Double-blind Treatment Period and Washout Period

Subjects in the Double-blind Period	FSC 100/50mcg	SM 50mcg	Total
Planned, n	270	270	540
Randomized, n	272	272	544
Completed, n (%)	239 (88%)	217 (80%)	456 (84%)
Genotype, n			
Arg/Arg, n	89	90	179
Gly/Gly, n	91	92	183
Arg/Gly, n	92	90	182
Number (%) withdrawn	30 (11%)	53 (19%)	83 (15%)
Arg/Arg	10 (11%)	21 (23%)	
Gly/Gly	12 (13%)	16 (17%)	
Arg/Gly	8 (9%)	16 (18%)	
Reason for withdrawal			
Adverse event, n (%)	5 (2%)	10 (4%)	15 (3%)
Arg/Arg	3 (3%)	1 (1%)	
Gly/Gly	1 (1%)	3 (3%)	
Arg/Gly	1 (1%)	6 (7%)	
Exacerbation, n (%)	2 (<1%)	7 (3%)	9 (2%)
Arg/Arg	1 (1%)	3 (3%)	
Gly/Gly	1 (1%)	3 (3%)	
Arg/Gly	0	1 (1%)	
Lost to follow-up, n (%)	4 (1%)	9 (3%)	13 (2%)
Arg/Arg	1 (1%)	4 (4%)	
Gly/Gly	3 (3%)	2 (2%)	
Arg/Gly	0	3 (3%)	
Protocol violation, n (%)	4 (1%)	8 (3%)	12 (2%)
Arg/Arg	1 (1%)	4 (4%)	
Gly/Gly	1 (1%)	3 (3%)	
Arg/Gly	2 (2%)	1 (1%)	
Consent withdrawn, n (%)	10 (4%)	12 (4%)	22 (4%)
Arg/Arg	0	6 (7%)	
Gly/Gly	6 (7%)	3 (3%)	
Arg/Gly	4 (4%)	3 (3%)	
Sponsor terminated study site, n (%)	0	1 (<1%)	1 (<1%)
Arg/Arg	0	1 (1%)	
Gly/Gly	0	0	
Arg/Gly	0	0	
Other, n (%)	5 (2%)	6 (2%)	11 (2%)
Arg/Arg	4 (4%)	2 (2%)	
Gly/Gly	0	2 (2%)	
Arg/Gly	1 (1%)	2 (2%)	

Disposition of Subjects in the ITT Population during the Washout Period

Subjects in the Washout Period	FSC 100/50mcg	SM 50mcg	
Number (%) withdrawn	3 (1%)	2 (<1%)	5 (<1%)
Arg/Arg	1 (1%)	1 (1%)	
Gly/Gly	0	0	
Arg/Gly	2 (2%)	1(1%)	
Reason for withdrawal			
Adverse event, n (%)	1 (<1%)	0	1 (<1%)
Arg/Arg	0	0	
Gly/Gly	0	0	
Arg/Gly	1 (1%)	0	
Exacerbation, n (%)	1 (<1%)	0	1 (<1%)
Arg/Arg	1 (1%)	0	
Gly/Gly	0	0	
Arg/Gly	0	0	
Lost to follow-up, n (%)	0	0	0
Arg/Arg	0	0	
Gly/Gly	0	0	
Arg/Gly	0	0	
Protocol violation, n (%)	1 (<1%)	0	1 (<1%)
Arg/Arg	0	0	
Gly/Gly	0	0	
Arg/Gly	1 (1%)	0	
Consent withdrawn, n (%)	0	0	0
Arg/Arg	0	0	
Gly/Gly	0	0	
Arg/Gly	0	0	
Sponsor terminated study/site, n (%)	0	1 (<1%)	1 (<1%)
Arg/Arg	0	1 (1%)	
Gly/Gly	0	0	
Arg/Gly	0	0	
Other, n (%)	0	1 (<1%)	1 (<1%)
Arg/Arg	0	0	
Gly/Gly	0	0	
Arg/Gly	0	1 (1%)	

Diagnosis and main criteria for inclusion:**Diagnosis**

Each subject had a diagnosis of persistent asthma as defined by the American Thoracic Society [American Thoracic Society, 1987] for at least 3 months prior to Visit 1. At the screening visit (Visit 1), the subject had a best FEV₁ that was $\geq 70\%$ and $\leq 100\%$ of predicted normal after withholding asthma medications as detailed in the protocol. Predicted FEV₁ was based on the National Health and Nutrition Examination Survey (NHANES III) predicted normal values for ages 8 years and older [Hankinson, 1999].

Main Criteria for Inclusion

- Reversible airways disease was demonstrated by an increase in FEV₁ of $\geq 12\%$ and 200ml over baseline within 30 minutes after the inhalation of 2-4 puffs (180 mcg - 360 mcg) of albuterol (with or without a spacer) or 1-2 nebulized albuterol (2 puffs = 1 nebule) treatments at Visit 1 or at a visit that was within the 7-day period immediately following Visit 1. If the subject failed to reverse at least 12% during Visit 1, a second attempt to reverse was allowed to be scheduled within 7 days.
Note: Documentation of historical reversibility within one year of the Screening Visit demonstrating an increase in FEV₁ of $\geq 12\%$ and 200ml over baseline was acceptable and precluded the requirement for reversibility testing at the Screening Visit.

If the second attempt to document reversibility was unsuccessful, a methacholine challenge test (MCT) was permitted. A PC₂₀ result of $< 8\text{mg/ml}$ obtained at a visit prior to Visit 2 was required. A historical PC₂₀ value of $< 8\text{mg/ml}$ that was documented at the investigative site within the past 12 months and was obtained using American Thoracic Society (ATS) or Asthma Clinical Research Network (ACRN) guidelines for MCT was also acceptable [American Thoracic Society, 2000; ACRN, 2002]. Methacholine challenge testing was performed only at sites that had past experience performing this test.

- Male or female subjects 12 years of age or older at Visit 1 were eligible to participate in the study. Females were eligible only if they were currently non-pregnant and non-lactating. There were no birth control restrictions for this study. Female subjects of childbearing potential had a urine pregnancy test at the beginning of the study (Visit 2) and at Visit 4, 6, 8, 10, and at the end of the study (Visit 11 or a Premature Discontinuation Visit). Any female who became pregnant during the study was withdrawn.
- Eligible subjects reported short-acting β_2 -agonist (e.g. albuterol) for use on a *prn* (or scheduled) basis for at least 4 weeks prior to Visit 1
- Each subject was judged by the investigator to be able to withhold short-acting β_2 -agonist therapy (albuterol) for at least 6 hours prior to clinic visits when FEV₁ was performed.

Treatment administration:

At Visit 2, (open-label albuterol period) eligible subjects were given open-label albuterol 90mcg for use as needed (*prn*) to relieve asthma symptoms for 8 weeks (56 days $\pm$ 2 days). Visit 3 occurred 4 weeks following Visit 2. After this 8-week treatment period, at Visit 4, (open-label ipratropium period), subjects were given open-label ipratropium 18mcg for use as needed (*prn*) to relieve asthma symptoms for 8 weeks (56 days $\pm$ 2 days). Subjects also received open-label albuterol 90mcg for *prn* use in the event that asthma symptoms responded incompletely to ipratropium, in which case albuterol would be used as a superceding medication. Visit 5 occurred 4 weeks following Visit 4.

At Visit 6 (randomization visit), subjects were assigned a double-blind treatment for 16 weeks (112 days $\pm$ 2 days). Each subject received a supply of study medication via the DISKUS for one of two possible treatment groups.

Subjects inhaled the first dose of double-blind study medication (either FSC 100/50mcg via a DISKUS inhaler BID or SM 50mcg via a DISKUS inhaler BID) in the clinic on the day of randomization (Visit 6). The subject was instructed to administer one inhalation each morning and one inhalation each evening, approximately 12 hours apart, after obtaining their morning and evening PEF measurements. Each subject was to be advised to adhere to this dosing regimen throughout the study.

All eligible subjects were given open-label ipratropium bromide 18mcg for use only as needed throughout the double-blind period of the trial. Subjects also received open-label albuterol 90mcg for *prn* use in the event that asthma symptoms respond incompletely to ipratropium bromide, in which case albuterol would be used as a superceding medication for acute relief.

All subjects who completed Visit 10 of the double-blind treatment period were given open-label ipratropium bromide 18mcg for use during the washout period. Subjects also received open-label albuterol 90mcg for *prn* use in the event that asthma symptoms responded incompletely to ipratropium bromide, in which case albuterol was to be used as a superceding medication for acute relief.

Criteria for evaluation:

The primary measure of efficacy was area under the curve describing AM PEF relative to baseline [AUC(bl)] over the 16 week double-blind treatment period. The primary comparison of interest was between the Arg/Arg and Gly/Gly genotypes in the FSC treatment group.

Secondary measures of efficacy included area under the curve (describing PM PEF and FEV₁ over time) relative to baseline [AUC(bl)]. Other secondary measures were change from baseline in percent of symptom free days, and supplemental Atrovent (ipratropium bromide) use.

Other evaluations included lung function assessed by AM PEF AUC(bl) during the last four weeks of open-label treatment with *prn* albuterol versus during the last four weeks of open-label treatment with *prn* ipratropium bromide by genotype. Other measures of efficacy also included the proportion of subjects requiring supplemental albuterol and evaluation of the maximum albuterol dose responses (MADR) by genotype. Evaluation of lung function was also assessed by AM PEF AUC(bl) in other *ADRB2* SNPs in the SM and FSC treatment groups over 16 weeks of treatment.

Safety measurements were the incidence of clinical adverse events and the incidence of asthma exacerbations.

Statistical methods:

The sample size calculation for this study was based on the primary efficacy measure of AM PEF, recorded by subjects in daily diaries over the course of the study. It was estimated that the standard deviation of mean change from baseline in AM PEF over the 16-week double-blind treatment period in subjects randomized to the FSC treatment group would be 50 L/min. Using 28.5 L/min as the non-inferiority criterion bound (lower confidence interval limit of -28.5 L/min), a sample size of 82 subjects per group (per genotype per treatment group) would provide >90% power to demonstrate non-inferiority of the Arg/Arg genotype to the Gly/Gly genotype within the FSC treatment group in terms of AM PEF mean change from baseline over the 16 week treatment period, based on a 2-sided significance level of 0.05.

The Intent-to-Treat (ITT) population included all subjects who were randomized to blinded study drug. The ITT population was the primary analysis population for summaries and analyses of demographic/background, efficacy and safety data. During the conduct of the study, one investigative site [REDACTED] was closed due to significant deviations in Good Clinical Practice (GCP) identified at the site. Subjects randomized at this site (10 subjects) were not included in the ITT efficacy analyses.

The primary comparison of interest was that of non-inferiority between the Arg/Arg and Gly/Gly genotypes in the FSC treatment group assessed in terms of overall mean AM PEF change from baseline for the 16-week double-blind treatment period. Other comparisons included Arg/Arg versus Gly/Gly in the salmeterol treatment group and Arg/Arg versus Arg/Gly and Arg/Gly versus Gly/Gly in both the FSC and salmeterol treatment groups. These comparisons also assessed non-inferiority with 95% 2-sided confidence intervals and the same non-inferiority criterion bound as the primary comparison in terms of overall mean AM PEF change from baseline for the 16-week double-blind treatment period. An analysis of covariance (ANCOVA) model, including terms for genotype, ethnicity stratum and baseline, was used to assess non-inferiority in AM PEF mean change from baseline for the overall 16-week double-blind treatment period.

Each of the additional 12 markers was analyzed using an ANCOVA to determine significance between genotypes within each treatment. This analysis also utilized baseline, age, gender, and racial/ethnicity stratum as covariates in the model. No correction was made for ascertainment bias (Arg16Gly genotype), with each SNP treated as an independent marker. There were no corrections for multiple comparisons. Markers at positions +491 (RS1800888) and +659 (RS3729943) had very low minor allele frequencies (<2%) and were not included in the analyses.

Summary:**Efficacy - Primary Endpoint – AM PEF (L/min)****FSC 100/50mcg Treatment Group**

AM PEF (L/min)	Arg/Arg	Gly/Gly	Arg/Gly
Subjects, n	87	90	91
Baseline [†] , n	84	89	91
Mean (SE)	352 (10.3)	371 (10.0)	373 (9.6)
Double-blind Period (Wks 1-16), n	86	89	91
Mean (SE)	382.6 (10.1)	394.3 (9.7)	399.3 (11.1)
Mean change (SE)	32.6 (4.7)	24.9 (5.9)	25.9 (4.8)
Washout (2 weeks), n	77	78	82
Mean (SE)	372 (10.3)	385 (10.6)	393 (11.3)
Mean change (SE)	27.2 (5.1)	9.1 (4.8)	17.0 (4.6)
Statistical Comparisons	Arg/Arg vs Gly/Gly	Arg/Gly vs Gly/Gly	Arg/Arg vs Arg/Gly
Double-blind Period (Weeks 1-16)			
LS means difference	7.9	0.8	7.1
95% Confidence Interval	-6.3, 22.1	-13.0, 14.6	-7.1, 21.3
p-value	0.276	0.910	0.325
Washout (2 Weeks)			
LS means difference	15.9	7.6	8.3
95% Confidence Interval	2.5, 29.2	-5.4, 20.5	-4.9, 21.5
p-value	0.020	0.250	0.218

[†]Baseline- calculated from diary data and defined as the average value for the 7 day period preceding randomization (Visit 6). Diary data was required for three (3) days to calculate a baseline for each subject.

Changes in AM PEF for all genotypes were not statistically different in the FSC 100/50mcg double blind treatment period (Weeks 1-16). During the washout period, a statistically significant difference was observed in AM PEF for the Arg/Arg genotype compared to the Gly/Gly genotype (treatment difference 15.9 L/min, p=0.020).

SM 50mcg Treatment Group

AM PEF (L/min)	Arg/Arg	Gly/Gly	Arg/Gly
Subjects, n	86	91	89
Baseline [†] , n	80	91	86
Mean (SE)	387 (11.5)	373 (10.2)	362 (9.4)
Double-blind Period (Weeks 1-16), n	81	89	86
Mean (SE)	403.1 (11.9)	385.1 (9.8)	388.9 (11.0)
Mean change (SE)	19.4 (3.9)	12.4 (3.1)	24.6 (5.4)
Washout (2 Weeks), n	65	75	73
Overall Mean (SE)	394 (13.0)	375 (10.8)	378 (12.6)
Mean change (SE)	11.6 (5.2)	1.1 (3.8)	18.3 (7.7)
Statistical Comparisons	Arg/Arg vs Gly/Gly	Arg/Gly vs Gly/Gly	Arg/Arg vs Arg/Gly
Double-blind Period(Weeks 1-16)			
LS means difference	9.8	11.1	-1.2
95% Confidence Interval	-1.7, 21.4	-0.2, 22.3	-13.0, 10.6
p-value	0.095	0.054	0.836
Washout (2 Weeks)			
LS means difference	12.1	16.7	-4.6
95% Confidence Interval	-4.5, 28.7	0.7, 32.6	-21.6, 12.4
p-value	0.153	0.041	0.596

[†]Baseline- calculated from diary data and defined as the average value for the 7 day period preceding randomization (Visit 6). Diary data was required for three (3) days to calculate a baseline for each subject.

Changes in AM PEF for all genotypes were not statistically significant in the SM 50mcg double blind treatment period (Weeks 1-16). During the washout period, a statistically significant difference was observed in AM PEF for the Arg/Gly genotype compared to the Gly/Gly genotype (treatment difference 16.7 L/min, p=0.041).

Secondary and Other Efficacy Endpoints**PM PEF**

- Differences in changes in PM PEF for the three genotypes were not statistically significant in the FSC 100/50mcg treatment group in the double blind treatment period (Weeks 1-16).
- Changes in PM PEF (AUC) were statistically significant in the SM 50mcg treatment group for Arg/Gly subjects compared to Gly/Gly subjects (LS means difference 14.6 L/min, p=0.017). No statistically significant differences were observed in PM PEF for Arg/Arg subjects compared to Arg/Gly subjects or for Arg/Arg subjects compared to Gly/Gly subjects.

FEV₁

- Changes from baseline in pre-dose FEV₁ were similar overall (Weeks 1-16) in all genotypes in the FSC 100/50mcg treatment group in the double blind treatment period
- Changes in pre-dose FEV₁ for Arg/Arg subjects compared to Gly/Gly subjects were statistically significant in the SM 50mcg treatment arm overall (Weeks 1-16) in the double blind treatment period (LS means difference 0.13 L/min, p=0.003). No statistically significant differences were observed in pre-dose FEV₁ for Arg/Gly subjects compared to Gly/Gly subjects or for Arg/Arg subjects compared to Arg/Gly subjects.

Other Endpoints of Interest

No statistically significant differences were observed overall during the double blind treatment period in the FSC 100/50mcg treatment group or in the SM 50mcg treatment group between any of the genotypes for the following:

- percent of symptom free days
- supplemental ipratropium use
- percent of subjects requiring supplemental albuterol

No statistically significant differences were observed for AM PEF in the last 4 weeks of the open-label treatment period with *prn* albuterol compared to the last 4 weeks of the open-label treatment period with *prn* ipratropium.

MADR

No statistically significant differences were observed in the FEV₁ response to a maximum albuterol dose (MADR) between any of the genotypes at Visit 4 (the end of the albuterol open-label period and the first visit of the open-label ipratropium period), Visit 6 (the end of the ipratropium open-label period and beginning of the double-blind treatment period), and Visit 10 (end of blinded treatment period) in the FSC 100/50mcg treatment group.

A statistically significant difference in FEV₁ response to a maximum albuterol dose for the Arg/Arg genotype compared to the Gly/Gly genotype was observed at Visit 10 in the SM 50mcg treatment group (LS means difference -3.8%, p=0.008).

SNPs and Haplotypes

- Observations from analyses of additional *ADRB2* SNPS and haplotypes were as follows:
 - For FSC 100/50mcg, there was only one significant SNP (-3459) during the treatment phase for AM PEF. There were no significances found in FEV₁, symptom free days or supplemental ipratropium use. Significant differences were observed during the washout period between markers -1818, -47, +46

(Arg16Gly), +1053 for AM PEF and FEV₁. No significant differences occurred in symptom free days. One marker, +523, was significant for ipratropium use. There were no consistent patterns between endpoints, and markers would not reach significance if adjusted for multiple comparisons.

- For SM 50mcg, marker +1053 was significant for AM PEF. Marker +46 (Arg16Gly), +523, and -1818 were significant for FEV₁ during the double-blind period. Marker -2387 was significant for ipratropium use overall. There were no significant effects for symptom free days. During the washout, there were no significant genotypes in AM PEF. Markers -2387 and +1053 were significant for FEV₁ washout. No significant genotypes were observed for symptom free days, but markers -2387, +523 and +1053 were significant for ipratropium use. There were no consistent patterns between endpoints, and markers would not reach significance if adjusted for multiple comparisons.
- No haplotype analyses were completed since this study recruited specific numbers of genotypes and it is not in Hardy-Weinberg equilibrium (HWE) which could lead to biased estimates of genetic effects and even less control of type I error rates.

Safety Results

Overall, Arg/Arg, Gly/Gly and Arg/Gly subjects were responsive to FSC 100/50mcg as well as to SM 50mcg during the double-blind 16 week treatment period.

- The frequency and type of adverse events reported by subjects were generally similar across the genotypes during the albuterol and ipratropium open-label periods.
- The frequency and type of adverse events reported by subjects were generally similar across the genotypes in each of the treatment groups.
- The frequency of drug-related adverse events was also generally similar and low across the genotypes in each of the treatment groups.

Most Common Adverse Events (3% or Greater Incidence) in the FSC 100/50mcg Treatment Group (Intent-to-Treat Population)

Adverse Event	Arg/Arg N=89	Gly/Gly N=91	Arg/Gly N=92	Total N= 272
Number (%) of subjects with any adverse event	43 (48%)	45 (49%)	44 (48%)	132 (49%)
Nervous system disorders				
Headache	8 (9%)	9 (10%)	19 (21%)	36 (13%)
Infections and infestations				
Nasopharyngitis	3 (3%)	12 (13%)	6 (7%)	21 (8%)
Upper respiratory tract infection	1 (1%)	4 (4%)	3 (3%)	8 (3%)
Respiratory, thoracic, and mediastinal disorders				
Pharyngolaryngeal pain	5 (6%)	2 (2%)	4(4%)	11 (4%)
Cough	1(1%)	1(1%)	6(7%)	8 (3%)

The overall incidence of adverse events was generally similar across the FSC 100/50mcg treatment group for the three genotypes. Adverse events reported with an incidence of $\geq 3\%$ for the treatment group were generally similar across the genotypes. The most commonly affected SOC was nervous system disorders with headache the most commonly reported adverse event within that SOC (9%, 10%, and 21% of subjects in each genotype).

Most Common Adverse Events (3% or Greater Incidence) in the SM 50mcg Treatment Group (Intent-to-Treat Population)

Adverse Event	Arg/Arg N=90	Gly/Gly N=92	Arg/Gly N=90	Total N=272
Number (%) of subjects with any adverse event	39 (43%)	44 (48%)	37 (41%)	120 (44%)
Nervous system disorders				
Headache	6 (7%)	12 (13%)	12 (13%)	30 (11%)
Infections and infestations				
Nasopharyngitis	6 (7%)	9 (10%)	3 (3%)	18 (7%)
Upper respiratory tract infection	7 (8%)	3 (3%)	2 (2%)	12 (4%)
Sinusitis	6 (7%)	2 (2%)	0	8 (3%)
Respiratory, thoracic, and mediastinal disorders				
Pharyngolaryngeal pain	1 (1%)	3 (3%)	3 (3%)	7 (3%)
Musculoskeletal & connective tissue disorders				
Back pain	0	6 (7%)	1 (1%)	7 (3%)

The overall incidence of adverse events was generally similar across the SM 50mcg treatment group. Adverse events reported with an incidence of $\geq 3\%$ were generally similar across the genotypes. The most commonly affected SOC was nervous system disorders with headache the most commonly reported adverse event within that SOC (7%, 13%, and 13% of subjects in each genotype).

Drug Related Adverse Events

Overall, the incidence of adverse events having a reasonable possibility of being drug-related was small and similar across the genotypes in the FSC 100/50mcg treatment group, affecting 6 (7%) Arg/Arg, 2 (2%) Gly/Gly, and 5 (5%) Arg/Gly subjects across the three genotypes. No drug-related adverse events were reported in any SOC by $>3\%$ of subjects in any of the genotypes.

The incidence of adverse events having a reasonable possibility of being drug-related was also small and similar across the genotypes in the SM 50mcg treatment group, affecting 1 (1%) Arg/Arg, 5 (5%) Gly/Gly, and 4 (4%) Arg/Gly subjects across the three genotypes. No drug-related adverse events were reported in any SOC by $>3\%$ of subjects in any of the genotypes.

Serious Adverse Events

One death was reported during the conduct of the study and occurred in the double-blind treatment period. [REDACTED]

[REDACTED] The death was not attributed to the investigational product.

During the double-blind treatment period, no SAEs were reported by subjects in the SFC 100/50mcg treatment group.

[REDACTED]
[REDACTED] No SAEs were reported for Arg/Arg and Gly/Gly subjects.

Asthma Exacerbations

- Exacerbations experienced by Arg/Arg subjects in the albuterol and ipratropium open-label periods were considered mild (1) to moderate (9), all of which were resolved. Gly/Gly subjects (2) experienced exacerbations that were considered moderate in severity and resolved.
- The incidence of asthma exacerbations reported in the FSC 100/50mcg treatment group was low (1, 1% Gly/Gly subject). The exacerbation was severe and resolved. The incidents of asthma exacerbations reported in the SM 50mcg treatment group were similar across the genotype groups (Arg/Arg 3, 3%, Gly/Gly 4, 4%, Arg/Gly 3, 3%). One exacerbation (severe) experienced by an Arg/Gly subject occurred in the SM 50mcg treatment group and was fatal.
- One (<1%) exacerbation was reported during the washout period was moderate and resolved (Arg/Arg subject) in the FSC 100/50mcg treatment group. One Arg/Gly subject in the SM 50mcg treatment group experienced a mild asthma exacerbation (<1%) that was resolved during the washout period.

Conclusions

There is no evidence that any single SNP in the *ADRB2* gene is associated with either a poor response to FSC or SM, or loss of response, as evaluated by pulmonary function and subject derived variables such as symptoms and rescue beta-agonist use. Nor does a comparison of the albuterol and ipratropium run-in periods suggest that the Arg/Arg genotype, or the Gly/Gly or Arg/Gly genotypes, respond better to a non-beta-agonist bronchodilator such as ipratropium.

Date of Report: October 2007

Title:

A Randomized, Parallel Group, Double-Blind, Comparative Trial Assessing Lung Function and Other Measures of Asthma Control in Adults and Adolescents, at least 12 Years of Age, with Persistent Asthma, Who Have Either a B16-Arg/Arg, a B16-Gly/Gly or a B-16 Arg/Gly Genotype and are Treated With Fluticasone Propionate/Salmeterol **DISKUS** Combination Product 100/50mcg or Salmeterol **DISKUS** 50mcg BID

Document Number: ZM2004/00008/02

Study Identifier: SFA100062

GSK Compound Number: CCI18781+GR33343

Issue Date: 14 JUNE 2005

Protocol Amendment Number: 02

Author(s): [REDACTED]

Revision**Chronology:**

ZM2004/00008/00	2004-JUN-15	Original
ZM2004/00008/01	2004-NOV-17	Amendment No.: 1 Includes Update sponsor contact information, removes the limitation that methacholine challenge testing can only be performed on subjects ≥ 18 yrs of age, add that historical PC20 < 8 mg/ml is acceptable, add an exercise-induced bronchospasm exclusion, modify Anti-Asthma Medications time intervals, clarify the use of corticosteroids in the exclusion criteria, add a peanut and soybean food allergy exclusion criterion, add AM PEF stability limits, add requirement to take vital signs during MADR testing, remove Appendix 5 & 7 and to correct administrative and typographical errors.

ZM2004/00008/02

2005-MAY-20

Amendment No. 2: This amendment includes clarification and revision of the following sections: Protocol Summary, Open-Label Treatment Periods (continuation criteria added at Visit 2); Study Population (number of screened subjects); Section 5. Inclusion Criteria Nos. 3, 6 and 7 regarding pregnancy testing, historical reversibility, and pre-study anti-asthma medication use required for participation; Section 5. Exclusion Criteria Nos. 4, 5, 6, 9, and 10 regarding EIB, prohibited anti-asthma medications, prohibited concurrent medications, respiratory tract infection and antibiotic use; Section 6. Study Assessments, Rescreening (use of historical reversibility), Visit 2 continuation criteria added, premature discontinuation visit (open-label and washout periods, exacerbations (during the open-label periods), methacholine challenge testing (manual), albuterol and ipatropium bromide use (during open-label, randomization, and washout periods); Section 7. Dosage and Administration to include the washout period; Section 8. Concomitant Medications, permitted and prohibited medications to agree with Section 5, inclusion and exclusion criteria; Section 9. Subject Completion to include a discontinuation visit and Withdrawal to include screen and open-label, washout failures (data collection); Section 11. Data Analysis and Statistical Considerations, Other Comparisons of Interest and Sample Size Considerations modified; and corrections of administrative and reference errors.

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Sponsor Signatory:

Signature:

Date:

 MD
Vice President, MDC
Clinical Respiratory, US



6/10/05

SPONSOR INFORMATION PAGE

Title: A Randomized, Parallel Group, Double-Blind, Comparative Trial
Assessing Lung Function and Other Measures of Asthma Control
in Adults and Adolescents, at least 12 Years of Age, with
Persistent Asthma, Who Have Either a B16-Arg/Arg, a B16-
Gly/Gly or a B-16 Arg/Gly Genotype and are Treated With
Fluticasone Propionate/Salmeterol **DISKUS** Combination Product
100/50mcg or Salmeterol **DISKUS** 50mcg BID

Study Identifier: SFA100062

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IND Number: fluticasone propionate/salmeterol combination product **DISKUS**- 50,703;
salmeterol **DISKUS** – 43,097, Ventolin HFA - 46-269

INVESTIGATOR PROTOCOL 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, any future amendments, and with any other study conduct procedures provided by GlaxoSmithKline (GSK).
- Not to implement any changes to the protocol without agreement from the sponsor and prior review and written approval from the Institutional Review Board (IRB) or Independent Ethics Committee (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 in this protocol, and any other information provided by the sponsor including, but not limited to, the following: the current Clinical Investigator's Brochure / Investigator's Brochure (CIB/IB) or equivalent document, CIB/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 a CIB/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 in the protocol.
- 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 physician.

Physician Name:

Physician Signature

Date

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ABBREVIATIONS

AE	Adverse Event
ADRB2	Adrenergic Beta ₂ receptor
AM	Morning
Arg	Arginine
ATS	American Thoracic Society
AUC	Area Under the Curve
BARGE	Beta Adrenergic Response by Genotype
BID	Twice Daily
CIB	Clinical Investigator's Brochure
CRF	Case Report Form
DNA	Deoxyribnucleic acid
EIRS	Expedited Investigator Safety Reports
FEV ₁	Forced Expiratory Volume in one second
FP	Fluticasone Propionate
FSC	Fluticasone propionate/salmeterol combination product
Gly	Glycine
GSK	GlaxoSmithKline
ICS	Inhaled corticosteroid
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
MADR	Maximum Albuterol Dose Response
mcg	Microgram
MCT	Methacholine challenge testing
MedDRA	Medical Dictionary for Regulatory Authorities
MSDS	Material Safety Data Sheet
Mg	Milligram
PEF	Peak Expiratory Flow
PFT	Pulmonary Function Test
PGx	Pharmacogenetics
PM	Evening
Prn	As needed
QC	Quality Control
QD	Once daily
QID	Four times daily
SABA	Short acting beta agonists
SAE	Serious Adverse Event
SCA	Standard Clarification Agreement
SCAD	A system for drug allocation
SDV	Source Document Verification
SM	Salmeterol
SNP	Single Nucleotide Polymorphism

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Atrovent

PROTOCOL SUMMARY

Rationale

The β_2 -adrenergic receptor is a 413 amino acid protein encoded for by an intronless gene (*ADRB2*) located on chromosome 5q31.32 [Kobilka, 1987]. Variation in the activity of this cell surface receptor is important because it mediates the effects of β_2 -agonists. Screens of *ADRB2* have identified polymorphisms which may influence response to β_2 -agonists [Reihnsaus, 1993; Israel, 2000]. In particular, the receptor variant characterized by substitution of glycine for arginine at position 16 (Arg16Gly) may be an important determinant of receptor function *in vitro* and occurs commonly in the population (minor allele frequency approximately 0.4-0.5) [Taylor, 2000]. It appears that the Gly-16 receptor exhibits enhanced down-regulation *in vitro* after β -agonist exposure, but data from clinical studies are inconsistent. To date, screens of *ADRB2* have identified at least 19 single nucleotide polymorphisms (SNPs) within the coding and promoter region. Theoretically, the SNPs can be combined to form 2^n possible SNP combinations; however, because these alleles are tightly linked, five SNP combinations account for over 95% of observed distributions. This set of polymorphic, linked alleles that are inherited together are referred to as a haplotype. Previous studies that have evaluated *ADRB2* pharmacogenetics in asthma patients suggest that these haplotypes may be more informative in characterizing genetic/phenotypic associations as compared to analysis of individual genotypes.

Data from clinical studies suggest that genetic variation at loci 16 of the β_2 -AR gene can influence the response to a variety of β_2 -agonists, but the clinical significance of this is not yet clear [Joos, 2002]. Some studies have reported no pharmacogenetic variation in bronchoprotection among asthma patients using either short-acting or long-acting β -agonists [Lipworth, 1999; Hancox, 1998]. Three studies have shown greater bronchodilator response in B16-Arg/Arg homozygotes following acute and chronic β_2 -agonist administration [Lipworth, 1999; Martinez, 1997]. In contrast, increased bronchial hyperresponsiveness to methacholine was reported for B16-Arg/Arg homozygotes [Hancox, 1998]. Similar results were reported by Israel and colleagues who showed that B16-Arg/Arg homozygotes had a significant decline in morning peak expiratory flow rate when receiving QID salbutamol, but no change when used on an as-needed basis [Israel, 2004]. In another study, major exacerbations were more frequent in B16-Arg/Arg homozygotes receiving QID salbutamol, but not regular salmeterol [Taylor, 2000].

Israel et al investigated the genotypes of 190 patients with asthma who had participated in a double-blind, placebo-controlled study comparing scheduled albuterol four times daily versus as-needed albuterol for 16 weeks [Israel, 2000; Israel, 2001].

No clinically significant differences in overall asthma control were found between the groups when genotype was not considered. By contrast, the results of the genotyping showed that there was a small decline in AM peak expiratory flow (PEF) (i.e., approximately 7 L/min over a 16-week period) in patients homozygous for Arg16 who used albuterol regularly. Gly16/Gly patients did not experience a decline in AM PEF with scheduled albuterol. PM PEF also declined in the Arg16/Arg patients on scheduled albuterol, but not in those who used as-needed albuterol. Of note, a similar response to albuterol QID in patients with the homozygous Arg16 genotype was observed in the BARGE study, a 16-week, crossover trial [[Israel, 2004](#)].

Most studies of genetic variation at loci 16 of the β_2 -AR gene on response to β_2 -agonists have been conducted with short-acting β_2 -agonists. Consequently, it is not known whether genetic variations at loci 16 of the β_2 -AR gene have clinical significance for asthma patients receiving maintenance treatment with long-acting β_2 -agonists. Therefore, an investigation of whether the phenotypic response to salmeterol is altered by genotypic variation at the B16 position is warranted. The role of corticosteroids in increasing β_2 -receptor gene expression and decreasing the potential for desensitization is also uncertain. Therefore, the phenotypic response to salmeterol in patients with genotypic variation at the B16 position will also be characterized in this study. Finally, since haplotypes may be more informative in characterizing genetic/phenotypic associations as compared with analyses of results using individual genotypes alone, haplotype analyses will also be performed.

Objective(s)

Primary

The primary objective of this study is to evaluate lung function as assessed by AM PEF AUC relative to baseline [AUC(bl)] in subjects who have the B16 Arg/Arg genotype compared with that of subjects who have the B16 Gly/Gly genotype over 16 weeks of treatment with FSC **DISKUS** 100/50mcg BID.

Secondary

The secondary objective of this study is to evaluate lung function as assessed by AM PEF AUC(bl) and other measures in other *ADRB2* genotypes in the SM and FSC treatment groups over 16 weeks of treatment.

Other

Other objectives include:

- Evaluation by genotype of lung function as assessed by AM PEF AUC(bl) and other measures during the last four weeks of open-label treatment with *prn* albuterol versus that during the last four weeks of open-label treatment with *prn* ipratropium bromide;

- Evaluation of maximum albuterol dose response (MADR) by genotype;
- Evaluation of lung function as assessed by AM PEF AUC(bl) in other *ADRB2* haplotype pairs in the SM and FSC treatment groups over 16 weeks of treatment;
- Evaluation of assay sensitivity;
- Evaluation of screen failures to address concerns regarding possible selection bias in the two prevalent genotypes.

Endpoint(s)

Primary

The primary measure of efficacy will be area under the curve describing AM PEF relative to baseline [AUC(bl)] over the sixteen-week double-blind treatment period. The primary comparison of interest will be between the Arg/Arg and Gly/Gly genotypes in the FSC treatment group.

Secondary

Secondary measures of efficacy will include area under the curve (describing PM PEF and FEV₁ over time) relative to baseline [AUC(bl)]. Other secondary measures will include change from baseline in percent of symptom free days, and supplemental Atrovent (ipratropium bromide) use.

Other Evaluations

Evaluation of lung function as assessed by AM PEF AUC(bl) during the last four weeks of open-label treatment with *prn* albuterol versus that during the last four weeks of open-label treatment with *prn* ipratropium bromide by genotype.

Other measures of efficacy will include the proportion of subjects requiring supplemental albuterol and an evaluation of maximum albuterol dose responses (MADR) by genotype.

Evaluation of lung function as assessed by AM PEF AUC(bl) in other *ADRB2* haplotype pairs in the SM and FSC treatment groups over 16 weeks of treatment.

Compliance with appropriate use of study medications will be evaluated.

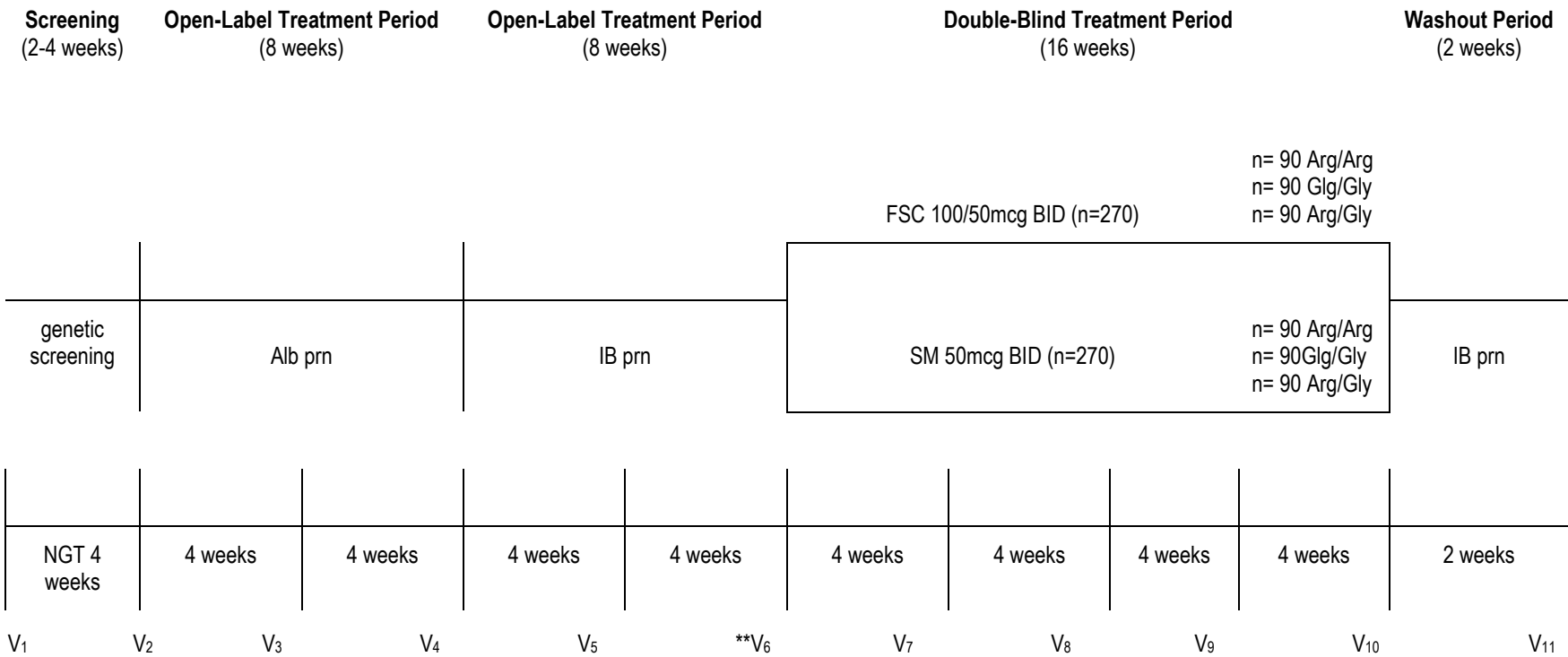
Assay sensitivity will be evaluated.

Safety Evaluations

Safety measurements will include the incidence of clinical adverse events and the incidence of asthma exacerbations.

Study Design

Short-acting beta₂-agonist only asthma patients



** Randomization visit

Alb – albuterol BID – twice daily FSC – fluticasone propionate/salmeterol combination product IB ipratropium bromide

NGT – not greater than Prn – as needed SM - salmeterol

This is a multi-center, randomized, double-blind, parallel group, active comparator controlled design. Approximately 60-80 centers will participate in the study. The study will be conducted in an outpatient population in study clinics. Information on genotypes will be blinded throughout the entire study. This information will be available only to the lab testing the blood samples, GSK Data Management and the IVR system.

All subjects must have reported short-acting β_2 -agonist for use on a prn (or scheduled) basis prior to screening (Visit 1) to manage their asthma. All subjects will remain on their pre-study short-acting β_2 -agonist until Visit 2.

The study includes a pharmacogenetic screening period, which is not to be greater than 4 weeks, followed by two 8-week open-label treatment periods, followed by randomization and a double-blind treatment period of 16 weeks. After subjects have completed the double-blind treatment period, they will enter a 2-week washout period and will be placed on open-label Atrovent (ipratropium bromide)¹ prn.

Screening

- At Visit 1, the informed consent must be signed prior to performing any study procedures or evaluations. Subjects must sign the informed consent before withholding any medications. If a bronchodilator was taken, refer to (Section 5.2.2, Exclusion Criteria), Anti-asthma medications, to determine how long the subject must wait before returning to the clinic. At Visit 1, inclusion/exclusion criteria will be assessed and procedures, including adverse event assessment, assessment of concomitant medications, pulmonary function testing, reversibility, physical examination, vital signs and medical history will be performed to ascertain eligibility to participate in the study. Subjects who qualify for the study based on Visit 1 (Screening Visit) and have at least one study procedure performed will be assigned a unique subject number. After eligibility is assessed and met, blood will be drawn.

Open-Label Treatment Periods

- At Visit 2, subjects will return to the clinic for assessment of concomitant medications, adverse event assessment, pregnancy testing (for females of childbearing potential), pulmonary function testing and a continuation assessment. All subjects will stop their pre-study short-acting β_2 -agonist and receive open-label albuterol 90mcg to be used as needed to relieve acute asthma symptoms for the first of two, 8-week open-label treatment periods. Eligible subjects will be provided with a peak flow meter and diary card and instructed to record asthma-related symptoms, medication use, as well as any other medical event that may occur between clinic

¹ Ipratropium bromide has been used in a number of asthma clinical trials as the primary rescue therapy [Tan 1997, Vathenen 1988, Israel, 2004]. No adverse outcomes have been reported as a result of this use of ipratropium. The experiences in clinical trials with this drug indicate that it can be used safely in this trial, as proposed.

visits. Each subject will also be instructed on appropriate study medication use, and advised to call the clinic to discuss any worsening of asthma.

- Subjects will return to the clinic in 4 weeks (Visit 3) for assessments of adverse events, use of concomitant medications, pulmonary function testing, continuation assessment, exchange and review of diary card records and collection and dispensing of study medications.
- Subjects will return to the clinic in 4 weeks (Visit 4) assessments of adverse events, use of concomitant medications, pregnancy testing (for females of childbearing potential), pulmonary function testing, continuation assessment, maximum albuterol dose response assessment, exchange and review of diary card records, collection of study medications and to begin the second open-label treatment period. Subjects will receive open-label ipratropium bromide 18mcg to be used as needed to relieve acute asthma symptoms for 8 weeks. Subjects will also receive open-label albuterol 90mcg for prn use in the event that asthma symptoms respond incompletely to ipratropium bromide, in which case albuterol will be used as a superceding medication.
- Subjects will return to the clinic in 4 weeks (Visit 5) for assessments of adverse events, use of concomitant medications, pulmonary function testing, continuation assessment, exchange and review of diary card records and collection and dispensing of study medications.

Double-Blind Treatment Period

- Subjects will return to the clinic for Visit 6 (randomization Visit), 4 weeks following Visit 5, for assessments of adverse events, use of concomitant medications, pregnancy testing (for females of childbearing potential), pulmonary function testing, continuation assessment, maximum albuterol dose response assessment, exchange and review of diary card records, and collection of study medications. Subjects will be randomized to treatment and dispensed double-blind study medication and rescue medications.
- Subjects will return to the clinic for Visit 7 (+4 weeks from randomization) for assessments of adverse events, use of concomitant medications, pulmonary function testing, exchange and review of diary card records and collection and dispensing study medications and rescue medications.
- Subjects will return to the clinic for Visit 8 (+8 weeks from randomization) for assessments of adverse events, use of concomitant medications, pulmonary function testing, pregnancy testing (for females of childbearing potential), exchange and review of diary card records, and to collect and dispense study medications and rescue medications.
- Subjects will return to the clinic for Visit 9 (+12 weeks from randomization) for assessments of adverse events, use of concomitant medications, pulmonary function testing, exchange and review of diary card records and to collect and dispense study medications and rescue medications.

- Subjects will return to the clinic for Visit 10 (+16 weeks from randomization) for assessments of adverse events, use of concomitant medications, physical exam, vital signs, pregnancy testing (for females of childbearing potential) pulmonary function testing, maximum albuterol dose response assessment, exchange and review of diary card records, collection of study medications and dispense rescue medications.

Washout Treatment Period

- Subjects will return to the clinic for Visit 11, 2 weeks following Visit 10, for assessments of adverse events, use of concomitant medications, pulmonary function testing, pregnancy testing (for females of childbearing potential), collection of diary card records and collection of study medication.

Study Population

Approximately 540 randomized subjects will provide data on 246 evaluable subjects per treatment group for FSC **DISKUS** 100/50 and SM 50mcg BID. Approximately 90 subjects per genotype (3) per blinded treatment arm (2) will be randomized in order to have at least 82 evaluable subjects per genotype per treatment arm.

An evaluable subject is defined as those subjects that complete at least 2 weeks of double-blind treatment, as documented in the patient diary card.

We will compare individuals with the Arg/Arg genotype (which occurs at a frequency of about 15% in the general population) to those with the Gly/Gly genotype (which occurs with approximately a 35% frequency) and to those with the Gly/Arg genotype (which occurs with approximately a 50% frequency). Thus, to recruit 90 subjects in each of the genotypic categories, we will need to screen a minimum of 1,200 subjects. Allowing for exclusions, refusals to participate and withdrawals, we may need to screen approximately 1840 subjects.

The population frequency for the B16Arg/Arg haplotype varies according to ethnicity. In the US, Hispanics and African Americans have higher frequencies for the Arg 16 alleles compared with the Caucasian group [[Drysdale](#), 2000]. In order to ensure that a representative sample of all haplotypes is obtained, study sites will be selected based on site demographics. In order to ensure that ethnic groups are equally represented across treatment arms, randomization to treatment groups will be stratified by genotype and race.

To date, screens of *ADRB2* have identified at least 19 single nucleotide polymorphisms (SNPs) within the coding and promoter region. Theoretically, the SNPs can be combined to form 2^n possible SNP combinations; however, because these alleles are tightly linked, five SNP combinations account for over 95% of observed distributions. This set of polymorphic, linked alleles that are inherited together are referred to as a haplotype. Previous studies that have evaluated *ADRB2* pharmacogenetics in asthma patients suggest that these haplotypes may be more informative in characterizing genetic/phenotypic associations as compared with analyses of individual genotypes alone.

Haplotype frequencies are estimated from individual SNPs using an expectation-maximization (EM) algorithm. Although much of the asthma pharmacogenetic work has centered on the Arg/Arg genotype at position 16, both Arg/Gly heterozygotes and Gly/Gly homozygotes will be needed to correctly apply the EM algorithm and estimate haplotype frequencies. Recruitment of 90 patients per Arg16Gly genotype is suitable for applying the EM algorithm to generate haplotype estimates.

Study Assessments and Procedures

The following assessments/procedures will be performed during the study:

- Blood samples drawn
- Medical history, physical examination, vital signs (blood pressure and pulse), concomitant medication assessment
- FEV₁ (including percent predicted and reversibility assessments at Visit 1)
- Methacholine Challenge Testing (performed once, only if subject fails reversibility twice)
- PEF Stability Limit calculation (at Visit 3)
- Maximum Albuterol Dose Response (MADR)
- Adverse event assessment
- Pregnancy test for all females of childbearing potential
- Review of daily diary data recorded by subject

Investigational Product(s)

Albuterol (90mcg), SM **DISKUS** (50mcg) and FSC **DISKUS** (100/50mcg) will be manufactured by GlaxoSmithKline.

Ipratropium bromide (18mcg) will be manufactured by Boehringer Ingelheim.

The two possible double-blind treatments are:

- FSC 100/50mcg **DISKUS** twice daily
- SM **DISKUS** 50mcg twice daily

1. INTRODUCTION

1.1. Background

The β_2 -adrenergic receptor is a 413 amino acid protein encoded for by an intronless gene (*ADRB2*) located on chromosome 5q31.32 [Kobilka, 1987]. Variation in the activity of this cell surface receptor is important because it mediates the effects of β_2 -agonists. Screens of *ADRB2* have identified polymorphisms which may influence response to β_2 -agonists [Reihnsaus, 1993; Israel, 2000]. In particular, the receptor variant characterized by substitution of glycine for arginine at position 16 (Arg16Gly) may be an important determinant of receptor function *in vitro* and occurs commonly in the population (minor allele frequency approximately 0.4-0.5) [Taylor, 2000]. It appears that the Gly-16 receptor exhibits enhanced down-regulation *in vitro* after β -agonist exposure, but data from clinical studies are inconsistent. To date, screens of *ADRB2* have identified at least 19 single nucleotide polymorphisms (SNPs) within the coding and promoter region. Theoretically, the SNPs can be combined to form 2^n possible SNP combinations; however, because these alleles are tightly linked, five SNP combinations account for over 95% of observed distributions. This set of polymorphic, linked alleles that are inherited together are referred to as a haplotype. Previous studies that have evaluated *ADRB2* pharmacogenetics in asthma patients suggest that these haplotypes may be more informative in characterizing genetic/phenotypic associations as compared to analysis of individual genotypes.

Data from clinical studies suggest that genetic variation at loci 16 of the β_2 -AR gene can influence the response to a variety of β_2 -agonists, but the clinical significance of this is not yet clear [Joos, 2002]. Some studies have reported no pharmacogenetic variation in bronchoprotection among asthma patients using either short-acting or long-acting β -agonists [Lipworth, 1999; Hancox, 1998]. Three studies have shown greater bronchodilator response in B16-Arg/Arg homozygotes following acute and chronic β_2 -agonist administration [Lipworth, 1999; Martinez, 1997]. In contrast, increased bronchial hyperresponsiveness to methacholine was reported for B16-Arg/Arg homozygotes [Hancox, 1998]. Similar results were reported by Israel and colleagues who showed that B16-Arg/Arg homozygotes had a significant decline in morning peak expiratory flow rate when receiving QID salbutamol, but no change when used on an as-needed basis [Israel, 2004]. In another study, major exacerbations were more frequent in B16-Arg/Arg homozygotes receiving QID salbutamol, but not regular salmeterol [Taylor, 2000].

Israel et al investigated the genotypes of 190 patients with asthma who had participated in a double-blind, placebo-controlled study comparing scheduled albuterol four times daily versus as-needed albuterol for 16 weeks [Israel, 2000; Israel, 2001]. No clinically significant differences in overall asthma control were found between the groups when genotype was not considered. By contrast, the results of the genotyping showed that there was a small decline in AM peak expiratory flow (PEF) (i.e., approximately 7 L/min over a 16-week period) in patients homozygous for Arg16 who used albuterol regularly. Gly16/Gly patients did not experience a decline in AM PEF with scheduled albuterol. PM PEF also declined in the Arg16/Arg patients on scheduled albuterol, but not in those who used as-needed albuterol. Of note, a similar response to albuterol QID in patients with the homozygous Arg16 genotype was observed in the BARGE study, a 16-week period, crossover trial [Israel, 2004].

1.2. Rationale

Most studies of genetic variation at loci 16 of the β_2 -AR gene on response to β_2 -agonists have been conducted with short-acting β_2 -agonists. Consequently, it is not known whether genetic variations at loci 16 of the β_2 -AR gene have clinical significance for asthma patients receiving maintenance treatment with long-acting β_2 -agonists. Therefore, an investigation of whether the phenotypic response to salmeterol is altered by genotypic variation at the B16 position is warranted. The role of corticosteroids in increasing β_2 -receptor gene expression and decreasing the potential for desensitization is also uncertain. Therefore, the phenotypic response to salmeterol in patients with genotypic variation at the B16 position will also be characterized in this study. Finally, since haplotypes may be more informative in characterizing genetic/phenotypic associations as compared with analyses of results using individual genotypes alone, haplotype analyses will also be performed.

2. OBJECTIVE(S)

2.1. Primary

The primary objective of this study is to evaluate lung function as assessed by AM PEF AUC relative to baseline [AUC(bl)] in subjects who have the B16 Arg/Arg genotype compared with that of subjects who have the B16 Gly/Gly genotype over 16 weeks of treatment with FSC **DISKUS** 100/50 mcg BID.

2.2. Secondary

The secondary objective of this study is to evaluate lung function as assessed by AM PEF AUC(bl) and other measures in other *ADRB2* genotypes in the SM and FSC treatment groups over 16 weeks of treatment.

2.3. Other

Other objectives include:

- Evaluation by genotype of lung function as assessed by AM PEF AUC(bl) and other measures during the last four weeks of open-label treatment with *prn* albuterol versus that during the last four weeks of open-label treatment with *prn* ipratropium bromide;
- Evaluation of maximum albuterol dose response (MADR) by genotype;
- Evaluation of lung function as assessed by AM PEF AUC(bl) in other *ADRB2* haplotype pairs in the SM and FSC treatment groups over 16 weeks of treatment;
- Evaluation of assay sensitivity;
- Evaluation of screen failures to address concerns regarding possible selection bias in the two prevalent genotypes.

3. ENDPOINT(S)

3.1. Primary

The primary measure of efficacy will be area under the curve describing AM PEF relative to baseline [AUC(bl)] over the sixteen-week double-blind treatment period. The primary comparison of interest will be between the Arg/Arg and Gly/Gly genotypes in the FSC treatment group.

3.2. Secondary

Secondary measures of efficacy will include area under the curve (describing PM PEF and FEV₁ over time) relative to baseline [AUC(bl)]. Other secondary measures will include change from baseline in percent of symptom free days, and supplemental Atrovent (ipratropium bromide) use.

3.3. Other

Evaluation of lung function as assessed by AM PEF AUC(bl) during the last four weeks of open-label treatment with *prn* albuterol versus that during the last four weeks of open-label treatment with *prn* ipratropium bromide by genotype.

Other measures of efficacy will include the proportions of subjects requiring supplemental albuterol and an evaluation of maximum albuterol dose responses (MADR) by genotype.

Evaluation of lung function as assessed by AM PEF AUC(bl) in other *ADRB2* haplotype pairs in the SM and FSC treatment groups over 16 weeks of treatment.

Compliance with appropriate use of study medications will be evaluated.

Assay sensitivity will be evaluated.

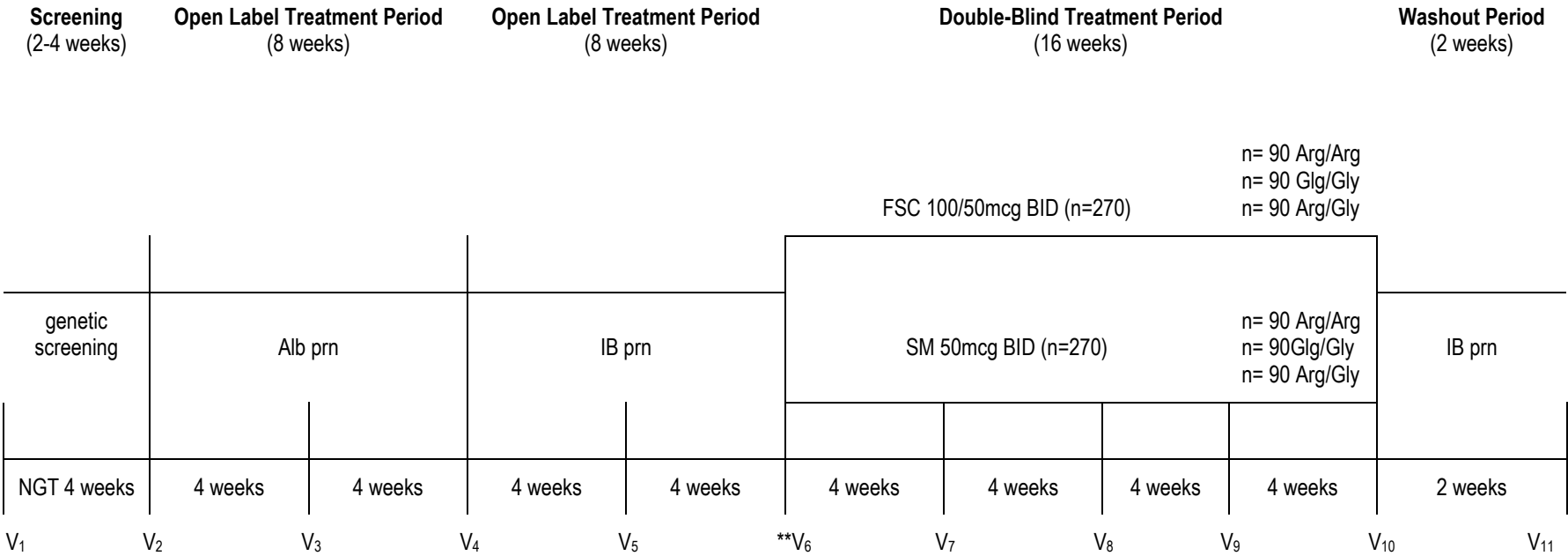
3.4. Safety

Safety measurements will include the incidence of clinical adverse events and the incidence of asthma exacerbations.

4. STUDY DESIGN

Figure 1 Study Schematic

Short-acting beta₂-agonist only asthma patients



** Randomization visit

Alb – albuterol

BID – twice daily

FSC – fluticasone propionate/salmeterol combination product

IB ipratropium bromide

NGT – not greater than

Prn – as needed

SM - salmeterol

This is a multi-center, randomized, double-blind, parallel group, active comparator controlled design. Approximately 60-80 centers will participate in the study. The study will be conducted in an outpatient population in study clinics. Information on genotypes will be blinded throughout the entire study. This information will be available only to the lab testing the blood samples, GSK Data Management and the IVR system.

All subjects must have reported short-acting β_2 -agonist for use on a prn (or scheduled) basis prior to screening (Visit 1) to manage their asthma. All subjects will remain on their pre-study short-acting β_2 -agonist until Visit 2. The study includes a pharmacogenetic screening period, which is not to be greater than 4 weeks, followed by two 8-week open-label treatment periods, followed by randomization and a double-blind treatment period of 16 weeks. After subjects have completed the double-blind treatment period, they will enter a 2-week washout period and will be placed on open-label Atrovent (ipratropium bromide)² prn.

5. STUDY POPULATION

5.1. Number of Subjects

Approximately 540 randomized subjects will provide data on 246 evaluable subjects per treatment group for FSC **DISKUS** 100/50 and SM 50 μg BID. Approximately 90 subjects per genotype (3) per blinded treatment arm (2) will be randomized in order to have at least 82 evaluable subjects per genotype per treatment arm.

An evaluable subject is defined as those subjects that complete at least 2 weeks of double-blind treatment, as documented in the patient diary card.

We will compare individuals with the Arg/Arg genotype (which occurs at a frequency of about 15% in the general population) to those with the Gly/Gly genotype (which occurs with approximately a 35% frequency) and to those with the Gly/Arg genotype (which occurs with approximately a 50% frequency). Thus, to recruit 90 subjects in each of the genotypic categories, we will need to screen a minimum of 1,200 subjects. Allowing for exclusions, refusals to participate and withdrawals, we may need to screen approximately 1840 subjects.

² Ipratropium bromide has been used in a number of asthma clinical trials as the primary rescue therapy [Tan 1997, Vathenen 1988, Israel, 2004]. No adverse outcomes have been reported as a result of this use of ipratropium. The experiences in clinical trials with this drug indicate that it can be used safely in this trial, as proposed.

The population frequency for the B16Arg/Arg haplotype varies according to ethnicity. In the US, Hispanics and African Americans have higher frequencies for the Arg 16 alleles compared with the Caucasian group [Drysdales, 2000]. In order to ensure that a representative sample of all haplotypes is obtained, study sites will be selected based on site demographics. In order to ensure that ethnic groups are equally represented across treatment arms, randomization to treatment groups will be stratified by genotype and race.

To date, screens of *ADRB2* have identified at least 19 single nucleotide polymorphisms (SNPs) within the coding and promoter region. Theoretically, the SNPs can be combined to form 2^n possible SNP combinations; however, because these alleles are tightly linked, five SNP combinations account for over 95% of observed distributions. This set of polymorphic, linked alleles that are inherited together are referred to as a haplotype. Previous studies that have evaluated *ADRB2* pharmacogenetics in asthma patients suggest that these haplotypes may be more informative in characterizing genetic/phenotypic associations as compared with analyses of individual genotypes alone.

Haplotype frequencies are estimated from individual SNPs using an expectation-maximization (EM) algorithm. Although much of the asthma pharmacogenetic work has centered on the Arg/Arg genotype at position 16, both Arg/Gly heterozygotes and Gly/Gly homozygotes will be needed to correctly apply the EM algorithm and estimate haplotype frequencies. Recruitment of 90 patients per Arg16Gly genotype is suitable for applying the EM algorithm to generate haplotype estimates.

5.2. Eligibility Criteria

5.2.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

1. **Type of Subject:** A subject must be treatable on an outpatient basis.
2. **Age:** A subject must be 12 years of age or older at Visit 1.
3. **Gender:** Male or Female.

Females are eligible to participate only if they are currently non-pregnant and non-lactating. There are no birth control restrictions for this study. Female subjects of childbearing potential will undergo a urine pregnancy test at the beginning of the study (Visit 2) and at Visit 4, 6, 8, 10 and at the end of the study (Visit 11 or a Premature Discontinuation Visit which may occur during the open-label periods, the double-blind treatment period, or the washout period.) Any female who becomes pregnant during the study will be withdrawn. Female subjects should not be enrolled if they plan to become pregnant during the time of study participation.

4. **Disease:** Each subject must have a diagnosis of persistent asthma for at least 3 months prior to Visit 1. Asthma is defined by the American Thoracic Society as follows:

“Asthma is a clinical syndrome characterized by increased responsiveness of the tracheobronchial tree to a variety of stimuli. The major symptoms of asthma are paroxysms of dyspnea, wheezing, and cough, which may vary from mild and almost undetectable to severe and unremitting (status asthmaticus). The primary physiological manifestation of this hyperresponsiveness is variable airways obstruction. This can take the form of spontaneous fluctuations in the severity of obstruction, substantial improvements in the severity of obstruction following bronchodilators or corticosteroids, or increased obstruction caused by drugs or other stimuli” [[American Thoracic Society](#), 1987].

5. **FEV₁ Component:** The subject has a best FEV₁ that is $\geq 70\%$ and $\leq 100\%$ of predicted normal at Visit 1 after withholding asthma medications as detailed in the protocol. Predicted FEV₁ will be based on the **National Health and Nutrition Examination Survey (NHANES III) predicted normal values for ages 8 years and older** [[Hankinson](#), 1999].
6. **Reversibility Component:** The subject has reversible airways disease as demonstrated by an increase in FEV₁ of $\geq 12\%$ and 200ml over baseline within 30 minutes after the inhalation of 2-4 puffs (180 μ g -360 μ g) of albuterol (with or without a spacer) or 1-2 nebulized albuterol (2 puffs = 1 nebule) treatments at Visit 1 or at a visit that is within the 7-day period immediately following Visit 1. If the subject fails to reverse at least 12% during Visit 1, a second attempt to reverse may be scheduled within 7 days.

If the second attempt to document reversibility is unsuccessful, the subject may undergo a methacholine challenge test (MCT). A PC₂₀ result of <8mg/ml obtained at an unscheduled visit prior to Visit 2 is required. An historical PC₂₀ value of <8mg/ml that has been documented at the investigative site within the past 12 months and was obtained using ATS or ACRN guidelines for MCT is also acceptable [[American Thoracic Society](#), 2000; [ACRN](#), 2002]. Methacholine challenge testing should be performed only at sites that have past experience performing this test.

NOTE: Documentation of historical reversibility within one year of the Screening Visit demonstrating an increase in FEV₁ of $\geq 12\%$ and 200ml over baseline is acceptable and will preclude the requirement for reversibility testing at the Screening Visit.

7. **Concurrent Anti-Asthma Therapy:** Eligible subjects must have reported short-acting β_2 -agonist for use on a prn (or scheduled) basis for at least 4 weeks prior to Visit 1. Each subject must be judged by the investigator to be able to withhold short-acting β_2 -agonist therapy for at least 6 hours prior to clinic visits when FEV₁ is performed.
8. The subject agrees to allow a venipuncture for blood draw.
9. The subject demonstrates correct use of the **DISKUS** device and a MDI, as well as correct use of a peak flow meter.
10. **Literacy:** A subject must be able to read, comprehend and record information.

5.2.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

1. **Life-Threatening Asthma:** A subject may not have life-threatening asthma. Life-threatening asthma is defined for this protocol as a history of significant asthma episode(s) requiring intubation, associated with hypercapnia, respiratory arrest, hypoxic seizures, or asthma-related syncopal episode(s).
2. **Asthma instability:** A subject must not have been hospitalized due to asthma within 6 months prior to Visit 1.
3. **Respiratory Disease:** Current evidence of cystic fibrosis, pneumonia, pneumothorax, atelectasis, pulmonary fibrotic disease, chronic bronchitis or any other respiratory abnormalities other than asthma excludes a subject from participation.
4. **Exercise-Induced Bronchospasm Alone:** A subject may not have been diagnosed with exercise-induced bronchospasm alone, in the absence of a diagnosis of persistent asthma within the last 3 months prior to Visit 1.
5. **Anti-Asthma Medications:** Asthma medications listed below must not have been used prior to Screening (Visit 1) for the required interval indicated below and not taken during study.

Oral short-acting beta ₂ -agonists	6 hours
Inhaled short-acting anticholinergics	6 hours
Inhaled long-acting anticholinergics	24 hours
Leukotriene modifiers	4 weeks
Inhaled long-acting beta ₂ -agonists	4 weeks
Theophylline products	48 hours
Oral long-acting beta ₂ -agonists	4 weeks
Inhaled corticosteroids	4 weeks
Inhaled corticosteroid/ Inhaled long-acting beta ₂ -agonist combination products	4 weeks
Oral corticosteroids	4 weeks ^{1,2}
Parenteral corticosteroids	4 weeks ²
Inhaled cromolyn sodium or nedocromil	4 weeks

1. Any subject who has received oral corticosteroid treatment for any reason for 2 months or longer must have discontinued use for at least 6 months prior to Visit 1.
 2. A subject must not have had two courses of oral or parenteral corticosteroids for any reason in the 6 months prior to Visit 1
6. **Concurrent medications:** Concurrent use of any of the following medications that may affect the course of asthma or interact with sympathomimetic amines will not be allowed. Specifically:
 - beta blockers
 - polycyclic antidepressants

- monoamine oxidase inhibitors
- phenobarbital
- rifampin

NOTE: Regular use of short-acting nasal decongestants is allowed. Other intranasal medications including antihistamines and intranasal corticosteroids for the treatment of rhinitis are also allowed. Topical hydrocortisone cream or ointment (1% or less) is also allowed.

7. **Immunosuppressive Medications:** Use of immunosuppressive medications is not allowed at any time during the study.

NOTE: Immunotherapy for the treatment of allergies is allowed during the study, provided that the subject has received a constant dose for 30 days prior to Visit 1, and that the same dose will be continued throughout the study.

8. **Other Medications:** The medications listed below must not have been used prior to Screening (Visit 1) for the required interval indicated below, and not taken during the study.

- Methotrexate, gold, cyclosporine and azathioprine 12 months
- Ritonovir 12 months

9. **Respiratory Tract Infection:** The subject has a respiratory infection that is suspected or diagnosed within 4 weeks immediately preceding Visit 1 or during the period from Visit 1 to Visit 2. The subject may be re-screened one time. Rescreening must be no sooner than 4 weeks following resolution of any suspected or diagnosed respiratory infection (whether treated or not).

10. **Antibiotic Usage:** The subject used an antibiotic (or other medication) for treatment of a suspected or diagnosed upper or lower respiratory tract infection within 4 weeks of Visit 1 or during the periods from Visit 1 to Visit 2. The subject may be re-screened one time. Antibiotics for other infections or acne are permitted.

11. **Other Concurrent Conditions/Diseases:** Any clinically significant, uncontrolled condition or disease state that, in the opinion of the investigator, would put the safety of the subject at risk through study participation or would confound the interpretation of the results if the condition/disease exacerbated during the study excludes a subject from participation. The list of conditions/diseases that will result in exclusion if determined to be clinically significant includes, but is not limited to: cardiac arrhythmias, congestive heart failure, coronary artery disease, Cushing's or Addison's disease, diabetes mellitus, dyspnea by any cause other than asthma, hematological, hepatic, neurological, thyroid, peptic ulcer, or renal disease, uncontrolled hypertension, immunologic compromise, current malignancy, current or quiescent tuberculosis.

12. **Drug Allergy:** The subject has any adverse reaction, including immediate or delayed hypersensitivity, to study medications, severe milk protein allergy or allergies to soya lecithin or related food products such as soybeans or peanuts.

13. **Tobacco Use:** The subject has a greater than a 10 pack-year history of cigarette smoking and/or use of any tobacco products within 1 year of Visit 1.

14. **Positive Pregnancy Test (for females of childbearing potential):** A current positive pregnancy test.
15. **Questionable Validity of Consent:** The subject or parent (caregiver) has a history of psychiatric disease, intellectual deficiency, poor motivation, substance abuse (including drug and alcohol), or other conditions which would limit the validity of informed consent to participate in the study.
16. **Investigational Drug:** A subject may not have been exposed to an investigational drug within 30 days prior to Visit 1.
17. **Affiliation with Investigational Site:** A subject may not participate if he/she is a participating investigator, sub-investigator, study coordinator, or employee of a participating investigator, or is an immediate family member of the aforementioned.
18. **Questionable Compliance with Medications or Visits:** A subject may not participate if he/she has an infirmity, disability or geographical location which seems likely, in the opinion of the investigator, to impair compliance with any aspect of this study protocol or scheduled visits.

5.2.3. 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: Clinical Investigator's Brochure provided by GSK and/or the approved product labels.

6. STUDY ASSESSMENTS AND PROCEDURES

The Time and Events Schedule details the timeframe in which visits should occur and the procedures to be performed at each study visit (see [Appendix 1](#), Time and Events Table).

All visits (when clinic FEV₁ is performed) should start between 6 AM and 11 AM.

- During the open-label periods, subjects should withhold all short-acting β_2 -agonist and ipratropium bromide medication(s) for at least 6 hours prior to spirometry.
- Subjects should withhold double-blind study medication on the mornings of clinic visits, as well as ipratropium (and albuterol) within 6 hours of spirometry.

Visits may be rescheduled once. See Section [6.5.1.2](#), Clinical FEV₁.

6.1. Demographic and Baseline Assessments

6.1.1. Informed Consent

The informed consent must be signed by the subject and witnessed prior to performance of any study procedures, evaluations or changes in medications required for study participation.

6.2. Study Visit Assessments

6.2.1. Screening Visit (Visit 1)

Written informed consent must be obtained **prior** to any study procedures or any withholding of asthma medications. Each subject will be evaluated to determine if the selection criteria have been met (Section 5.2.1, Inclusion Criteria and Section 5.2.2, Exclusion Criteria).

All procedures in this period must be completed and results made available prior to Visit 2. All procedures should be performed on the day of Visit 1 (see [Appendix 1](#), Time and Events Table).

The following assessments/procedures will be performed at Visit 1:

- Verification of inclusion/exclusion criteria
- Medical history
- Physical examination (results recorded in source documents only)
- Concomitant medication assessment
- Vital signs (blood pressure and pulse)
- Clinic FEV₁ (including calculation of FEV₁ percent predicted)
- FEV₁ reversibility assessment
- Blood draw
- Adverse event assessment (study participation related events only)

The blood samples will be taken on a single occasion unless a duplicate sample is required due to inability to utilize the original sample. It is required that the blood samples be taken at Visit 1, unless the patient does not meet the FEV₁ or reversibility requirement and plans to re-screen, in which case, the blood samples should be drawn during the re-screening visit.

Re-Screening: If a subject does not meet the Screening (Visit 1) inclusion criteria based upon FEV₁ percent predicted or reversibility, the subject may be rescheduled once within 1 week to conduct the Visit 1 PFTs again (see Section 5.2.1, Inclusion Criteria). The subject must wait at least 48 hours before returning to the site to repeat pulmonary function testing for FEV₁ percent predicted or reversibility and the conduct of other Visit 1 procedures.

If a subject is required to be re-screened for reasons other than failure to achieve criteria for FEV₁ percent predicted or reversibility, historical reversibility obtained at Visit 1 is acceptable to allow the subject to participate, if all other required inclusion and exclusion criteria are met.

If methacholine challenge testing is performed and a PC₂₀ of <8mg/ml is obtained within 2 weeks, adverse events reported and medication use must be recorded. If methacholine challenge testing is performed more than 2 weeks following Visit 1, then all other Visit 1 procedures should be performed on the date MCT is performed.

NOTE: A subject must meet **both** FEV₁ criteria (FEV₁ percent predicted and reversibility) on the same day.

6.2.2. Visit 2 (Open-Label Treatment Period 1 - Albuterol)

NOTE: No subject may experience more than one exacerbation between Visit 2 and Visit 6 and remain in the study. Any subject who experiences an exacerbation at or following Visit 6 must be discontinued from the study. See Section 6.4.5. Asthma Exacerbations.

Visit 2 will be conducted after the pharmacogenetic testing has been determined. This should not be greater than 4 weeks +2 days after Visit 1.

The following assessments/procedures will be performed at Visit 2:

- Adverse event assessment (study participation related events only)
- Concomitant medication assessment
- Urine pregnancy test for all females of childbearing potential
- Clinic FEV₁
- Assess continuation criterion
- Dispense peak flow meter
- Dispense diary card
- Dispense open-label study medication (albuterol)

6.2.3. Visit 3

Visit 3 will be conducted 4 weeks ±2 days after Visit 2.

The following assessments/procedures will be performed at Visit 3:

- Adverse event assessment
- Concomitant medication assessment
- Clinic FEV₁
- Assess continuation criteria
- Collect and review diary card
- Collect study medication
- Calculate PEF Stability Limit

- Dispense diary card
- Dispense open-label study medication (albuterol)

6.2.4. Visit 4 (Open-Label Treatment Period 2 - Ipratropium bromide)

Visit 4 will be conducted 4 weeks $\pm$ 2 days after Visit 3.

The following assessments/procedures will be performed at Visit 4:

- Adverse event assessment
- Concomitant medication assessment
- Urine pregnancy test for all females of childbearing potential
- Clinic FEV₁
- Assess continuation criteria
- Maximum albuterol dose assessment (MADR)
- Collect and review diary card
- Collect study medication
- Dispense diary card
- Dispense open-label study medication (ipratropium bromide & albuterol)

6.2.5. Visit 5

Visit 5 will be conducted 4 weeks $\pm$ 2 days after Visit 4.

The following assessments/procedures will be performed at Visit 5:

- Adverse event assessment
- Concomitant medication assessment
- Clinic FEV₁
- Assess continuation criteria
- Collect and review diary card
- Collect study medication
- Dispense diary card
- Dispense open-label study medication (ipratropium bromide & albuterol)

6.2.6. Visit 6 (Randomization Visit – Double Blind Period)

Visit 6 will be conducted 4 weeks $\pm$ 2 days after Visit 5.

The following assessments/procedures will be performed at Visit 6:

- Adverse event assessment
- Concomitant medication assessment
- Urine pregnancy test for all females of childbearing potential
- Clinic FEV₁
- Assess continuation criteria
- Maximum albuterol dose response (MADR)
- Collect and review diary card
- Collect study medication
- Dispense diary card
- Dispense rescue medication (ipratropium bromide & albuterol)
- Dispense double-blind study medication

6.2.7. Visit 7

Visit 7 will be conducted 4 weeks $\pm$ 2 days after Visit 6.

The following assessments/procedures will be performed at Visit 7:

- Adverse event assessment
- Concomitant medication assessment
- Clinic FEV₁
- Collect and review diary card
- Collect study medication
- Dispense diary card
- Dispense rescue medication (ipratropium bromide & albuterol)
- Dispense double-blind study medication

6.2.8. Visit 8

Visit 8 will be conducted 4 weeks ± 2 days after Visit 7.

The following assessments/procedures will be performed at Visit 8:

- Adverse event assessment
- Concomitant medication assessment
- Urine pregnancy test for all females of childbearing potential
- Clinic FEV₁
- Collect study medication
- Collect and review diary card
- Dispense rescue medication (ipratropium bromide & albuterol)
- Dispense double blind study medication
- Dispense diary card

6.2.9. Visit 9

Visit 9 will be conducted 4 weeks ± 2 days after Visit 8.

The following assessments/procedures will be performed at Visit 9:

- Adverse event assessment
- Concomitant medication assessment
- Clinic FEV₁
- Collect and review diary card
- Collect study medication
- Dispense diary card
- Dispense rescue medication (ipratropium bromide & albuterol)
- Dispense double-blind study medication

6.2.10. Visit 10

Visit 10 will be conducted 4 weeks ± 2 days after Visit 9.

The following assessments/procedures will be performed at Visit 10:

- Physical examination (results recorded in source documents only, unless there is a clinically significant change from baseline)
- Adverse event assessment

- Concomitant medication assessment
- Vital signs (blood pressure and pulse)
- Urine pregnancy test for all females of childbearing potential
- Maximum albuterol dose assessment (MADR)
- Clinic FEV₁
- Collect study medication
- Collect and review diary card
- Dispense rescue medication (ipratropium bromide & albuterol)
- Dispense diary card

6.2.11. Visit 11 (Washout Period)

Visit 11 will be conducted 2 weeks $\pm$ 2 days after Visit 10.

The following assessments/procedures will be performed at Visit 11:

- Adverse event assessment
- Concomitant medication assessment
- Urine pregnancy test for all females of childbearing potential
- Clinic FEV₁
- Collect study medication
- Collect and review diary card

At this visit, each subject will be provided with instructions on continued self-monitoring of pulmonary function, medications, and timely communication with a healthcare provider to help assure informed management of his/her asthma.

6.2.12. Premature Discontinuation Visit

The following assessments/procedures will be performed at a Premature Discontinuation visit that may occur during the open-label period(s), double-blind treatment period, or washout period:

- Physical examination (results recorded in source documents only, unless there is a clinically significant change from baseline)
- Adverse event assessment
- Concomitant medication assessment
- Vital signs (blood pressure and pulse)
- Urine pregnancy test for all females of childbearing potential
- Clinic FEV₁

- Collect and review diary card
- Collect study medication.

At this visit, each subject will be provided with instructions on continued self-monitoring of pulmonary function, medications, and timely communication with a healthcare provider to help assure informed management of his/her asthma. See Section 9.2.1 Subject Withdrawal from Study for further details related to medications prescribed, unfavourable changes noted during a physical examination, and adverse events or SAEs reported during the premature discontinuation visit.

6.3. Clinical Laboratory Tests

It is required that whole blood samples be taken at Visit 1, unless the patient does not meet the FEV₁ or reversibility requirement and plans to re-screen, in which case, the blood samples should be drawn during the re-screening visit. The blood samples will be collected using tubes containing EDTA. The samples will be labeled (or “coded”) with a study specific number that can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers such as name or social security number. The blood samples will be taken on a single occasion unless a duplicate sample is required due to inability to utilize the original sample.

Blood samples will be collected for:

- Genotyping of the *ADRB2* genotype needed to determine study eligibility
- Pharmacogenetic analysis (see Appendix 4, Pharmacogenetics)

6.4. Safety

Safety will be assessed by monitoring adverse events, and asthma exacerbations. In addition, physical examinations will be performed at Visit 1 and Visit 10 or Premature Discontinuation visit and results maintained in site source documents.

6.4.1. Medical History

A detailed medical history, including a review of systems, will be obtained from each subject during Visit 1. Each subject will be questioned regarding past medical history relevant to asthma. Information on the duration of the disease, smoking history, and history of pharmacotherapy will be collected. Medical history related to concurrent diseases, concurrent drug use, and drug/food allergies will also be obtained.

6.4.2. Physical examination

A physical examination will be conducted at Screening (Visit 1) and the last visit (Visit 10 or Premature Discontinuation) by the investigator, sub-investigator, nurse practitioner, or physician’s assistant listed on the FDA Form 1572. Physical examination results will be documented in the source documents only, unless there is a clinically significant change from baseline. As detailed in Section 10.4, Clinical Laboratory Abnormalities

and other Abnormal Assessments as AEs and SAEs, any clinically significant findings (change from baseline) would need to be captured as an AE/SAE.

6.4.3. Vital signs

Blood pressure (systolic and diastolic) and pulse will be determined with the subject in the sitting position. The subject must be seated at least 5 minutes before the measurements are taken. Blood pressure and pulse will be taken at Visit 1 and Visit 10 (or Premature Discontinuation) prior to any pulmonary function testing.

To ensure subject safety during Maximum Albuterol Dose Response (MADR) testing, vital signs will be taken before MADR is performed, and at least once after each dose of albuterol is administered. If, in the opinion of the investigator, significant hypertension, tachycardia, arrhythmia or other side effects of albuterol occur, MADR testing should be stopped and appropriate medical measures should be taken. MADR testing is performed at Visits 4, 6 and 10.

Vital signs will be documented in the source documents only, unless there is a clinically significant change from baseline. As detailed in Section 10.4, Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs and SAEs, any clinically significant findings (change from baseline) would need to be captured as an AE/SAE.

6.4.4. Clinical adverse events

Each subject will be instructed to record on the diary card, any medical problems experienced, and any medications used to treat the medical problem during the trial. Site personnel will review and resolve discrepancies at each clinic visit and record adverse events in the adverse events section of the CRF. Subjects will also be questioned about the occurrence of adverse events by site personnel (see Section 10.5, Time Period, Frequent and Method of Detecting AEs and SAEs). Only adverse event data recorded in the CRF will be used in the final analysis of safety.

6.4.5. Asthma exacerbations

A clinical exacerbation is defined as worsening asthma requiring emergency intervention, hospitalization, or treatment with asthma medication in addition to those allowed by the protocol. If a subject is withdrawn for a clinical exacerbation based upon the above definition, the reason for withdrawal noted in the CRF should be recorded as "Exacerbation".

Subjects who experience an exacerbation during the screening period between Visit 1 and Visit 2 must be discontinued.

For the purposes of this study, a subject may experience one exacerbation during the 16 week combined open-label period that is successfully treated within 10 days and remain in the study, predicated on consultation with GSK. If a subject experiences more than one exacerbation during the open-label treatment periods the subject must be discontinued.

A subject will be withdrawn due to worsening asthma if he/she experiences an exacerbation during the double-blind treatment period or the washout period. In addition, the investigator may discontinue a subject at any time, if the investigator believes that the subject is at risk by remaining in the study.

For subjects who enter the screening period between Visit 1 and Visit 2 and experience an exacerbation, worsening asthma data will be recorded only in the source documents. For all subjects who are in the open-label, double-blind, and washout treatment periods, asthma exacerbation data will be recorded in the source documents and the Asthma Exacerbation section of the CRF.

If an exacerbation meets the definition of a SAE (Section 10.2, Definition of a SAE), worsening asthma data must be collected as a SAE for all subjects who sign an informed consent and participate in this study.

6.4.6. Pregnancy

6.4.6.1. Pregnancy testing

Urine pregnancy testing will be performed on all females of childbearing potential at Visit 2, 4, 6, 8, 10 and the last clinic visit (Visit 11 or Premature Discontinuation Visit).

6.4.6.2. Time period for collecting pregnancy information

The time period for collecting pregnancy information is from Visit 2 through study completion (Visit 11 or Premature Discontinuation Visit).

6.4.6.3. Action to be taken if pregnancy occurs

The investigator, or his/her designee, will collect pregnancy information on any female subject 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.

Subjects that become pregnant will be withdrawn from the study.

6.5. Efficacy

6.5.1. Assessment of Pulmonary Function

6.5.1.1. PEF

Peak expiratory flow (PEF) measurements will be collected via a study-issued Peak Flow Meter. The subject will be instructed on proper use of the peak flow meter and on recording the results on the diary card.

Each subject will be instructed to perform triplicate PEF measurements in the morning and evening of each day during the study. The morning determinations should be performed prior to the subject taking the morning dose of study medication or rescue medication. The evening measurements should be performed after recording the asthma symptom scores and prior to the subject taking the evening dose of study medication or rescue medication. The **highest** of the 3 values of morning and evening PEF must be recorded on the subject diary card.

AM PEF Stability Limits

For those who qualify for the study, an AM PEF Stability Limit will be calculated at Visit 3 as follows:

- The AM PEF Stability Limit will be calculated using the mean morning PEF from the 7 consecutive days preceding Visit 3, using the morning PEF from the day **prior** to Visit 3 as day 7. The AM PEF Stability Limit will be defined as 80% of the mean morning PEF and used for the duration of the study.

The subject will be counselled on the usefulness of the peak flow meter as a means of monitoring his/her asthma status. Subjects will be informed of their AM PEF Stability Limit and educated to be alert to a pattern of **consistently decreasing PEF** as a warning of possible worsening of asthma/asthma exacerbation. Subjects will be instructed to call the investigator if such a profile of declining PEF is observed, or if their PEF falls below the AM PEF Stability Limit for 2 or more consecutive days. If such a pattern is observed, it is not a protocol-defined exacerbation unless it meets the definition in Section 6.4.5., Asthma Exacerbations.

6.5.1.2. Clinic FEV₁

FEV₁ will be performed on all subjects using the site's spirometer. The equipment must meet or exceed the minimal performance recommendations of the ATS.

Spirometry equipment used to perform FEV₁ will be calibrated according to the manufacturer's recommendation on a frequent and regular schedule, but not less than once per week. The calibration results will be recorded on a PFT calibration log, which will be monitored during site visits.

For each time observation, triplicate measurements will be performed with the subject in one position (i.e. sitting or standing) for all his/her PFT determinations. For the FEV₁, the "best effort" is defined as the effort (or each triplicate set) with the highest value. This result will be entered into the CRF.

It is the responsibility of the investigator (or designee), to print a hard copy of each measurement and review the results to ensure that the subject meets all inclusion criteria, continuation criteria, and randomization criteria. The hard copy of each measurement will be maintained in the subject's study file.

The FEV₁ should be performed between 6:00 – 11:00 AM on clinic visits (see [Appendix 1](#), Time and Events Table for visits where FEV₁ is performed). In addition, FEV₁ should be performed:

- ≥ 6 hours after use of albuterol
- ≥ 6 hours after use of ipratropium bromide
- ≥ 6 hours after caffeine consumption
- ≥ 2 hours after exercise (or strenuous activity)
- ≥ 15 minutes after prolonged exposure to cold air
- Prior to the administration of the morning dose of double-blind study medication.

NOTE: If all these criteria are not met prior to testing, the visit should be scheduled for another day within the ± 2 day window. A visit may only be rescheduled once.

Prior to Visit 1, asthma medications must not be used for the required interval indicated in Section [5.2.2](#) Exclusion Criteria.

Calculation of FEV₁ percent predicted

Each subject must demonstrate an FEV₁ value ≥ 70-100% of normal predicted at Visit 1. The FEV₁ percent predicted is calculated using the best effort clinic FEV₁ as follows:

$$\% \text{ Predicted} = \frac{\text{FEV}_1 (\text{Highest})}{\text{FEV}_1 (\text{Predicted})} \times 100$$

FEV₁ percent predicted is based on the **National Health and Nutrition Examination Survey (NHANES III) predicted normal values for ages 8 years and older** [[Hankinson, 1999](#)].

Reversibility assessment

Documentation of historical reversibility within one year of Visit 1 demonstrating an increase in FEV₁ of ≥12% and 200ml over baseline is acceptable and will preclude the requirement for reversibility testing the Visit 1.

If documentation of historical reversibility within one year of Visit 1 is not available, the subject must demonstrate a ≥ 12% improvement in FEV₁ in order to qualify for participation in the study.

Upon confirming at Visit 1 that no asthma medications have been used for the required intervals specified in Section 5.2.2.Exclusion Criteria, pulmonary reversibility will be assessed after the subject self-administers 2-4 inhalations or 1-2 nebulized inhalation of albuterol (2 puffs = 1 nebule). The FEV₁ will then be repeated, in triplicate, within 30 minutes. Reversibility should be calculated as follows:

$$\% \text{ Reversibility} = \frac{\text{FEV}_1 \text{ after albuterol MDI} - \text{FEV}_1 \text{ before albuterol MDI}}{\text{FEV}_1 \text{ before albuterol}} \times 100$$

Reversibility documentation will be maintained in the CRF.

6.5.1.3. Methacholine Challenge Tests

The subject may undergo methacholine challenge testing (MCT) once if the second attempt to document reversibility is unsuccessful. A PC₂₀ result of <8mg/ml obtained at an unscheduled visit prior to Visit 2 is required. An historical PC₂₀ value of <8mg/ml that has been documented at the investigative site within the past 12 months and was obtained using ATS or ACRN guidelines for MCT is also acceptable [[American Thoracic Society, 2000](#); [ACRN, 2002](#)]. Methacholine challenge testing should be performed only at sites with past experience performing this test. The testing should be performed between 6 AM and 11 AM. All females of childbearing potential must have a negative urine pregnancy test prior to initiation of the methacholine challenge. Any female with a positive pregnancy test will be excluded from study participation.

See Appendix 14.5. Methacholine Challenge Dilution schedule: Also refer to the Manual of Procedures that is provided to each investigator if a methacholine challenge test is performed during the conduct of this study.

6.5.1.4. Maximum Albuterol Dose Assessment (MADR)

The bronchodilator response to albuterol has been found to vary by genotype at the B16 locus, and the maximum bronchodilator effect of albuterol may become attenuated during prolonged use (tachyphylaxis) [[Martinez, 1997](#); [Tan, 1997](#)]. It is therefore appropriate to take measurements of the maximum albuterol dose response (**MADR**) in order to

determine whether its magnitude varies by 2-adrenergic receptor genotype during prolonged albuterol use. Maximum albuterol dose response (MADR) will be defined as the best FEV₁ recorded after four, six, or eight puffs of albuterol.

To obtain the MADR, each subject will perform baseline spirometry and will then be administered four puffs of albuterol. Fifteen minutes following the administration of the albuterol, the subject will again perform spirometry, followed by two additional puffs of albuterol, for a cumulative dose of six puffs. After fifteen minutes, spirometry will be repeated once more, and the current FEV₁ value compared with the FEV₁ obtained after the first four puffs. If the relative change in FEV₁ is 5% or less, the procedure will be stopped; if the relative change is more than 5%, then two additional puffs of albuterol will be administered, for a cumulative dose of eight puffs, followed by a final spirometry assessment 15 minutes later.

During the MADR testing albuterol should be administered using a metered-dose inhaler. The use of spacers and nebulers is not permitted.

To ensure subject safety during MADR testing, vital signs will be taken before MADR is performed, and at least once after each dose of albuterol is administered. If, in the opinion of the investigator, significant hypertension, tachycardia, arrhythmia or other side effects of albuterol occur, MADR testing should be stopped and appropriate medical measures should be taken.

6.5.1.5. Continuation Assessment

Subjects will be required to meet the following criterion at Visit 2 to continue in the study:

A best FEV₁ $\geq$ 70% of predicted.

Subjects will be required to meet the following criteria at Visits 3, 4, 5 and 6 to continue in the study:

A best FEV₁ $\geq$ 70% of predicted **and** $<$ 56 puffs per week of medication.

6.5.2. Diary Card Data

6.5.2.1. Albuterol open-label diary card

Subjects will be instructed to record on daily diary cards:

- Morning and evening peak flow measurements
- Total daily albuterol use
- Total daily asthma symptom scores
- Any medical problems the subject may have experienced (all AEs/SAEs will be transcribed into the CRF)
- Any medications taken (other than albuterol)

6.5.2.2. Ipratropium bromide open-label diary card

Subjects will be instructed to record on daily diary cards:

- Morning and evening peak flow measurements
- Total daily ipratropium bromide use
- Total daily supplemental albuterol use (in the event that asthma symptoms respond incompletely to ipratropium bromide)
- Total daily asthma symptom scores
- Any medical problems the subject may have experienced (all AEs/SAEs will be transcribed into the CRF)
- Any medications taken (other than ipratropium bromide or albuterol)

6.5.2.3. Double-blind treatment diary card

Subjects will be instructed to record on daily diary cards:

- Morning and evening peak flow measurements
- Total daily supplemental ipratropium bromide use
- Total daily supplemental albuterol use (in the event that asthma symptoms respond incompletely to ipratropium bromide)
- Total daily asthma symptom scores
- Any medical problems the subject may have experienced (all AEs/SAEs will be transcribed into the CRF)
- Any medications taken (other than study medication)

Subjects will be instructed to return completed diary cards at each clinic visit.

NOTE: Diary cards **must** be reviewed by site personnel while the subject is in the clinic and any discrepancies and/or missing data will be reviewed with the subject and resolved, if possible.

6.5.2.4. Subject recorded symptom scores

Throughout the entire study, each subject will be instructed to record an asthma symptom score **prior** to performing the evening peak flow measurement and taking the PM dose of blinded study medication or rescue medication. Subjects will be instructed to select a rating from the following list that best describes any asthma-related symptoms such as wheeze, shortness of breath or chest tightness experienced during the day and previous night (preceding 24 hours):

0 = No symptoms during the day or previous night

1 = Symptoms for one short period during the day or previous night

2 = Symptoms for two or more short periods during the day or previous night

3 = Symptoms for most of the day or previous night that did not affect my normal daily activities

4 = Symptoms for most of the day or previous night that did affect my normal daily activities

5 = Symptoms so severe that I could not go to school or perform normal daily activities.

The study coordinator must review the diaries at each clinic visit for completeness, legibility, and consistency with patient-reported adverse events. Signs and symptoms of asthma (chest tightness, shortness of breath, wheeze) noted by the subject on the diary pages will not be considered adverse events and will not be recorded in the case report form.

6.5.2.5. Albuterol use in the open-label, double-blind treatment and washout period

All use of open-label treatment with albuterol will be recorded by the subject or parent/caregiver on the diary card.

Subjects will receive open-label albuterol 90mcg for prn use to treat acute asthma symptoms during the first open-label treatment period.

During the second open-label period, in the event that asthma symptoms respond incompletely to ipratropium bromide, albuterol will be used as a superceding treatment medication. It will also be use as a superceding relief medication during the randomization and washout periods. The subject will be reminded that for subsequent acute asthma symptoms they should continue to take ipratropium bromide first, as medication for acute relief during the second open-label period and during the randomization and washout periods.

Subjects will be reminded that if their requirement for albuterol during the first open-label period or supplemental medication during the second open-label period and/or during the double-blind and washout periods increases markedly or if their requirement equals or exceeds a total of 12 puffs per day (daytime and nighttime combined) for 2 out of 7 consecutive days they should contact the study site.

6.5.2.6. Ipratropium bromide use in the open-label, double-blind treatment and washout periods

All use of open-label ipratropium bromide will be recorded by the subject or parent/caregiver on the diary card.

Subjects will receive open-label Atrovent (ipratropium bromide) 18mcg to be used as needed to treat acute asthma symptoms for 8 weeks during the second open-label period prior to randomization.

Subjects will also receive open-label Atrovent (ipratropium bromide) 18mcg to be used as need to relieve acute asthma symptoms for 16 weeks during the double-blind treatment period. In addition, subjects will receive open-label albuterol 90mcg for prn use in the event that asthma symptoms respond incompletely to ipratropium bromide during the second open-label period and during the randomization and washout periods, in which case albuterol will be used as a superceding medication.

Subjects will be reminded that if their requirement for Atrovent (ipratropium bromide) during the second open-label period or during the double-blind and washout periods increases markedly or if their requirement equals or exceeds a total of 12 puffs per day (daytime and nighttime combined) for 2 out of 7 consecutive days they should contact the study site.

7. INVESTIGATIONAL PRODUCT(S)

7.1. Description of Investigational Product

Albuterol (90mcg), SM **DISKUS** (50mcg) and FSC **DISKUS** (100/50mcg) will be manufactured by GlaxoSmithKline.

Ipratropium bromide (18mcg) will be manufactured by Boehringer Ingelheim.

The two possible double-blind treatments are:

- FSC **DISKUS** 100/50mcg twice daily
- SM **DISKUS** 50mcg twice daily

7.2. Dosage and Administration

At Visit 2, eligible subjects will be given open-label albuterol 90mcg for use as needed to relieve asthma symptoms for 8 weeks (56 days $\pm$ 2 days). After this 8-week treatment period, at Visit 4, subjects will be given open-label ipratropium bromide 18mcg for use as needed to relieve asthma symptoms for 8 weeks (56 days $\pm$ 2 days). Subjects will also receive open-label albuterol 90mcg for prn use in the event that asthma symptoms respond incompletely to ipratropium, in which case albuterol would be used as a superceding medication.

At Visit 6, subjects will be assigned a double-blind treatment for 16 weeks (112 days $\pm$ 2 days). Each subject will receive a supply of study medication via the **DISKUS** for one of two possible treatment groups. Double-blind medication will be dispensed according to the [Appendix 1](#), Time and Events Table.

Subjects will inhale the first dose of double-blind study medication in the clinic on the day of randomization (Visit 6). Subjects will receive a **DISKUS** inhaler. The subject will be instructed to administer one inhalation from the inhaler each morning and one inhalation from the inhaler each evening, approximately 12 hours apart, after obtaining

their morning and evening PEF measurements. Each subject should be advised to adhere to this dosing regimen throughout the study.

All eligible subjects will be given open-label ipratropium bromide 18mcg for use only as needed throughout the double-blind period of the trial. Subjects will also receive open-label albuterol 90mcg for prn use in the event that asthma symptoms respond incompletely to ipratropium bromide, in which case albuterol would be used as a superceding medication for acute relief.

All subjects who complete Visit 10 of the double-blind treatment period will be given open-label ipratropium bromide 18mcg for use during the washout period. Subjects will also receive open-label albuterol 90mcg for prn use in the event that asthma symptoms respond incompletely to ipratropium bromide, in which case albuterol would be used as a superceding medication for acute relief.

7.3. Dose Rationale

Doses of blinded study medication were selected for the following reasons.

The 100/50mcg strength of FSC **DISKUS** is approved in the US for the maintenance treatment of asthma in adults and adolescents at least 12 years of age and will provide subjects with the lowest approved daily dose of FSC and SM. SM 50mcg BID via the **DISKUS** inhaler is approved in the US for the maintenance treatment of asthma in adults and children 4 years of age and older.

7.4. Blinding

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.

This study will utilize an interactive voice response system (IVRS) for the emergency unblinding.

7.5. Treatment Assignment

7.5.1. Assignment of Subject Number

At Visit 1, a unique Subject Number will be assigned to any subject who has at least one Visit 1 procedure performed, other than informed consent. This Subject Number will be used to identify individual subjects during the course of the study. If the subject repeats Visit 1 for any reason, the original subject number assigned is retained.

7.5.2. Assignment of Randomization Number

Subjects who are eligible to participate in the double-blind phase of the trial will be randomized to a treatment group through a telephone call to the designated IVRS system. During this call, the IVRS will confirm the subject's CRF number (Subject Number) and provide two additional numbers:

- A medication pack number that will identify the **DISKUS** of double-blind medication that should be dispensed to the subject from the Investigator's inventory.
- A randomization number (Treatment Number) which is an identification number that will be assigned from a randomization schedule created by GlaxoSmithKline.

For subsequent visits when study medication is to be dispensed (see [Appendix 1](#), Time and Events Table), a telephone call must be made to the IVRS for the next medication pack number to be assigned from the investigator's inventory.

Although study medication is stored at each site, the investigator, or designee, must telephone into the IVRS to obtain study medication assignments. All calls to the IVRS are confirmed with faxes that are sent to the investigator upon completion of each call. Detailed IVRS use instructions and worksheets will be provided at study start.

7.5.3. Assignment of Study Drug

Subjects will be assigned to study treatment in accordance with the randomization schedule. This study will utilize an IVRS, which will provide a means for systematic central allocation of drug (SCAD). Each investigator will be supplied with sufficient supplies to conduct the trial. Additional double-blind medication packs will be supplied as needed to the sites.

7.6. Packaging and Labelling

The contents of the label will be in accordance with all applicable regulatory requirements.

7.7. 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.

7.8. 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.

7.9. Assessment of Compliance

At each visit during open-label treatment, study site personnel are to assess subject compliance with study drug by assessing subjects' diary card. At each visit during double-blind treatment, study site personnel are to assess subject compliance with study drug by assessing the subjects' diary card and by the number of doses remaining in the **DISKUS** device per the counter contained within the device. The number of doses remaining will be recorded in the subjects' source documents and in the CRF whenever a new **DISKUS** device is dispensed (see [Appendix 1](#), Time and Events Table).

7.10. Treatment of Investigational Product Overdose

An overdose is defined as a dose greater than the total doses described above which results in clinical signs and symptoms. In the event of an overdose of study medication, the investigator should use clinical judgement in treating the overdose and contact the study medical monitor.

GlaxoSmithKline (GSK) is not recommending specific treatment guidelines for overdose and toxicity management. The investigator is advised to refer to the relevant document(s) for detailed information regarding warnings, precautions, contraindications, adverse events, and other significant data pertaining to the study drug(s) being used in this study. Such documents may include, but not be limited to, the Clinical Investigator's Brochure (CIB) or equivalent document provided by GSK, the approved product label (if applicable), or both. Clinical judgement should be used in treating the overdose.

7.11. Occupational Safety

Investigational product is not expected to pose significant occupational safety risk to site staff under normal conditions of use and administration. However, precautions are to be taken to avoid direct skin contact, eye contact, and generating aerosols or mists. In the case of unintentional occupational exposure, treat as if the substance contains the active pharmaceutical even though it is absent from placebo formulations, and notify the monitor. 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

Short acting beta₂-agonist medication(s) and any other anti-asthma medications taken 4 weeks prior to Visit 1 will be recorded in the CRF. All concomitant medications and any anti-asthma medications other than study medications taken during the study will be recorded in the CRF.

8.2. Prohibited Medications

Concurrent use of any of the following medications that may affect the course of asthma or interact with sympathomimetic amines will not be allowed. Specifically:

- beta blockers
- polycyclic antidepressants
- monoamine oxidase inhibitors
- phenobarbital
- rifampin
- methotrexate, gold, cyclosporine and azathioprine
- ritonavir

Also see Section 5.2.2. Exclusion Criteria for anti-asthma medications that must not be taken during the conduct of this study. Exception: a short course of an oral corticosteroid is allowed for the treatment of an exacerbation during the open-label period.

8.3. Medical Devices

Diary PEF will be measured by the subject using a peak flow meter in accordance with specific instructions explained by the study staff. The subject should demonstrate correct use of the peak flow meter at Visit 2.

9. SUBJECT COMPLETION AND WITHDRAWAL

9.1. Subject Completion

A subject who completes the 16-week double-blind treatment period and undergoes all Visit 11 evaluations has completed the study. At the conclusion of Visit 11, each subject will be provided with instructions on continued self-monitoring of pulmonary function, medications, and timely communication with a healthcare provider to help assure informed management of his/her asthma.

NOTE: Medications (asthma **and** non-asthma) that are prescribed at the last clinic visit will only be recorded in the subject's source documents and **not** recorded on the subject's CRF unless the medication is administered prior to the completion of all study procedures at the last clinic visit.

Any clinically significant adverse events or clinically significant unfavorable changes on physical examination observed during Visit 11 (Completion Visit) will necessitate that the subject be followed or treated until satisfactory resolution occurs.

9.2. Subject Withdrawal

9.2.1. Subject Withdrawal from Study

Screening period

Subject withdrawal from the screening period (Visit 1 to Visit 2) of the study is required, when:

- A subject is significantly non-compliant with the requirements of the protocol
- A subject becomes pregnant
- A subject has an adverse event that would, in the investigator's judgement, make continued participation in the study an unacceptable risk
- The subject experiences an asthma exacerbation as defined by the protocol (see Section 6.4.5 Asthma exacerbations)
- The number subjects per genotype required for each treatment group is met.
- GlaxoSmithKline discontinues the study.

Open-label period

A subject who takes open-label study drug, but either does not complete the 16 week open-label treatment period or does not complete Visit 6 evaluations will be considered **prematurely discontinued**.

Subject withdrawal from the open-label period of the study is required, and discontinuation procedures are performed, when:

- A subject is significantly non-compliant with the requirements of the protocol
- A subject becomes pregnant
- A subject has an adverse event that would, in the investigator's judgement, make continued participation in the study an unacceptable risk
- The subject experiences more than one asthma exacerbation as defined by the protocol (see Section 6.4.5 Asthma exacerbations)
- The number of subjects per genotype required for each treatment group is met.
- GlaxoSmithKline discontinues the study.

Double-blind Period

A subject who takes double-blinded study drug, but either does not complete the 16 week treatment period or does not complete Visit 10 evaluations will be considered **prematurely discontinued**. Prematurely discontinued subjects, who have been correctly randomized according to the Inclusion/Exclusion criteria, will not be replaced.

Subject withdrawal from the study is required, and Discontinuation Visit procedures are performed, when:

- A subject is significantly non-compliant with the requirements of the protocol
- A subject becomes pregnant
- A subject has an adverse event that would, in the investigator's judgement, make continued participation in the study an unacceptable risk
- The treatment blind is broken for a subject
- The subject experiences an asthma exacerbation as defined by the protocol (see Section 6.4.5 Asthma exacerbations)
- GlaxoSmithKline discontinues the study.

Washout Period

A subject who takes study drug during the washout period, but either does not complete the 2 week treatment period or does not complete Visit 11 evaluations will be considered **prematurely discontinued**.

Subject withdrawal from the study is required, and Discontinuation Visit procedures are performed, when:

- A subject is significantly non-compliant with the requirements of the protocol
- A subject becomes pregnant

- A subject has an adverse event that would, in the investigator's judgement, make continued participation in the study an unacceptable risk
- The treatment blind is broken for a subject
- The subject experiences an asthma exacerbation as defined by the protocol (see Section 6.4.5 Asthma exacerbations)
- GlaxoSmithKline discontinues the study.

A subject may voluntarily discontinue participation in this study at any time. The investigator may also, at his/her discretion; discontinue the subject from participating in this study at any time. If a subject is prematurely discontinued from participation in the study for any reason, the investigator must make every effort to perform all evaluations specified for the Discontinuation Visit. (See Section 6.2.12 Premature Discontinuation Visit for discontinuation procedures.) At the conclusion of the Discontinuation Visit, each subject will be provided with instructions on continued self-monitoring of pulmonary function, medications, and timely communication with a healthcare provider to help assure informed management of his/her asthma.

NOTE: Medications (asthma **and** non-asthma) that are prescribed at the last clinic visit will only be recorded in the subject's source documents and **not** recorded on the subject's CRF **unless** the medication is administered prior to the completion of all study procedures at the last clinic visit.

Any clinically significant adverse events or clinically significant unfavorable changes on physical examination observed during the discontinuation visit will necessitate that the subject be followed or treated until satisfactory resolution occurs.

In the event that a subject is prematurely discontinued from the study at any time due to an AE as defined in Section 10.1. Definition of an AE, or SAE as defined in Section 10.2. Definition of a SAE, a Discontinuation Visit must be performed.

9.2.2. Subject Withdrawal from Investigational Product

If study drug is permanently discontinued during the course of the study, the subject must be withdrawn from the study. The investigator should make every effort to perform the evaluations specified for the Discontinuation Visit. Subjects who are discontinued from the study due to premature discontinuation of study drug will not be replaced.

9.3. Screen and Open-label Failures

A subject who has at least one study procedure performed (in addition to signing a consent form), and is assigned a subject number (see Section 7.5.1 Assignment of Study Number), but does not participate in the open-label period(s) is classified as having **failed screening (Visit 1)**. The following information will be collected in the CRF on subjects who fail at the Screening Visit (Visit 1) or any time prior to Visit 2. The following information will also be collected in the CRF on subjects who fail at Visit 2 or any time during the open-label periods prior to Visit 6:

- Demographic information (including race, age and gender)
- Inclusion/exclusion criteria
- Duration of asthma
- Asthma concomitant medications
- Non-asthma concomitant medications
- Reversibility assessment
- Pulmonary function tests (including MADR, if applicable)
- Continuation criteria, if applicable
- Reason subject was a screening or open-label failure
- Pharmacogenetic (PGx) information
- Investigational product information
- Asthma exacerbation data
- Any adverse events/SAEs that occur during the screening and open-label periods
- Investigator comments
- Investigator signature
- Diary cards, if applicable.

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.

10.1. Definition of an AE

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. 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).

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-patient 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., vital signs, physical examination) 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

Study participation SAE's will be collected from the time informed consent is obtained to Visit 2. AEs/SAEs will be collected from Visit 2 through the last visit (Visit 11/or Discontinuation Visit). After the subject has had an opportunity to spontaneously mention any problems, the investigator should inquire about AEs by asking the following standard questions:

1. "Have you had any (other) medical problems since your last visit/assessment?"
2. "Have you taken any new medicines, other than those given to you in this study, since your last visit/assessment?"
3. "How do you feel after taking each dose of study medication?"

Diary cards will be reviewed at each visit and if the subject does not mention an event that is recorded, he/she should be questioned for further information in order to determine if there was some occurrence of an adverse event. If an AE is unresolved at the time of the last visit (Visit 11/or Discontinuation Visit), refer to Section 10.8. Follow-Up of AEs and SAEs for follow-up requirements.

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, Prompt Reporting of SAEs to GSK.

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.

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).

This protocol has been filed under an Investigational New Drug (IND) application with the US Food and Drug Administration (FDA). A given SAE may qualify as an IND Safety Report if the SAE is both attributable to the investigational product and unexpected. In this case, all investigators filed to the IND (and associated INDs for the same compound) will receive an Expedited Investigator Safety Report (EISR), identical in content to the IND Safety Report submitted to the FDA.

EISRs 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.

When a site receives from GSK an Initial or Follow-up EISR or other safety information e.g., revised Clinical Investigator's Brochure/Investigator's Brochure, the responsible person according to local requirements is required to promptly notify his or her IRB or IEC.

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. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

For the purposes of this study, an evaluable subject will be defined as one for whom the primary efficacy measure can be calculated. Since the primary efficacy measure is a function of morning PEF recorded after randomization to study drug, an evaluable subject is defined as one who completes at least 2 weeks of double-blind treatment, as documented in the patient diary card.

11.1. Hypotheses

The primary hypotheses associated with the comparison of the Arg/Arg and Gly/Gly genotypes in the FSC treatment group with respect to AM PEF AUC(bl) are

$$H_0: \text{AUC(bl)}_{\text{Arg/Arg}} - \text{AUC(bl)}_{\text{Gly/Gly}} < \Delta \text{ versus}$$

$$H_A: \text{AUC(bl)}_{\text{Arg/Arg}} - \text{AUC(bl)}_{\text{Gly/Gly}} \geq \Delta$$

where $\text{AUC(bl)}_{\text{Arg/Arg}}$ and $\text{AUC(bl)}_{\text{Gly/Gly}}$ are the estimated areas under the curve describing morning PEF by time for the Arg/Arg and Gly/Gly genotypes, respectively, and where Δ is the acceptable difference for equivalence, 30L/min. Rejection of H_A implies that the treatment response with respect to AM PEF AUC(bl) is at least as great in the Arg/Arg genotype as that of the Gly/Gly genotype.

11.2. Comparisons of Interest

The primary comparisons of interest in this study are between particular genotypes within a given treatment group.

11.2.1. Primary Comparisons of Interest

The primary comparison of interest will be between the Arg/Arg and Gly/Gly genotypes in the FSC 100/50mcg BID treatment group, and will be assessed in terms of AM PEF AUC(bl).

11.2.2. Other Comparisons of Interest

Other comparisons of interest, assessed in terms of AM PEF AUC(bl), will include the following:

- The Arg/Arg and Gly/Gly genotypes in the SM 100/50 BID treatment group;
- The Arg/Arg and Arg/Gly genotypes in the FSC 100/50 BID treatment group;
- The Arg/Arg and Arg/Gly genotypes in the SM 50mcg BID treatment group;
- The Gly/Gly and Arg/Gly genotypes in the FSC BID treatment group;
- The Gly/Gly and Arg/Gly genotypes in the SM 50mcg BID treatment group;
- In addition, there is clinical interest in the comparison of lung function as demonstrated at the end of each open-label period. This comparison will be made within each genotype separately as outlined below:
- The *prn* albuterol open-label period vs the *prn* ipratropium bromide open-label period in the Arg/Arg genotype;
- The *prn* albuterol open-label period vs the *prn* ipratropium bromide open-label period in the Gly/Gly genotype;
- The *prn* albuterol open-label period vs the *prn* ipratropium bromide open-label period in the Arg/Gly genotype.

In order to demonstrate assay sensitivity, comparisons of the change from the screening FEV₁ to the endpoint FEV₁ will be made for each pair of genotypes within each treatment group. Also, to address concerns regarding possible selection bias in the two prevalent genotypes, Gly/Gly and Arg/Gly, population demographic characteristics and lung function will be summarized within each of these genotypes, for screening failures, open-label period failures, and subjects who are randomized.

11.3. Interim Analysis

No interim analyses are planned.

11.4. Sample Size Considerations

It is anticipated that 540 subjects will be enrolled at approximately 60-80 investigational sites to achieve an analysis population of approximately 492 evaluable subjects (82 evaluable subjects per treatment arm per genotype). A 10% drop-out rate is assumed after randomization based on the fact that the asthmatic population is stable and mild. Assuming that 15% of the general population has the Arg/Arg genotype, it is anticipated that in order to recruit 90 subjects in each of the genotypic categories, a minimum of 1,200 subjects will need to be screened. Allowing for exclusions, refusals to participate and withdrawals, approximately 1840 subjects may need to be screened.

11.4.1. Sample Size Assumptions

It is estimated that the standard deviation of AM PEF AUC(bl) over the course of the treatment period in subjects randomised to the FSC group will be 50 L/min. It is hypothesized that the upper bound of the confidence interval around the difference between treatment response in Arg/Arg subjects and in Gly/Gly subjects will be no greater than 28.5 L/min. These estimates, in conjunction with a two-sided t-test and a significance level of $\alpha=0.05$, indicate that a sample size of at least 82 evaluable patients per genotype per treatment group will afford 90% power to show non-inferiority of the Arg/Arg genotype to the Gly/Gly genotype within the FSC group in terms of AM PEF AUC(bl).

11.4.2. Sample Size Sensitivity

The power calculation is partly a function of the standard deviation and difference between the groups being compared. Thus, any deviations from the estimates used in the power calculation could affect the power of the study to detect meaningful differences between genotypes.

Given the sample size of 82 subjects per genotype per treatment group, and assuming that the estimated standard deviation of 50 L/min remains constant, and that the difference between the means of two genotypes with respect to AM PEF AUC(bl) lies between 1 and 10L/min, then the lower bound of the confidence interval around the difference between treatment response in genotypes will range from -25 to -28L/min.

Conversely, given the sample size of 82 subjects per genotype per treatment group and assuming that the difference between the two genotypes with respect to AM PEF AUC(bl) is zero, if the sample standard deviation lies between 40 and 75L/min, then the lower bound of the confidence interval around the difference between treatment response in genotypes will range from -42 to -23L/min.

11.4.3. Sample Size Re-estimation

There are no plans to re-estimate the required sample size during the conduct of this study.

11.5. Analysis Populations

The Intent-to-Treat population, defined as all subjects who are assigned to randomized study drug, is the only population defined in this study.

11.5.1. Data Sets

Since all analyses will be based on the Intent-to-Treat population, no special datasets will be created for this study.

11.6. General Considerations for Data Analysis

Statistical significance will be assessed at the $\alpha=0.05$ level for all primary and secondary measurements, subject to the multiplicity adjustment rules outlined in Section [11.6.5](#)
Other Issues: Multiplicity.

11.6.1. Withdrawal

Should any subjects withdraw prematurely from the study, all data up to the time of withdrawal will be included in the analyses.

11.6.2. Missing Data

No interpolation of missing data will be done. All available data for a given subject will be used in the analysis, regardless of whether or not the subject discontinued prematurely from the study.

11.6.3. Derived and Transformed Data

Diary data for the baseline, treatment period, and changes from baseline will be reported in terms of means. Baseline for analyses of diary data will be defined as the arithmetic average of the data on the diary during the 6 days prior to randomization and on Treatment Day 1. Endpoint for a given subject will be calculated as the average of the appropriate values recorded on the diary during the last seven days of the subject's treatment period. Endpoint will be calculated for those efficacy measures which are to be analyzed in terms of change from baseline (i.e., the proportion of symptom-free days, and rescue ipatropium bromide and albuterol use) as the average of the data available during the last seven days the subject was in the double-blind treatment period.

Comparisons of treatment response during the two open-label periods will be based on the averages of the last seven days' worth of available data in each open-label period.

AM and PM PEF and FEV₁ will be analyzed in terms of the area underneath the response-by-time curve, relative to baseline [AUC(bl)]. AUC(bl) will be calculated as the area described by the peak flow – by – time curve, with the area of the curve corresponding to the baseline value subtracted from the final quantity.

Maximum albuterol dose response (MADR) will be defined as the best FEV₁ recorded after four, six, or eight puffs of albuterol.

11.6.4. Assessment Windows

No data will be omitted from analyses based on their collection relative to protocol-defined assessment windows.

11.6.5. Other Issues

Deviations from analyses

Any deviation(s) from the analysis as outlined in the protocol will be documented both in the analysis plan and in the final clinical study report.

Premature discontinuation of study

There are no contingency plans for the premature discontinuation of this study.

General hypothesis testing issues

All hypothesis tests will be two-tailed. Statistical significance will be assessed at the $\alpha=0.05$ level, or equivalently, with a 95% confidence interval. All tests of primary and secondary efficacy measures in terms of change from baseline will use a mixed effects analysis of covariance model with baseline value as a covariate and main effects for genotype and ethnic origin. Potential interactions between genotype and ethnic origin will also be investigated. No subgroups have been identified *a priori* for analysis.

Secondary efficacy measures will each be assessed at a significance level of $\alpha=0.05$, but will be subject to disclosure-of-results restrictions as described in the next section.

Multiplicity

The primary treatment comparison in this study, and the main focus of this section, is between the Arg/Arg and the Gly/Gly genotype in the FSC 50mcg BID treatment group.

The hypothesis test for differences between the Arg/Arg and the Gly/Gly genotypes in AM PEF AUC(bl) will be assessed in terms of a 95% confidence interval.

The secondary efficacy measures include PM PEF AUC(bl), morning predose FEV₁AUC(bl), and the change from baseline in the percentage of symptom-free days, the proportion of subjects requiring supplemental albuterol use, and in rescue ipatropium bromide use. This set of secondary efficacy measures will be subject to the following disclosure-of-results scheme. Reporting the results of one measure in the set requires reporting results of all other measures in the set, regardless of the statistical significance associated with the tests of the measures. Conversely, choosing not to report any one measure in the set requires that none of the other measures in the set be reported. Each secondary efficacy measure will be evaluated at a significance level of $\alpha=0.05$.

Treatment differences between the Arg/Arg and the Arg/Gly and the Gly/Gly and Arg/Gly genotypes in the SM and FSC treatment groups, and between the Arg/Arg and the Gly/Gly genotypes in the FCS treatment group will be summarized and analyzed in a manner similar to that described above for the primary treatment comparison. The same multiple comparisons rules defined above will apply to each family of efficacy measures for these comparisons, as well.

11.7. Efficacy Analyses

11.7.1. Primary Analysis

The primary efficacy measure, AM PEF AUC(bl) for, compared between the Arg/Arg and Gly/Gly genotypes in the FSC treatment group, will be calculated as the area under the response-by-time curve. These data will be summarized by genotype and analyzed using a mixed effects analysis of covariance model that includes baseline as the covariate and terms for genotype and ethnic origin. Potential interactions between genotype and ethnic origin will also be investigated.

11.7.2. Secondary and Other Analyses

Mean PM PEF and AM pre-dose FEV1 will be assessed in terms of AUC(bl) and will be analyzed in a manner similar to that described above in Section 11.7.1., Primary Analysis. Other secondary measures, including mean change from baseline in the proportion of symptom-free days, and ipratropium bromide use will be analyzed using models similar to that described above in Section 11.7.1., Primary Analysis. The proportion of subjects requiring supplemental albuterol will be assessed using a Cochran-Mantel-Haenszel chi-square test. Secondary and other comparisons, including pairwise comparisons of other genotypes and comparison of the two open-label treatment periods, will also use models similar to that described above in Section 11.7.1., Primary Analysis.

11.7.3. Estimating Haplotype Pair Probabilities

The expectation-maximization (EM) algorithm will be used to estimate haplotype pair probabilities. Given the stated recruitment and randomization procedures, *ADRB2* genotype distributions will not be in Hardy-Weinberg equilibrium (HWE). Because the EM algorithm is dependent on the assumption of HWE, it will not be possible to estimate haplotype pair probabilities in this study population. Rather, genotype data from this trial will be pooled with previously collected asthma clinical trials estimates (i.e., by pooling the asthma clinical trial collections, it is assumed that the HWE assumption will be met enabling use of the EM algorithm).

11.8. Safety Analyses

Safety measures will include adverse events (AEs) and asthma exacerbations.

11.8.1. Extent of Exposure

The extent of exposure, calculated as the number of days between start and end of treatment (i.e., treatment stop date - treatment start date + 1), will be summarized by treatment group and genotype.

11.8.2. Adverse Events

Adverse events (AEs) will be summarized and grouped by body system and by AE within body system. Terms recorded in the CRF by the investigators will be mapped into coded terms. Results will be displayed in order of decreasing frequency, both across body systems and within each body system. Drug-related AEs will be summarized in a similar manner. AE's and drug-related AE's will be summarized by genotype and treatment group.

11.8.3. Asthma Exacerbations

The number of subjects experiencing at least one exacerbation during the treatment period and the number of exacerbations by suspected cause and setting of care will be summarized by genotype and treatment group.

12. STUDY ADMINISTRATION

12.1. Regulatory and Ethical Considerations

12.1.1. 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.

12.1.2. 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.

12.1.3. 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.

12.1.4. Investigator Reporting Requirements

As indicated in Section 10.10, Regulatory Reporting Requirement for SAEs, 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.

12.2. 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 12.4. Study and Site Closure.

12.3. 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.

12.4. 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 clarifications/resolutions.
- Accountability, reconciliation, and arrangements for unused investigational product(s).
- Review of site study records for completeness.

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.

12.5. 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.

12.6. 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.

12.7. 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 industrial 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 industrial 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.

12.8. 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.

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14. APPENDICES

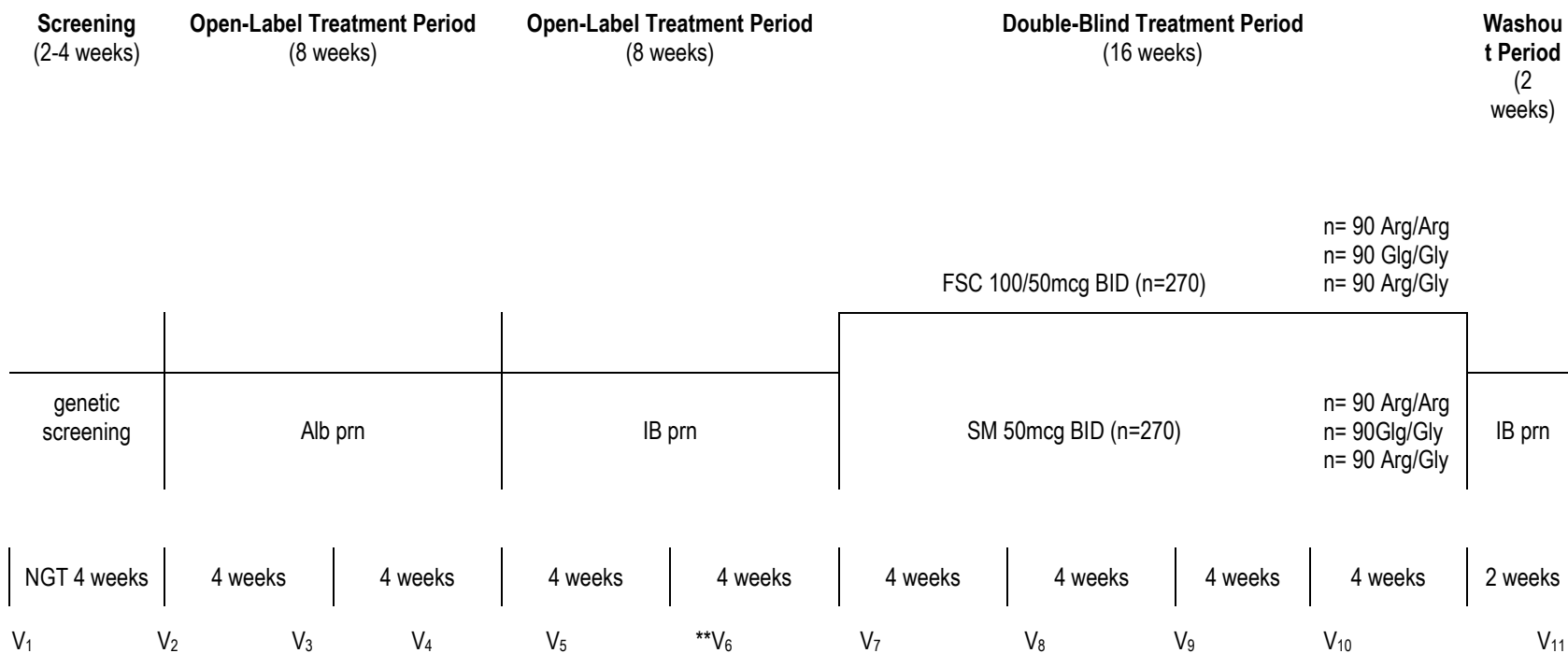
14.1. Appendix 1: Time and Events Table

Screening, Open-label, and Blinded Treatment Periods	Screen	Open-label	Open-label	Open-label	Open-label	Blinded	Blinded	Blinded	Blinded	Blinded	Washout	Premature Dis.
Visit	1	2	3	4	5	6	7	8	9	10	11	
Week		-16	-12	-8	-4	0	4	8	12	16	18	
Number of Days from Visit 6						0	28±2	56±2	84±2	112±2	126±2	
Informed consent	X ^a											
Medical history	X											
Physical exam	X									X		X
Adverse event assessment	X ^b	X ^b	X	X	X	X	X	X	X	X	X	X
Concomitant medication assessment	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X									X		X
Venipuncture	X ^c											
Urinalysis for pregnancy		X		X		X		X		X	X	X
Clinic FEV ₁	X ^d	X	X ^f	X ^f	X ^f	X ^f	X	X	X	X	X	X
Reversibility	X ^e											
Maximum Albuterol Dose Response assessment (MADR)				X ^g		X ^g				X ^g		
Dispense Peak Flow Meter		X										
Dispense Study medication (rescue, open-label, blinded)		X	X	X	X	X	X	X	X	X		
Collect study medication (rescue, open-label, blinded)			X	X	X	X	X	X	X	X	X	X
Dispense Diary Card		X	X	X	X	X	X	X	X	X		
Collect/review diary data			X	X	X	X	X	X	X	X	X	X

- Consent must be signed prior to the withholding of any medication
- Study participation events only
- Take 2 tubes of blood at Visit 1, one for genotyping and one for pharmacogenetics
- Visit 1 FEV₁ percent predicted assessment
- If reversibility assessment is failed twice, site can perform methacholine challenge testing
- Continuation assessment
- Take vital signs before MADR and at least once after each dose of albuterol is administered

14.2. Appendix 2: Study Schematic Diagram

Short-acting beta₂-agonist only asthma patients



** Randomization visit

Alb – albuterol

BID – twice daily

FSC – fluticasone propionate/salmeterol combination product

IB ipratropium bromide

NGT – not greater than

prn – as needed

SM - salmeterol

14.3. Appendix 3: Country Specific Requirements

No country-specific requirements exist.

14.4. Appendix 4: Pharmacogenetics

Pharmacogenetics-Background

Pharmacogenetics (PGx) is the study of variability in drug handling or response due to hereditary factors in different populations. There is increasing evidence that an individual's genetic composition (i.e. his or her genotype) may impact drug handling or response, or clinical outcome. Genetic markers may be used to help understand and predict drug handling or response in terms of efficacy and/or safety and tolerability. Some reported examples of PGx analysis include:

Drug	Disease	Gene	Outcome
Clozapine	Schizophrenia [Arranz, 1995]	5HT2A	Patients homozygous for the C102 allele appear more frequently in the non-responder (53%) than in the responder group (26%)
Pravastatin	Coronary Atherosclerosis [Kuivenhoven, 1998]	Cholesteryl ester transfer protein (CETP)	Progression of coronary atherosclerosis slowed in B1/B1 homozygotes but not in B2/B2 homozygotes receiving pravastatin
Desipramine	Depression [Daly, 1995]	CYP2D6	Poor metabolizing genotypes at risk of drug accumulation and associated toxicity
Isoniazid	Tuberculosis [Nebert, 1997]	NAT-2 (N-acetyl transferase)	High incidence of peripheral neuropathy in patients with slow acetylator genotypes
Abacavir	HIV [Hetherington, 2002 and Mallal, 2002]	HLA (human leukocyte antigen)	Caucasian males with HLA B57 variant were at increased risk for experiencing hypersensitivity to abacavir
Tranilast	Restenosis prevention following coronary bypass [Roses, 2002]	UGT1A1	Drug induced hyperbilirubinaemia explained by high proportion of affected patients having 7/7 TA repeat genotype, consistent with clinically benign Gilbert's Syndrome
ABT-761	Asthma [Drazen, 1999]	ALOX5	ALOX5 Sp1 promoter genotype (x,x) associated with reduced response to 5-lipoxygenase inhibitor ABT-761

A key component to successful PGx research is the collection of samples during the conduct of clinical studies. Collection of whole blood samples, even when no *a priori* hypothesis has been identified, may enable PGx analysis to be conducted if at any time it appears that there is a potential unexpected or unexplained variation in handling or response to FSC or SM.

For the whole genome SNP scan approach, SNP or other genetic marker sets across the genome may be evaluated to identify those markers associated with differential drug handling or response.

The need to conduct further PGx analysis may be identified after a study (or set of studies) of FSC and SM **DISKUS** have been completed and the study data reviewed. For this reason, samples may be kept for up to 15 years after the last subject completes the study or GSK may destroy the samples before then. In special cases, the samples may not be studied. This might happen if there are not enough subjects, if the study is stopped for other reasons, or if no questions are raised about how people respond to or handle FSC and SM **DISKUS**.

In the performance of the PGx analysis, GSK may use subjects' medical information, samples and/or research results. This PGx research is not designed to determine whether other members of the subject's family are at risk of developing asthma or their response to or handling of FSC and SM **DISKUS**.

Sample Quality Control (QC)

If deoxyribonucleic acid (DNA) is extracted from blood samples taken from the clinical study, the DNA may be subjected to sample quality control (QC) analysis. This analysis will involve the genotyping of several genetic markers to confirm the integrity of individual samples. If inconsistencies are noted in the analysis, then those samples may be destroyed.

Objectives

If at any time it appears there is potential variability in FSC and SM **DISKUS** response or handling (e.g., pharmacokinetics, safety, and/or efficacy) in this clinical study or in a series of clinical studies, the following objectives may be investigated (assuming sample number is adequate and the availability of genotyping assays):

- Relationship between genetic variants and safety and/or tolerability of investigational product
- Relationship between genetic variants and efficacy of investigational product

Study Population

Any subject who has given informed consent to participate in the clinical study, has met all the criteria required for entry into the clinical study, and receives investigational product will take part in the PGx research. Any subject who has received a bone marrow transplant must be excluded from the PGx research.

No administration of investigational product beyond that detailed in the clinical study is associated with the PGx research.

Pharmacogenetics Study Assessments

In addition to any blood samples taken for the clinical study, a whole blood sample (~10ml) will be collected for the PGx research using a tube containing EDTA. The PGx sample is labeled (or “coded”) with a study specific number that can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number). The blood sample will be taken on a single occasion unless a duplicate sample is required due to inability to utilize the original sample.

Subject Withdrawal from Study

If a subject who has consented to participate in PGx research withdraws from the clinical study for any reason other than lost to follow-up, the subject will be given the following options concerning the PGx sample if already collected:

- PGx research continues per the subject’s consent; or,
- Any remaining sample is destroyed.

If a subject withdraws consent from the PGx research or requests sample destruction, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records. In either case, GSK will only keep and study information collected/generated up to that point.

Screen and Baseline Failures

If a blood sample for PGx research has been collected and it is determined that the subject does not meet the inclusion and exclusion criteria for participation in the clinical study, then the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records.

Pharmacogenetics Analyses

If at any time it appears that there is a potential unexpected or unexplained variation in drug handling or response (e.g., pharmacokinetics, efficacy and/or safety) that may be attributable to genetic variation, then PGx analysis may be conducted. In these circumstances the analysis undertaken will be limited to PGx analysis of response to or handling of FSC and SM **DISKUS**.

Generally GSK will utilize two approaches to explore genetic variation in drug handling or response.

1. Hypothesis driven approach: A specific hypothesis is generated about sections of DNA (or individual single nucleotide polymorphisms (SNPs) or other genetic markers) that may be associated with differential drug handling or response. Specific sections of DNA may be selected from areas of the genome (e.g., candidate genes) known to encode the drug target, drug metabolizing enzymes, areas associated with mechanisms underlying adverse events, and those linked to study disease and, thus, linked to drug response.
2. Genome-wide approach utilizing polymorphic markers (e.g., SNPs): By evaluating large numbers of polymorphic markers throughout the genome, sets of markers may be identified that correspond to differential drug response or handling.

Analysis of genetic markers (e.g., whether within candidate genes or SNPs studied in a genome-wide analysis) will include the following considerations. The genotypic frequencies of each polymorphism will be evaluated for conformity to those expected under normal conditions by employing Hardy-Weinberg Equilibrium testing. Any departure from expectation will be taken into account, possibly signaling a data error or alternatively a connection between the polymorphism and asthma.

For pairs of polymorphisms, the degree to which alleles from the two sites are correlated (linkage disequilibrium) may also be evaluated. If the genotypes at two polymorphic sites within a gene are shown to be statistically associated with a response to investigational product, the degree of linkage disequilibrium will aid interpretation in that it will indicate the extent to which the two sites are exerting independent effects.

A decision regarding the construction and analysis of marker haplotypes -- combinations of alleles from different polymorphic sites that are inherited from one parent -- may be guided by the assessment of linkage disequilibrium. For example, if there is no linkage disequilibrium between polymorphic sites, then haplotype construction will be uninformative.

Differences in baseline clinical characteristics and potential contributing covariates may be summarized and compared among genotype (or haplotype) subgroups.

Analyses may be carried out to evaluate the degree of association between subject genotype (or haplotype) and selected parameters (e.g., pharmacokinetics, efficacy and safety). Where such genotypic tests are inappropriate (for example, where the number of marker genotypes is too large and/or the frequency of individual genotypes too small), allelic tests may be conducted. Allelic tests evaluate whether the frequency of each marker allele is the same in responders and non-responders.

In addition to evaluating the main effects of the genotypes (haplotypes or alleles) on the selected parameters, the possibility of a treatment group by genotype (haplotype or allele) interaction may also be explored. If appropriate, the joint effects of multiple markers (gene-gene interactions) may also be evaluated.

Sample Size Considerations

The ability to detect differential drug response or handling among genotypes at a polymorphic site depends on the total number of subjects genotyped and the frequency distribution of the different genotypes. Consequently, genotyping analyses are plausible for those polymorphic sites where the number of subjects comprising the genotypic groups is sufficiently large; however, these frequencies will not be known until sufficient samples have been collected and genotyping is complete.

Estimates of sample sizes required to demonstrate genotype effects vary considerably, depending on the assumptions made about allele frequency, genetic effect size, and mechanism of inheritance [Cardon, 2000]. In the work by Palmer and Cookson [Palmer, 2001], which assumed a genotype relative risk of 1.5, it was estimated that more than 300 cases and 600 controls would be needed to conduct a genetic association analysis. In contrast, McCarthy and Hilfiker [McCarthy, 2000] showed that with a genotype relative risk of 2.16 and a relatively commonly occurring genotype, only 30 cases and 30 controls would be needed to demonstrate an association. Consequently, it is quite possible that effects with relatively large genotype relative risks may be detectable in individual Phase I or Phase II studies. A range of examples exist to demonstrate robust and clinically relevant PGx data may be generated from PGx studies with sample sizes far less than the sizes proposed by Palmer and Cookson.

Published PGx examples include abacavir hypersensitivity reaction [Hetherington, 2002; Mallal, 2002] and tranilast induced hyperbilirubinemia [Roses, 2002] where genetic markers have been found to significantly associate with hypersensitivity reaction (abacavir) and hyperbilirubinemia (tranilast). These examples show that small sample sizes typically encountered in Phase I and Phase II studies may be sufficient to identify clinically relevant genetic associations.

Informed Consent

Subjects who do not wish to participate in the PGx research may not participate in the clinical study. The informed consent for the PGx research must be obtained in addition to the subject's consent to participate in the clinical study

Provision of Study Results and Information to Investigators

GSK may list and summarize the PGx research results from coded samples by subject number in the clinical study report. In this event, the investigator and study staff would have access to the research results and would be able to link the results to a particular subject. The investigator and study staff would be directed to hold this information confidentially.

Information Disclosure and Inventions- Ownership

This includes the results of the PGx assessments included in the study.

Data Management

Data from the case report forms and PGx research using the coded sample will be stored electronically. International regulations for information on computers and relevant laws on processing personal information will be followed.

Confidentiality of Subject's PGx Data

GSK advises that participation in this PGx research, withdrawal from this research, sample destruction, and/or PGx results should not be documented in the subject's medical records. Storage of information regarding the PGx research with source documents for the study is permissible if stored in the site study files.

Coded PGx samples and results will be associated with the subject's study specific number in computer databases. Coded PGx research results may be submitted to regulatory agencies as part of an investigational product submission and/or included in a research publication.

Individual genotype results will only be shared with a subject through the investigator if the subject requests to see their results and it is a requirement of a governmental agency or other legal authority that GSK make these results available. GSK will not release individual PGx results to anyone else (e.g., family members, primary care physicians, insurers, or employers) under any circumstance, unless required by law.

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14.5. Appendix 5: Methacholine Challenge Dilution schedule

Before conducting the test, the vials of reconstituted methacholine should be removed from the refrigerator for at least 30 minutes to allow them to warm to room temperature. Since the temperature of the solution can affect the output of the nebulizer, they should not be administered until they are at room temperature. The vials of methacholine solution should be arranged in the order of administration starting with diluent and increasing to 16.0 mg/ml. See the Manual of Procedures for complete instructions on methodology and assessments of a methacholine challenge performed during this study.

METHACHOLINE TEST SEQUENCE

<u>Solution (vial) number</u>	<u>Concentration of methacholine</u>
1 (Control)	Diluent
2	0.031 mg/ml
3	0.0625 mg/ml
4	0.125 mg/ml
5	0.25 mg/ml
6	0.5 mg/ml
7	1.0 mg/ml
8	2.0 mg/ml
9	4.0 mg/ml
10	8.0 mg/ml
11	16.0 mg/ml

Great care should be taken to administer the lowest concentration of methacholine first, and then increase concentrations in the prescribed order. You should make sure that all of the test vials are marked with the concentration of the methacholine. You should never transfer solution from unmarked vials. If you are in doubt, it is better to discard the sample and draw up another.

14.6. Appendix 6: Protocol Amendment 1

This amendment applies to all study sites participating in SFA100062.

Rationale

This protocol amendment is being implemented to:

- update the sponsor contact information,
- remove the limitation that methacholine challenge testing can only be performed on subjects ≥ 18 yrs of age,
- add that historical PC20 $< 8\text{mg/ml}$ within the past 12 months is acceptable,
- add an exercise-induced bronchospasm exclusion criterion to the protocol,
- modify Anti-Asthma Medications time intervals,
- clarify the use of corticosteroids in the exclusion criteria,
- add a peanut and soybean food allergy exclusion criterion to the protocol,
- add AM PEF stability limits,
- add requirement to take vital signs during MADR testing,
- remove Appendix 5 & 7 and
- correct administrative and typographical errors.

Page 2, Sponsor Information Page

Original text

Sponsor Contact Information: [REDACTED] MD [REDACTED]

IND Number: fluticasone propionate/salmeterol combination product **DISKUS**- 50,703;
Salmeterol **DISKUS** – 35,239; Ventolin HFA - 46-269

Amended text

Sponsor Contact Information: [REDACTED] MD [REDACTED]

IND Number: fluticasone propionate/salmeterol combination product **DISKUS**- 50,703;
Salmeterol **DISKUS** – 43,097; Ventolin HFA - 46-269

Page 10, 11, 18, 19 update referenceOriginal text[Israel, 2003]Amended text[Israel, 2004]**Page 14, Open-Label Treatment Periods**Original text

If a subject qualifies for the study based on Visit 1 (Screening Visit) and on the results of pharmacogenetic screening, they will be contacted and Visit 2 will be scheduled. At Visit 2, subjects will return to the clinic for assessment of concomitant medications, adverse event assessment, pregnancy testing (for females of childbearing potential), and pulmonary function testing. All subjects will stop their pre-study SABA and receive open-label albuterol 90mcg to be used as needed to relieve acute asthma symptoms for the first of two, 8-week open-label treatment periods. Eligible subjects will be provided with a peak flow meter and diary card and instructed to record asthma-related symptoms, rescue medication use, as well as any other medical event that may occur between clinic visits. Each subject will also be instructed on appropriate study medication use, including rescue medications, and advised to call the clinic to discuss any worsening of asthma.

Amended text

At Visit 2, subjects will return to the clinic for assessment of concomitant medications, adverse event assessment, pregnancy testing (for females of childbearing potential), and pulmonary function testing. All subjects will stop their pre-study SABA and receive open-label albuterol 90mcg to be used as needed to relieve acute asthma symptoms for the first of two, 8-week open-label treatment periods. Eligible subjects will be provided with a peak flow meter and diary card and instructed to record asthma-related symptoms, rescue medication use, as well as any other medical event that may occur between clinic visits. Each subject will also be instructed on appropriate study medication use, including rescue medications, and advised to call the clinic to discuss any worsening of asthma.

Page 14, Open-Label Treatment Periods add reference to footnoteOriginal text

Ipratropium bromide has been used in a number of asthma clinical trials as the primary rescue therapy [Tan, 1997; Vathenen, 1988]. No adverse outcomes have been reported as a result of this use of ipratropium. The experiences in clinical trials with this drug indicate that it can be used safely in this trial, as proposed.

Amended text

Ipratropium bromide has been used in a number of asthma clinical trials as the primary rescue therapy [Tan, 1997; Vathenen, 1988; Israel, 2004]. No adverse outcomes have been reported as a result of this use of ipratropium. The experiences in clinical trials with this drug indicate that it can be used safely in this trial, as proposed.

Page 23, Section 5.2.1 Inclusion CriteriaOriginal text

4. Disease: Each subject must have a diagnosis of persistent asthma for at least 3 months prior to Visit 1, defined by the American Thoracic Society as follows:

Amended text

4. Disease: Each subject must have a diagnosis of persistent asthma for at least 3 months prior to Visit 1. Asthma is defined by the American Thoracic Society as follows:

Page 24, Section 5.2.1 Inclusion CriteriaOriginal text

6. **Reversibility Component:** The subject has reversible airways disease as demonstrated by an increase in FEV₁ of $\geq 12\%$ and 200ml over baseline within 30 minutes after the inhalation of 2-4 puffs (180 μ g -360 μ g) of albuterol (with or without a spacer) or 1-2 nebulized albuterol (2 puffs = 1 nebulizer) treatments at Visit 1 or at a visit that is within the 7-day period immediately following Visit 1. If the subject fails to reverse at least 12% during Visit 1, a second attempt to reverse may be scheduled within 7 days. If the second attempt to document reversibility is unsuccessful, the subject may undergo a methacholine challenge test (MCT). If a PC₂₀ <8mg/ml is documented during an unscheduled visit prior to Visit 2, the subject is eligible. A MCT is not to be performed on any subject less than 18 years of age. Methacholine challenge testing should be performed only at sites with past experience performing this test.

Amended text

6. **Reversibility Component:** The subject has reversible airways disease as demonstrated by an increase in FEV₁ of $\geq 12\%$ and 200ml over baseline within 30 minutes after the inhalation of 2-4 puffs (180 μ g -360 μ g) of albuterol (with or without a spacer) or 1-2 nebulized albuterol (2 puffs = 1 nebulizer) treatments at Visit 1 or at a visit that is within the 7-day period immediately following Visit 1. If the subject fails to reverse at least 12% during Visit 1, a second attempt to reverse may be scheduled within 7 days. If the second attempt to document reversibility is unsuccessful, the subject may undergo a methacholine challenge test (MCT). A PC₂₀ result of <8mg/ml obtained at an unscheduled visit prior to Visit 2 is required. An historical PC₂₀ value of <8mg/ml that has been documented at the investigative site within the past 12 months and was obtained using ATS or ACRN guidelines for MCT is also acceptable ATS, 2000; ACRN, 2002.

Methacholine challenge testing should be performed only at sites with past experience performing this test.

Page 25, Section 5.2.2. Exclusion Criteria

Addition of text

4. Exercise-Induced Bronchospasm Alone: A subject may not have been diagnosed with exercise-induced bronchospasm alone, in the absence of a diagnosis of persistent asthma within the last 12 months prior to Visit 1.

Page 25, Section 5.2.2. Exclusion Criteria

Original text

4. Anti-Asthma Medications: Asthma medications listed below must not have been used prior to Screening (Visit 1) for the required interval indicated below, and not taken during the study.

Inhaled short-acting beta ₂ -agonists	6 hours
Oral short-acting beta-agonists	6 hours
Nebulized short-acting beta-agonists	6 hours
Inhaled anticholinergics	6 hours
Theophylline products	24 hours
Oral long-acting beta ₂ -agonists	24 hours
Inhaled long-acting beta ₂ -agonists	24 hours
Inhaled corticosteroids	4 weeks
Oral corticosteroids	4 weeks ^{1,2}
Parenteral corticosteroids	4 weeks ²
Inhaled cromolyn sodium or nedocromil	4 weeks
Leukotriene modifiers	4 weeks
1. Any subject who has received oral corticosteroid treatment for 2 months or longer must have discontinued use for at least 6 months prior to Visit 1.	
2. Subject must not have had two courses of oral or parenteral corticosteroids for the treatment of asthma in the 6 months prior to Visit 1	

Amended text

5. Anti-Asthma Medications: Asthma medications listed below must not have been used prior to Screening (Visit 1) for the required interval indicated below, and not taken during the study.

Inhaled short-acting beta2-agonists	6 hours
Nebulized short-acting beta-agonists	6 hours
Oral short-acting beta-agonists	6 hours
Inhaled short-acting anticholinergics	6 hours
Inhaled long-acting anticholinergics	24 hours
Leukotriene modifiers	24 hours
Inhaled long-acting beta2-agonists	24 hours
Theophylline products	48 hours
Oral long-acting beta2-agonists	48 hours
Inhaled corticosteroids	4 weeks
Inhaled corticosteroid/ Inhaled long-acting beta2-agonist combination products	4 weeks
Oral corticosteroids	4 weeks ^{1,2}
Parenteral corticosteroids	4 weeks ²
Inhaled cromolyn sodium or nedocromil	4 weeks
1. Any subject who has received oral corticosteroid treatment for any reason for 2 months or longer must have discontinued use for at least 6 months prior to Visit 1.	
2. Subject must not have had two courses of oral or parenteral corticosteroids for any reason in the 6 months prior to Visit 1.	

Page 26, Section 5.2.2. Exclusion Criteria

Original text

11. Drug Allergy: The subject has any adverse reaction, including immediate or delayed hypersensitivity, to study medications or a severe milk protein allergy.

Amended text

12. Drug Allergy: The subject has any adverse reaction, including immediate or delayed hypersensitivity, to study medications, severe milk protein allergy or allergies to soya lecithin or related food products such as soybeans or peanuts.

Page 28, Section 6.2.2. Subject Contact

Removed this section from Protocol, renumbered subsequent sections.

Page 28, Section 6.2.1. Screening Visit (Visit 1) Re-Screening

Original text

If the subject meets the PFT entry criteria on the second attempt, then **all** other Visit 1 procedures should be performed on this date.

Amended text

If the subject meets the PFT entry criteria on the second attempt, then **all** other Visit 1 procedures should be performed on this date.

If methacholine challenge testing is performed and a PC20 of <8mg/ml is obtained, then all other Visit 1 procedures should be performed on the date MCT is performed.

Page 34, Section 6.4.1. Medical History

Original text

Medical history related to concurrent diseases, concurrent drug use, and drug allergies will also be obtained.

Amended text

Medical history related to concurrent diseases, concurrent drug use, and drug/food allergies will also be obtained.

Page 33, Section 6.4.3. Vital signs

Original text

Blood pressure (systolic and diastolic) and pulse will be determined with the subject in the sitting position. The subject must be seated at least 5 minutes before the measurements are taken. Blood pressure and pulse will be taken at Visit 1 and Visit 10, but should be taken prior to any pulmonary function testing. Vital signs will be documented in the source documents only, unless there is a clinically significant change from baseline. As detailed in section 10.4, any clinically significant findings (change from baseline) would need to be captured as an AE/SAE.

Amended text

Blood pressure (systolic and diastolic) and pulse will be determined with the subject in the sitting position. The subject must be seated at least 5 minutes before the measurements are taken. Blood pressure and pulse will be taken at Visit 1 and Visit 10, but should be taken prior to any pulmonary function testing.

To ensure subject safety during Maximum Albuterol Dose Response (MADR) testing, vital signs will be taken before MADR is performed, and at least once after each dose of albuterol is administered. If, in the opinion of the investigator, significant hypertension, tachycardia, arrhythmia or other side effects of albuterol occur, MADR testing should be stopped and appropriate medical measures should be taken. MADR testing is performed at Visits 4, 6 and 10.

Vital signs will be documented in the source documents only, unless there is a clinically significant change from baseline. As detailed in section 10.4, any clinically significant findings (change from baseline) would need to be captured as an AE/SAE.

Page 36, Section 6.5.1.1. PEFOriginal text

Each subject will be instructed to perform triplicate PEF measurements in the morning and evening of each day during the study. The morning determinations should be performed after recording the asthma symptom scores and prior to the subject taking the morning dose of study medication or rescue medication. The evening measurements should be performed after recording the asthma symptom scores and prior to the subject taking the evening dose of study medication or rescue medication. The **highest** of the 3 values of morning and evening PEF must be recorded on the subject diary card.

Amended text

Each subject will be instructed to perform triplicate PEF measurements in the morning and evening of each day during the study. The morning determinations should be performed prior to the subject taking the morning dose of study medication or rescue medication. The evening measurements should be performed after recording the asthma symptom scores and prior to the subject taking the evening dose of study medication or rescue medication. The **highest** of the 3 values of morning and evening PEF must be recorded on the subject diary card.

AM PEF Stability Limits

For those who qualify for the study, an AM PEF Stability Limit will be calculated at Visit 3 as follows:

- The AM PEF Stability Limit will be calculated using the mean morning PEF from the 7 consecutive days preceding Visit 3, using the morning PEF from the day **prior** to Visit 3 as day 7. The AM PEF Stability Limit will be defined as 80% of the mean morning PEF and used for the duration of the study.

The subject will be counseled on the usefulness of the peak flow meter as a means of monitoring his/her asthma status. Subjects will be informed of their AM PEF Stability Limit and educated to be alert to a pattern of **consistently decreasing PEF** as a warning of possible worsening of asthma/asthma exacerbation. Subjects will be instructed to call the investigator if such a profile of declining PEF is observed, or if their PEF falls below the AM PEF Stability Limit for 2 or more consecutive days. If such a pattern is observed, it is not a protocol-defined exacerbation unless it meets the definition in Section 11.8.3.

Page 38, Section 6.5.1.2. Clinic FEV₁Removed text

NOTE: A downward adjustment of 12% will be made in the predicted value for African-Americans. FEV₁ percent predicted documentation will be maintained in the CRF.

Page 38, Section 6.5.1.3. Methacholine Challenge TestOriginal text

The subject may undergo methacholine challenge testing (MCT) once if the second attempt to document reversibility is unsuccessful. If a PC20 <8mg/ml is documented during an unscheduled visit prior to Visit 2, the subject is eligible for study inclusion. A MCT is not to be performed on any subject less than 18 years of age. Methacholine challenge testing should be performed only at sites with past experience performing this test. The testing should be performed between 6 AM and 11 AM. All females of childbearing potential must have a negative urine pregnancy test prior to initiation of the methacholine challenge. Any female with a positive pregnancy test will be excluded from study participation.

See Appendix 5, Methacholine Challenge Dilution schedule.

Amended text

The subject may undergo methacholine challenge testing (MCT) once if the second attempt to document reversibility is unsuccessful. A PC20 result of <8mg/ml obtained at an unscheduled visit prior to Visit 2 is required. An historical PC20 value of <8mg/ml that has been documented at the investigative site within the past 12 months and was obtained using ATS or ACRN guidelines for MCT is also acceptable ATS, 2000; ACRN, 2002. Methacholine challenge testing should be performed only at sites with past experience performing this test. The testing should be performed between 6 AM and 11 AM. All females of childbearing potential must have a negative urine pregnancy test prior to initiation of the methacholine challenge. Any female with a positive pregnancy test will be excluded from study participation.

See Appendix 5, Methacholine Challenge Dilution schedule.

Page 38, Section 6.5.1.4. Maximum Albuterol Dose ResponseOriginal text

To obtain the MADR, each subject will perform baseline spirometry and will then be administered four puffs of albuterol. Fifteen minutes following the administration of the albuterol, the subject will again perform spirometry, followed by two additional puffs of albuterol, for a cumulative dose of six puffs. After fifteen minutes, spirometry will be repeated once more, and the current FEV₁ value compared with the FEV₁ obtained after the first four puffs. If the relative change in FEV₁ is 5% or less, the procedure will be stopped; if the relative change is more than 5%, then two additional puffs of albuterol will be administered, for a cumulative dose of eight puffs, followed by a final spirometry assessment.

Amended text

To obtain the MADR, each subject will perform baseline spirometry and will then be administered four puffs of albuterol. Fifteen minutes following the administration of the albuterol, the subject will again perform spirometry, followed by two additional puffs of albuterol, for a cumulative dose of six puffs. After fifteen minutes, spirometry will be repeated once more, and the current FEV₁ value compared with the FEV₁ obtained after the first four puffs. If the relative change in FEV₁ is 5% or less, the procedure will be stopped; if the relative change is more than 5%, then two additional puffs of albuterol will be administered, for a cumulative dose of eight puffs, followed by a final spirometry assessment.

During the MADR testing albuterol should be administered using a metered-dose inhaler. The use of spacers and nebulers is not permitted.

To ensure subject safety during MADR testing, vital signs will be taken before MADR is performed, and at least once after each dose of albuterol is administered. If, in the opinion of the investigator, significant hypertension, tachycardia, arrhythmia or other side effects of albuterol occur, MADR testing should be stopped and appropriate medical measures should be taken.

Page 46, Section 8.3. Medical DevicesOriginal text

Diary PEF will be measured by the subject using a peak flow meter in accordance with specific instructions explained by the study staff (see Appendix 5, Instructions for Use of Peak Flow Meters). The subject should demonstrate correct use of the peak flow meter at Visit 2.

Amended text

Diary PEF will be measured by the subject using a peak flow meter in accordance with specific instructions explained by the study staff. The subject should demonstrate correct use of the peak flow meter at Visit 2.

Page 46, Section 9.1. Subject CompletionOriginal text

A subject who completes the 16-week double-blind treatment period and undergoes all Visit 10 evaluations has completed the study. Following these procedures, alternative asthma medication will be prescribed, and the subject will be followed as judged to be medically appropriate by the investigator.

Amended text

A subject who completes the 16-week double-blind treatment period and undergoes all Visit 10 evaluations has completed the study. Following Visit 11, alternative asthma medication will be prescribed, and the subject will be followed as judged to be medically appropriate by the investigator.

Page 66, Section 13. ReferencesAdded Text

American Thoracic Society. Guidelines for methacholine and exercise challenge testing-1999. Am J Respir Crit Care Med 2000;161:309-329.

Asthma Clinical Research Network (ACRN), National Heart, Lung, and Blood Institute: Methacholine Challenge Manual, February 2002.

Israel E., Chinchilli V., Ford J., et al. Use of regularly scheduled albuterol treatment in asthma: genotype-stratified, randomized, placebo-controlled cross-over trial. Lancet 2004; 364:1505-12.

Deleted Text

Israel E et al. BARGE Study presented at NHLBI Symposium at ATS Meeting, Seattle, WA. 2003.

Page 68, Appendix 1: Time and Events Table

Original text

Screening, Open-label, and Blinded Treatment Periods	Screen	Phone Contact	Open-label	Open-label	Open-label	Open-label	Blinded	Blinded	Blinded	Blinded	Blinded	Washout	Premature Dis.
Visit	1		2	3	4	5	6	7	8	9	10	11	
Week			-16	-12	-8	-4	0	4	8	12	16	18	
Number of Days from Visit 6							0	28±2	56±2	84±2	112±2	126±2	
Informed consent	X ^a												
Medical history	X												
Physical exam	X										X		X
Adverse event assessment	X ^e		X ^e	X	X	X	X	X	X	X	X	X	X
Concomitant medication assessment	X		X	X	X	X	X	X	X	X	X	X	X
Vital signs	X										X		X
Venipuncture	X												
Urinalysis for pregnancy			X		X		X		X		X	X	X
Clinic FEV ₁	X ^b		X	X ^d	X ^d	X ^d	X ^d	X	X	X	X	X	X
Reversibility	X ^c												
Maximum Albuterol Dose Response assessment (MADR)					X		X				X		
Dispense Peak Flow Meter			X										
Dispense Study medication (rescue, open-label, blinded)			X	X	X	X	X	X	X	X	X		
Collect study medication (rescue, open-label, blinded)				X	X	X	X	X	X	X	X	X	X
Dispense Diary Card			X	X	X	X	X	X	X	X	X		
Collect/review diary data				X	X	X	X	X	X	X	X	X	X

- Consent must be signed prior to the withholding of any medication
- Visit 1 percent predicted assessment
- If reversibility assessment is failed twice, site can perform methacholine challenge testing
- Continuation assessment
- Study participation events only

Amended text

Screening, Open-label, and Blinded Treatment Periods	Screen	Open-label	Open-label	Open-label	Open-label	Blinded	Blinded	Blinded	Blinded	Blinded	Washout	Premature Dis.
Visit	1	2	3	4	5	6	7	8	9	10	11	
Week		-16	-12	-8	-4	0	4	8	12	16	18	
Number of Days from Visit 6						0	28±2	56±2	84±2	112±2	126±2	
Informed consent	X ^a											
Medical history	X											
Physical exam	X									X		X
Adverse event assessment	X ^b	X ^b	X	X	X	X	X	X	X	X	X	X
Concomitant medication assessment	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X									X		X
Venipuncture	X ^c											
Urinalysis for pregnancy		X		X		X		X		X	X	X
Clinic FEV ₁	X ^d	X	X ^f	X ^f	X ^f	X ^f	X	X	X	X	X	X
Reversibility	X ^e											
Maximum Albuterol Dose Response assessment (MADR)				X ^g		X ^g				X ^g		
Dispense Peak Flow Meter		X										
Dispense Study medication (rescue, open-label, blinded)		X	X	X	X	X	X	X	X	X		
Collect study medication (rescue, open-label, blinded)			X	X	X	X	X	X	X	X	X	X
Dispense Diary Card		X	X	X	X	X	X	X	X	X		
Collect/review diary data			X	X	X	X	X	X	X	X	X	X

- Consent must be signed prior to the withholding of any medication
- Study participation events only
- Take 2 tubes of blood at Visit 1, one for genotyping and one for pharmacogenetics
- Visit 1 FEV₁ percent predicted assessment
- If reversibility assessment is failed twice, site can perform methacholine challenge testing
- Continuation assessment
- Take vital signs before MADR and at least once after each dose of albuterol is administered

Removed Appendices 5 & 7

14.7. Appendix 7: Protocol Amendment 02

This amendment applies to all study sites participating in SFA1000062. The following sections are revised. **Note:** Numbers and/or text bolded for ease of understanding revisions in this appendix are not bolded in the body of the protocol.

Protocol Summary, Study Design (study schematic)

Original Text

β_2 -agonist only asthma patients

Amended Text

Short-acting beta₂-agonist only asthma patients

Protocol Summary, Open-label Treatment Periods

Original Text

At Visit 2, subjects will return to the clinic for assessment of concomitant medications, adverse event assessment, pregnancy testing (for females of childbearing potential), and pulmonary function testing. All subjects will stop their pre-study SABA and receive open-label albuterol 90mcg to be used as needed to relieve acute asthma symptoms for the first of two, 8-week open-label treatment periods. Eligible subjects will be provided with a peak flow meter and diary card and instructed to record asthma-related symptoms, **rescue** medication use, as well as any other medical event that may occur between clinic visits. Each subject will also be instructed on appropriate study medication use, **including rescue medications**, and advised to call the clinic to discuss any worsening of asthma.

Amended Text (deleted “rescue” and “including rescue medications”, added “a continuation assessment”, no other text/ paragraphs revised)

At Visit 2, subjects will return to the clinic for assessment of concomitant medications, adverse event assessment, pregnancy testing (for females of childbearing potential), pulmonary function testing and **a continuation assessment**. All subjects will stop their pre-study SABA and receive open-label albuterol 90mcg to be used as needed to relieve acute asthma symptoms for the first of two, 8-week open-label treatment periods. Eligible subjects will be provided with a peak flow meter and diary card and instructed to record asthma-related symptoms, medication use, as well as any other medical event that may occur between clinic visits. Each subject will also be instructed on appropriate study medication use, and advised to call the clinic to discuss any worsening of asthma.

Protocol Summary, Study Population

Original Text

We will compare individuals with the Arg/Arg genotype (which occurs at a frequency of about 15% in the general population) to those with the Gly/Gly genotype (which occurs with approximately a 35% frequency) and to those with the Gly/Arg genotype (which occurs with approximately a 50% frequency). Thus, to recruit 90 subjects in each of the genotypic categories, we will need to screen a minimum of 1,200 subjects. Allowing for exclusions, refusals to participate and withdrawals, we may need to screen as many as 1320 subjects.

Amended Text (no other text/paragraphs revised)

We will compare individuals with the Arg/Arg genotype (which occurs at a frequency of about 15% in the general population) to those with the Gly/Gly genotype (which occurs with approximately a 35% frequency) and to those with the Gly/Arg genotype (which occurs with approximately a 50% frequency). Thus, to recruit 90 subjects in each of the genotypic categories, we will need to screen a minimum of 1,200 subjects. Allowing for exclusions, refusals to participate and withdrawals, we may need to screen **approximately 1840** subjects.

Protocol Summary, Assessments and Procedures

Original Text

The following assessments/procedures will be performed during the study:

- Blood samples drawn
- Medical history, physical examination, vital signs (blood pressure and pulse), concomitant medication assessment
- FEV₁ (including percent predicted and reversibility assessments at Visit 1)
- Methacholine Challenge Testing (performed once, only if subject fails reversibility twice)
- Maximum Albuterol Dose Response (MADR)
- Adverse event assessment
- Pregnancy test for all females of childbearing potential
- Review of daily diary data recorded by subject

Amended Text

The following assessments/procedures will be performed during the study:

- Blood samples drawn
- Medical history, physical examination, vital signs (blood pressure and pulse), concomitant medication assessment
- FEV₁ (including percent predicted and reversibility assessments at Visit 1)
- Methacholine Challenge Testing (performed once, only if subject fails reversibility twice)
- **PEF Stability Limit calculation(at Visit 3)**
- Maximum Albuterol Dose Response (MADR)
- Adverse event assessment
- Pregnancy test for all females of childbearing potential
- Review of daily diary data recorded by subject

Section 4 Study Design, Figure 1 Study SchematicOriginal Text

Figure 1 Study Schematic

β₂-agonist only asthma patients

Amended Text

Short-acting beta₂-agonist only asthma patients

Section 5.1 Number of SubjectsOriginal Text

We will compare individuals with the Arg/Arg genotype (which occurs at a frequency of about 15% in the general population) to those with the Gly/Gly genotype (which occurs with approximately a 35% frequency) and to those with the Gly/Arg genotype (which occurs with approximately a 50% frequency). Thus, to recruit 90 subjects in each of the genotypic categories, we will need to screen a minimum of 1,200 subjects. Allowing for exclusions, refusals to participate and withdrawals, we may need to screen as many as 1320 subjects.

Amended Text (number revised, no other text/paragraphs revised)

We will compare individuals with the Arg/Arg genotype (which occurs at a frequency of about 15% in the general population) to those with the Gly/Gly genotype (which occurs with approximately a 35% frequency) and to those with the Gly/Arg genotype (which occurs with approximately a 50% frequency). Thus, to recruit 90 subjects in each of the genotypic categories, we will need to screen a minimum of 1,200 subjects. Allowing for exclusions, refusals to participate and withdrawals, we may need to screen **approximately 1840** subjects.

Section 5.2.1 Inclusion Criteria, No. 3. Gender: Male or Female

Original Text

Females are eligible to participate only if they are currently non-pregnant and non-lactating. There are no birth control restrictions for this study. Female subjects of childbearing potential will undergo a urine pregnancy test at the beginning of the study (Visit 2) and at Visit 4, 6, 8, 10 and at the end of the study (Visit 11 or Premature Discontinuation). Any female who becomes pregnant during the study will be withdrawn. Female subjects should not be enrolled if they plan to become pregnant during the time of study participation.

Amended Text

Females are eligible to participate only if they are currently non-pregnant and non-lactating. There are no birth control restrictions for this study. Female subjects of childbearing potential will undergo a urine pregnancy test at the beginning of the study (Visit 2) and at Visit 4, 6, 8, 10 and at the end of the study (Visit 11 or a **Premature Discontinuation Visit which may occur during the open-label periods, the double-blind treatment period, or the washout period.**) Any female who becomes pregnant during the study will be withdrawn. Female subjects should not be enrolled if they plan to become pregnant during the time of study participation.

Section 5.2.1 Inclusion Criteria, No. 6. Reversibility Component

Original Text

Text not currently in this section.

Amended Text (no other text/paragraphs revised)

NOTE: Documentation of historical reversibility within one year of Visit 1 demonstrating an increase in FEV₁ of $\geq 12\%$ and 200ml over baseline is acceptable and will preclude the requirement for reversibility testing at Visit 1.

Section 5.2.1 Inclusion Criteria, No. 7. Concurrent Anti-Asthma Therapy

Original Text

Eligible subjects must have reported β_2 -agonist for use on a prn (or scheduled) basis prior to the Visit 1. Each subject must be judged by the investigator to be able to withhold short-acting β_2 -agonist therapy for at least 6 hours prior to clinic visits when FEV₁ is performed.

Amended Text

Eligible subjects must have reported **short-acting** β_2 -agonist for use on a prn (or scheduled) basis **for at least 4 weeks** prior to the Visit 1. Each subject must be judged by the investigator to be able to withhold short-acting β_2 -agonist therapy for at least 6 hours prior to clinic visits when FEV₁ is performed

Section 5.2.2 Exclusion Criteria, No. 4. Exercise-Induced Bronchospasm Alone

Original Text

A subject may not have been diagnosed with exercise-induced bronchospasm alone, in the absence of a diagnosis of persistent asthma within the last 12 months prior to Visit 1.

Amended Text

A subject may not have been diagnosed with exercise-induced bronchospasm alone, in the absence of a diagnosis of persistent asthma within the last **3** months prior to Visit 1.

Section 5.2.2 Exclusion Criteria, No. 5. Anti-Asthma Medications

Original Text

Asthma medications listed below must not have been used prior to Screening (Visit 1) for the required interval indicated below, and not taken during the study.

Inhaled short-acting beta ₂ -agonists	6 hours
Nebulized short-acting beta-agonists	6 hours
Oral short-acting beta-agonists	6 hours
Inhaled short-acting anticholinergics	6 hours
Inhaled long-acting anticholinergics	24 hours
Leukotriene modifiers	24 hours
Inhaled long-acting beta ₂ -agonists	24 hours
Theophylline products	48 hours
Oral long-acting beta ₂ -agonists	48 hours
Inhaled corticosteroids	4 weeks
Inhaled corticosteroid/ Inhaled long-acting beta ₂ -agonist combination products	4 weeks
Oral corticosteroids	4 weeks ^{1,2}
Parenteral corticosteroids	4 weeks ²
Inhaled cromolyn sodium or nedocromil	4 weeks
1. Any subject who has received oral corticosteroid treatment for any reason for 2 months or longer must have discontinued use for at least 6 months prior to Visit 1.	
2. Subject must not have had two courses of oral or parenteral corticosteroids for any reason in the 6 months prior to Visit 1	

Amended Text

Asthma medications listed below must not have been used prior to Screening (Visit 1) for the required interval indicated below, and not taken during the study.

Nebulized short-acting beta ₂ -agonists	6 hours
Oral short-acting beta ₂ -agonists	6 hours
Inhaled short-acting anticholinergics	6 hours
Inhaled long-acting anticholinergics	24 hours
Leukotriene modifiers	4 weeks
Inhaled long-acting beta ₂ -agonists	4 weeks
Theophylline products	48 hours
Oral long-acting beta ₂ -agonists	4 weeks
Inhaled corticosteroids	4 weeks
Inhaled corticosteroid/ Inhaled long-acting beta ₂ -agonist combination products	4 weeks
Oral corticosteroids	4 weeks ^{1,2}
Parenteral corticosteroids	4 weeks ²
Inhaled cromolyn sodium or nedocromil	4 weeks
1. Any subject who has received oral corticosteroid treatment for any reason for 2 months or longer must have discontinued use for at least 6 months prior to Visit 1.	
2. A subject must not have had two courses of oral or parenteral corticosteroids for any reason in the 6 months prior to Visit 1	

Section 5.2.2 Exclusion Criteria, No. 6. Concurrent MedicationsOriginal Text

Concurrent use of any of the following medications that may affect the course of asthma or interact with sympathomimetic amines will not be allowed. Specifically:

- beta blockers
- polycyclic antidepressants
- monoamine oxidase inhibitors
- phenobarbital
- rifampin

NOTE: Regular use of short-acting nasal decongestants and/or other intranasal medications for the treatment of rhinitis is allowed.

Amended Text

Concurrent use of any of the following medications that may affect the course of asthma or interact with sympathomimetic amines will not be allowed. Specifically:

- beta blockers
- polycyclic antidepressants
- monoamine oxidase inhibitors
- phenobarbital
- rifampin

NOTE: Regular use of short-acting nasal decongestants is allowed. Other intranasal medications including antihistamines and intranasal corticosteroids for the treatment of rhinitis are also allowed. Topical hydrocortisone cream or ointment (1% or less) is also allowed.

Section 5.2.2 Exclusion Criteria, No. 9. Respiratory Tract InfectionOriginal Text

The subject has a respiratory infection that is suspected or diagnosed within 4 weeks immediately preceding Visit 1 or during the period from Visit 1 to Visit 6. The subject may be re-screened one time. Rescreening must be no sooner than 4 weeks following resolution of any suspected or diagnosed respiratory infection (whether treated or not).

Amended Text

The subject has a respiratory infection that is suspected or diagnosed within 4 weeks immediately preceding Visit 1 or during the period from Visit 1 to **Visit 2**. The subject may be re-screened one time. Rescreening must be no sooner than 4 weeks following resolution of any suspected or diagnosed respiratory infection (whether treated or not).

Section 5.2.2 Exclusion Criteria, No. 10. Antibiotic UsageOriginal Text

The subject used an antibiotic (or other medication) for treatment of a suspected or diagnosed upper or lower respiratory tract infection within 4 weeks of Visit 1 or during the periods from Visit 1 to Visit 6. The subject may be re-screened one time. Antibiotics for other infections or acne are permitted.

Amended Text

The subject used an antibiotic (or other medication) for treatment of a suspected or diagnosed upper or lower respiratory tract infection within 4 weeks of Visit 1 or during the periods from Visit 1 to **Visit 2**. The subject may be re-screened one time. Antibiotics for other infections or acne are permitted.

Section 6 Study Assessments and ProceduresOriginal Text

The Time and Events Schedule details the timeframe in which visits should occur and the procedures to be performed at each study visit (see Appendix 1, Time and Events Table).

All visits (when clinic FEV₁ is performed) should start between 6 AM and 11 AM. Subjects should withhold double-blind study medication on the mornings of clinic visits. If rescue albuterol or ipratropium has been used within 6 hours of spirometry, then the visit must be rescheduled (see Section 6.5.1.2, Clinical FEV₁).

Amended Text

The Time and Events Schedule details the timeframe in which visits should occur and the procedures to be performed at each study visit (see Appendix 1, Time and Events Table).

All visits (when clinic FEV₁ is performed) should start between 6 AM and 11 AM.

- During the open-label periods, subjects should withhold short-acting β_2 -agonist and ipratropium bromide medication(s) for at least 6 hours prior to spirometry.
- Subjects should withhold double-blind study medication on the mornings of clinic visits, as well as ipratropium (and albuterol) within 6 hours of spirometry.

Visits may be rescheduled once. See Section 6.5.1.2. Clinical FEV₁.

Section 6.2.1 Screening Visit (Visit 1)

Original Text

Re-Screening: If a subject does not meet the Screening (Visit 1) inclusion criteria based upon FEV₁ percent predicted or reversibility, the subject may be rescheduled once to conduct the Visit 1 PFTs again. (See Section 5.2.1, Inclusion Criteria). If a subject does not meet the Screening (Visit 1) inclusion criteria based upon FEV₁ percent predicted or reversibility the subject must wait at least 48 hours before returning to the site for re-screening. If the subject meets the PFT entry criteria on the second attempt, then **all** other Visit 1 procedures should be performed on this date.

If methacholine challenge testing is performed and a PC₂₀ of <8mg/ml is obtained, then all other Visit 1 procedures should be performed on the date MCT is performed.

Amended Text (no other text/paragraphs revised)

Re-Screening: If a subject does not meet the Screening (Visit 1) inclusion criteria based upon FEV₁ percent predicted or reversibility, the subject may be rescheduled once **within one week** to conduct the Visit 1 PFTs again (see Section 5.2.1, Inclusion Criteria). The subject must wait at least 48 hours before returning to the site to repeat pulmonary function testing for FEV₁ percent predicted or reversibility and the conduct of other Visit 1 procedures.

If a subject is required to be re-screened for reasons other than failure to achieve criteria for FEV₁ percent predicted or reversibility, historical reversibility obtained at Visit 1 is acceptable to allow the subject to participate, if all other required inclusion and exclusion criteria are met.

If methacholine challenge testing is performed and a PC₂₀ of <8mg/ml is obtained within 2 weeks, adverse events reported and medication use must be recorded. If methacholine challenge testing is performed more than 2 weeks following Visit 1, then all other Visit 1 procedures should be performed on the date MCT is performed.

Section 6.2.2 Visit 2 (Open-Label Treatment Period 1 – Albuterol)

Original Text

NOTE: A subject who experiences an exacerbation between Visit 1 and Visit 6 may be re-screened one time. No subject may experience more than 1 exacerbation between Visit 1 and Visit 6 and remain in the study. Any subject who experiences an exacerbation at or following Visit 6 must be discontinued from the study.

Visit 2 will be conducted after the pharmacogenetic testing has been determined. This should not be greater than 4 weeks $\pm$ 2 days after Visit 1.

The following assessments/procedures will be performed at Visit 2:

- Adverse event assessment (study participation related events only)
- Concomitant medication assessment
- Urine pregnancy test for all females of childbearing potential
- Clinic FEV1
- Dispense peak flow meter
- Dispense diary card
- Dispense open-label study medication (albuterol)

Amended Text

NOTE: No subject may experience more than one exacerbation between Visit 2 and Visit 6 and remain in the study. Any subject who experiences an exacerbation at or following Visit 6 must be discontinued from the study. See Section 6.4.5. Asthma Exacerbations.

Visit 2 will be conducted after the pharmacogenetic testing has been determined. This should not be greater than 4 weeks +2 days after Visit 1.

The following assessments/procedures will be performed at Visit 2:

- Adverse event assessment (study participation related events only)
- Concomitant medication assessment
- Urine pregnancy test for all females of childbearing potential
- Clinic FEV1
- Assess continuation criterion
- Dispense peak flow meter
- Dispense diary card
- Dispense open-label study medication (albuterol)

Section 6.2.3 Visit 3

Original Text

Visit 3 will be conducted 4 weeks $\pm$ 2 days after Visit 2.

The following assessments/procedures will be performed at Visit 3:

- Adverse event assessment
- Concomitant medication assessment

- Clinic FEV1
- Assess continuation criteria
- Collect and review diary card
- Collect study medication
- Dispense diary card
- Dispense open-label study medication (albuterol)

Amended Text

Visit 3 will be conducted 4 weeks ± 2 days after Visit 2.

The following assessments/procedures will be performed at Visit 3:

- Adverse event assessment
- Concomitant medication assessment
- Clinic FEV1
- Assess continuation criteria
- Collect and review diary card
- Collect study medication
- Calculate PEF Stability Limit
- Dispense diary card
- Dispense open-label study medication (albuterol)

Section 6.2.11 Visit 11 (Washout Period)

Original Text

Visit 11 will be conducted 2 weeks ± 2 days after Visit 10.

The following assessments/procedures will be performed at Visit 11:

- Adverse event assessment
- Concomitant medication assessment
- Urine pregnancy test for all females of childbearing potential
- Clinic FEV1
- Collect study medication
- Collect and review diary card

Amended Text

Visit 11 will be conducted 2 weeks $\pm$ 2 days after Visit 10.

The following assessments/procedures will be performed at Visit 11:

- Adverse event assessment
- Concomitant medication assessment
- Urine pregnancy test for all females of childbearing potential
- Clinic FEV₁
- Collect study medication
- Collect and review diary card

At completion of this visit, each subject will be provided with instructions on continued self-monitoring of pulmonary function, medications, and timely communication with a healthcare provider to help assure informed management of his/her asthma.

Section 6.2.12 Premature Discontinuation VisitOriginal Text

The following assessments/procedures will be performed at the Premature Discontinuation visit:

- Physical examination (results recorded in source documents only, unless there is a clinically significant change from baseline)
- Adverse event assessment
- Concomitant medication assessment
- Vital signs (blood pressure and pulse)
- Urine pregnancy test for all females of childbearing potential
- Clinic FEV₁
- Collect and review diary card
- Collect study medication.

Amended Text

The following assessments/procedures will be performed at a **Premature Discontinuation visit that may occur during the open-label period(s), double-blind treatment period, or washout period:**

- Physical examination (results recorded in source documents only, unless there is a clinically significant change from baseline)
- Adverse event assessment
- Concomitant medication assessment
- Vital signs (blood pressure and pulse)
- Urine pregnancy test for all females of childbearing potential
- Clinic FEV1
- Collect and review diary card
- Collect study medication.

At completion of this visit, each subject will be provided with instructions on continued self-monitoring of pulmonary function, medications, and timely communication with a healthcare provider to help assure informed management of his/her asthma. See Section 9.2.1 Subject Withdrawal from Study for further details related to medications prescribed, unfavourable changes noted during a physical examination, and adverse events or SAEs reported during the premature discontinuation visit.

Section 6.4.3 Vital signs

Original Text

Blood pressure (systolic and diastolic) and pulse will be determined with the subject in the sitting position. The subject must be seated at least 5 minutes before the measurements are taken. Blood pressure and pulse will be taken at Visit 1 and Visit 10, but should be taken prior to any pulmonary function testing.

Amended Text (no other text/paragraphs revised)

Blood pressure (systolic and diastolic) and pulse will be determined with the subject in the sitting position. The subject must be seated at least 5 minutes before the measurements are taken. Blood pressure and pulse will be taken at Visit 1 and Visit 10 **(or Premature Discontinuation)**, prior to any pulmonary function testing.

Section 6.4.5 Asthma exacerbations

Original Text

A clinical exacerbation is defined as worsening asthma requiring emergency intervention, hospitalization, or treatment with asthma medication in addition to those allowed by the protocol. For the purposes of this study, a subject will be withdrawn due to worsening asthma if they experience a clinical asthma exacerbation during the double blind treatment period. Worsening asthma should be treated as deemed necessary by the investigator and all treatments should be recorded in the CRF.

If a subject is withdrawn for a clinical exacerbation based upon the above definition, the reason for withdrawal will be based upon “Exacerbation”.

For subjects who are in the double-blind treatment period, asthma exacerbation data will be recorded in the source documents and the Asthma Exacerbation section of the CRF. If the exacerbation meets the definition of and SAE (Section 10.2, Definition of a SAE), then the exacerbation must also be collected as an SAE. For subjects who enter the run-in period who are not randomized to blinded study drug, worsening asthma data will be recorded only in the CRF.

A subject may experience an exacerbation one time during the open-label treatment periods. If a subject experiences an exacerbation during the open-label treatment period, they will need to be re-screened and all Visit 1 procedures should be repeated, except for the blood draw. If a subject experiences more than one exacerbation during the open-label treatment period, the subject must be discontinued. In addition, the investigator may discontinue a subject at any time, if the investigator believes that the subject is at risk by remaining in the study.

Amended Text

A clinical exacerbation is defined as worsening asthma requiring emergency intervention, hospitalization, or treatment with asthma medication in addition to those allowed by the protocol. If a subject is withdrawn for a clinical exacerbation based upon the above definition, the reason for withdrawal noted in the CRF should be recorded as “Exacerbation”.

Subjects who experience an exacerbation during the screening period between Visit 1 and Visit 2 must be discontinued.

For the purposes of this study, a subject may experience one exacerbation during the 16 week combined open-label periods that is successfully treated within ten days and remain in the study, predicated on consultation with GSK. If a subject experiences more than one exacerbation during the open-label treatment periods, the subject must be discontinued.

A subject will be withdrawn due to worsening asthma if he/she experiences an exacerbation during the double-blind treatment period or the washout period. In addition, the investigator may discontinue a subject at any time, if the investigator believes that the subject is at risk by remaining in the study.

For subjects who enter the screening period between Visit 1 and Visit 2 and experience an exacerbation, worsening asthma data will be recorded only in the source documents. For all subjects who are in the open-label, double-blind, and washout treatment periods, asthma exacerbation data will be recorded in the source documents and the Asthma Exacerbation section of the CRF.

If an exacerbation meets the definition of a SAE (Section 10.2 Definition of a SAE), worsening asthma data must be collected as a SAE for all subjects who sign an informed consent and participate in this study.

Section 6.5.1.1 PEF

Original Text

The subject will be counselled on the usefulness of the peak flow meter as a means of monitoring his/her asthma status. Subjects will be informed of their AM PEF Stability Limit and educated to be alert to a pattern of **consistently decreasing PEF** as a warning of possible worsening of asthma/asthma exacerbation. Subjects will be instructed to call the investigator if such a profile of declining PEF is observed, or if their PEF falls below the AM PEF Stability Limit for 2 or more consecutive days. If such a pattern is observed, it is not a protocol-defined exacerbation unless it meets the definition in Section 11.8.3.

Amended Text (reference number revised, no other text/paragraphs revised)

The subject will be counselled on the usefulness of the peak flow meter as a means of monitoring his/her asthma status. Subjects will be informed of their AM PEF Stability Limit and educated to be alert to a pattern of **consistently decreasing PEF** as a warning of possible worsening of asthma/asthma exacerbation. Subjects will be instructed to call the investigator if such a profile of declining PEF is observed, or if their PEF falls below the AM PEF Stability Limit for 2 or more consecutive days. If such a pattern is observed, it is not a protocol-defined exacerbation unless it meets the definition in **Section 6.4.5. Asthma Exacerbations**

Section 6.5.1.2 Clinic FEV₁

Original Text

It is the responsibility of the investigator, to print a hard copy of each measurement and review the results to ensure that the subject meets all inclusion/randomization/continuation criteria. The hard copy of each measurement will be maintained in the subject's study file.

Amended Text (no other text/paragraphs revised)

It is the responsibility of the investigator (**or designee**), to print a hard copy of each measurement and review the results to ensure that the subject meets all inclusion criteria, continuation criteria and randomization criteria. The hard copy of each measurement will be maintained in the subject's study file.

Reversibility assessment

Original Text

Upon confirming at Visit 1 that no asthma medications have been used for the required intervals specified in Section 5.2.2, subjects pulmonary reversibility will be assessed. The subject must demonstrate a $\geq 12\%$ improvement in FEV₁ in order to qualify for participation in the study.

Reversibility will be assessed after the subject self-administers 2-4 inhalations or 1-2 nebulized inhalation of albuterol (2 puffs = 1 nebule). The FEV₁ will then be repeated, in triplicate, within 30 minutes. Reversibility should be calculated as follows:

$$\% \text{ Reversibility} = \frac{\text{FEV}_1 \text{ after albuterol MDI} - \text{FEV}_1 \text{ before albuterol MDI}}{\text{FEV}_1 \text{ before albuterol}} \times 100$$

Reversibility documentation will be maintained in the CRF.

Amended Text

Documentation of historical reversibility within one year of Visit 1 demonstrating an increase in FEV₁ of ≥12% and 200ml over baseline is acceptable and will preclude the requirement for reversibility testing the Visit 1.

If documentation of historical reversibility within one year of Visit 1 is not available, the subject must demonstrate a ≥ 12% improvement in FEV₁ in order to qualify for participation in the study.

Upon confirming at Visit 1 that no asthma medications have been used for the required intervals specified in Exclusion Criteria Section 5.2.2, pulmonary reversibility will be assessed after the subject self-administers 2-4 inhalations or 1-2 nebulized inhalation of albuterol (2 puffs = 1 nebule). The FEV₁ will then be repeated, in triplicate, within 30 minutes. Reversibility should be calculated as follows:

$$\% \text{ Reversibility} = \frac{\text{FEV}_1 \text{ after albuterol MDI} - \text{FEV}_1 \text{ before albuterol MDI}}{\text{FEV}_1 \text{ before albuterol}} \times 100$$

Reversibility documentation will be maintained in the CRF.

Section 6.5.1.3 Methacholine Challenge Tests

Original Text

See Appendix 5: Methacholine Challenge Dilution schedule.

Amended Text (no other text/paragraphs revised)

See Appendix 5: Methacholine Challenge Dilution schedule. **Also refer to the Manual of Procedures that is provided to each investigator if a methacholine challenge test is performed during the conduct of this study.**

Section 6.5.1.4 Maximum Albuterol Dose Assessment (MADR)

Original Text

The bronchodilator response to albuterol has been found to vary by genotype at the B16 locus, and the maximum bronchodilator effect of albuterol may become attenuated during prolonged use (tachyphylaxis) [Martinez, 1997; Tan, 1997]. It is therefore appropriate to take measurements of the maximum albuterol dose response (**MADR**) in order to determine whether its magnitude varies by 2-adrenergic receptor genotype during prolonged albuterol use. Maximum albuterol dose response (MADR) will be defined as the best FEV₁ recorded after four, six, or eight puffs of albuterol. To obtain the MADR, each subject will perform baseline spirometry and will then be administered four puffs of albuterol. Fifteen minutes following the administration of the albuterol, the subject will again perform spirometry, followed by two additional puffs of albuterol, for a cumulative dose of six puffs. After fifteen minutes, spirometry will be repeated once more, and the current FEV₁ value compared with the FEV₁ obtained after the first four puffs. If the relative change in FEV₁ is 5% or less, the procedure will be stopped; if the relative change is more than 5%, then two additional puffs of albuterol will be administered, for a cumulative dose of eight puffs, followed by a final spirometry assessment.

Amended Text (no other text/paragraphs revised)

The bronchodilator response to albuterol has been found to vary by genotype at the B16 locus, and the maximum bronchodilator effect of albuterol may become attenuated during prolonged use (tachyphylaxis) [Martinez, 1997; Tan, 1997]. It is therefore appropriate to take measurements of the maximum albuterol dose response (**MADR**) in order to determine whether its magnitude varies by 2-adrenergic receptor genotype during prolonged albuterol use. Maximum albuterol dose response (MADR) will be defined as the best FEV₁ recorded after four, six, or eight puffs of albuterol.

To obtain the MADR, each subject will perform baseline spirometry and will then be administered four puffs of albuterol. Fifteen minutes following the administration of the albuterol, the subject will again perform spirometry, followed by two additional puffs of albuterol, for a cumulative dose of six puffs. After fifteen minutes, spirometry will be repeated once more, and the current FEV₁ value compared with the FEV₁ obtained after the first four puffs. If the relative change in FEV₁ is 5% or less, the procedure will be stopped; if the relative change is more than 5%, then two additional puffs of albuterol will be administered, for a cumulative dose of eight puffs, followed by a final spirometry assessment **15 minutes later**.

Section 6.5.1.5 Continuation Assessment

Original Text

Subjects will be required to meet the following criteria at Visits 3, 4 and 5 to continue in the study:

A best FEV₁ $\geq$ 70% of predicted **and** <56 puffs per week of rescue medication.

The baseline FEV₁ value for the blinded treatment period will be the pre-medication FEV₁ measurement (best of three attempts) obtained at Visit 6 (**Randomization** Visit). At Visit 6, subjects will be required to meet continuation criteria as follows:

A best Visit 6 FEV₁ $\geq$ 70% of predicted **and** <56 puffs per week of rescue medication.

At study completion, each subject will be provided with instructions on continued self-monitoring of pulmonary function, medications, and timely communication with a healthcare provider to help assure informed management of his/her asthma symptoms.

Amended Text

Subjects will be required to meet the following criterion at Visit 2 to continue in the study:

A best FEV₁ $\geq$ 70% of predicted.

Subjects will also be required to meet the following criteria at **Visits 3, 4, 5 and 6** to continue in the study:

A best FEV₁ $\geq$ 70% of predicted **and** <56 puffs per week of r medication.

Last paragraph deleted. Text is now located in Section 6.2.11 Visit 11 (Washout Period) and Section 6.2.12. Premature Discontinuation Visit.

Section 6.5.2.5 Albuterol use during the open-label, double-blind and washout periods

Original Text

Section 6.5.2.6 Supplemental albuterol use

In the event that asthma symptoms respond incompletely to ipratropium bromide, albuterol will be used as a superceding rescue medication. The subject will be reminded that for subsequent acute asthma symptoms they should continue to take ipratropium bromide first, as the rescue medication.

All use of supplemental albuterol will be recorded by the subject/parent/caregiver on the diary card.

The subject will be reminded that if the requirement for supplemental rescue medication increases markedly or if their requirement equals or exceeds a total of 12 puffs per day (daytime and nighttime combined) for 2 out of 7 consecutive days they should contact the study site.

Amended Text

Section 6.5.2.5 Albuterol use in the open-label, double-blind and washout periods

All use of open-label treatment with albuterol will be recorded by the subject or parent/caregiver on the diary card.

Subjects will receive open-label albuterol 90mcg for prn use to treat acute asthma symptoms during the first open-label treatment period.

During the second open-label period, in the event that asthma symptoms respond incompletely to ipratropium bromide, albuterol will be used as a superceding treatment medication. It will also be used as a superceding relief medication during the randomization and washout periods. The subject will be reminded that for subsequent acute asthma symptoms they should continue to take ipratropium bromide first, as medication for acute relief during the second open-label period and during the randomization and washout periods.

Subjects will be reminded that if their requirement for albuterol during the first open-label period or supplemental medication during the second open-label period and/or during the randomization and washout periods increases markedly or if their requirement equals or exceeds a total of 12 puffs per day (daytime and nighttime combined) for 2 out of 7 consecutive days they should contact the study site.

Section 6.5.2.6 Ipratropium bromide use

Original Text

Section 6.5.2.5 Supplemental ipratropium bromide use

All use of supplemental ipratropium bromide will be recorded by the subject/parent/caregiver on the diary card.

Subjects will receive open-label Atrovent (ipratropium bromide) 18mcg to be used as needed to relieve acute asthma symptoms for 16 weeks during the double-blind treatment period. Subjects will also receive open-label albuterol 90mcg for prn use in the event that asthma symptoms respond incompletely to ipratropium bromide, in which case albuterol will be used as a superceding rescue medication.

The subject will be reminded that if the requirement for supplemental rescue medication increases markedly or if their requirement equals or exceeds a total of 12 puffs per day (daytime and nighttime combined) for 2 out of 7 consecutive days they should contact the study site.

Amended Text**Section 6.5.2.6 Ipratropium bromide use in the open-label, double-blind and washout periods**

All use of open-label ipratropium bromide will be recorded by the subject or parent/caregiver on the diary card.

Subjects will receive open-label Atrovent (ipratropium bromide) 18mcg to be used as needed to treat acute asthma symptoms for 8 weeks during the second open-label period prior to randomization.

Subjects will also receive open-label Atrovent (ipratropium bromide) 18mcg to be used as need to relieve acute asthma symptoms for 16 weeks during the double-blind treatment period. In addition, subjects will receive open-label albuterol 90mcg for prn use in the event that asthma symptoms respond incompletely to ipratropium bromide during the second open-label period, or during the double-blind and washout periods, in which case albuterol will be used as a superceding medication.

Subjects will be reminded that if their requirement for Atrovent (ipratropium bromide) during the second open-label period or during the double-blind and washout periods increases markedly or if their requirement equals or exceeds a total of 12 puffs per day (daytime and nighttime combined) for 2 out of 7 consecutive days they should contact the study site.

Section 7.2 Dosage and AdministrationOriginal Text

Subjects will inhale the first dose of double-blind study medication in the clinic on the day of randomization (Visit 6). Subjects will receive a **DISKUS** inhaler. The subject will be instructed to administer one inhalation from the inhaler each morning and one inhalation from the inhaler each evening, approximately 12 hours apart, after obtaining their morning and evening PEF measurements. Each subject should be advised to adhere to this dosing regimen throughout the study. All eligible subjects will be given open-label ipratropium bromide 18mcg for use only as needed throughout the trial. Subjects will also receive open-label albuterol 90mcg for prn use in the event that asthma symptoms respond incompletely to ipratropium bromide, in which case albuterol would be used as a superceding rescue medication.

Amended Text (no other text/paragraphs revised)

Subjects will inhale the first dose of double-blind study medication in the clinic on the day of randomization (Visit 6). Subjects will receive a **DISKUS** inhaler. The subject will be instructed to administer one inhalation from the inhaler each morning and one inhalation from the inhaler each evening, approximately 12 hours apart, after obtaining their morning and evening PEF measurements. Each subject should be advised to adhere to this dosing regimen throughout the study.

All eligible subjects will be given open-label ipratropium bromide 18mcg for use only as needed throughout the **double-blind period** of the trial. Subjects will also receive open-label albuterol 90mcg for prn use in the event that asthma symptoms respond incompletely to ipratropium bromide, in which case albuterol would be used as a superceding medication for acute relief.

All subjects who complete Visit 10 of the double-blind treatment period will be given open-label ipratropium bromide 18mcg for use during the washout period. Subjects will also receive open-label albuterol 90mcg for prn use in the event that asthma symptoms respond incompletely to ipratropium bromide, in which case albuterol would be used as a superceding medication.

Section 8.1 Permitted Medications

Original Text

All concomitant medications taken during the study will be recorded in the CRF.

Amended Text

Short acting beta₂-agonist medication(s) and any other anti-asthma medications taken 4 weeks prior to Visit 1 will be recorded in the CRF. All concomitant medications and any anti-asthma medications other than study medications taken during the study will be recorded in the CRF.

Section 8.2 Prohibited Medications

Original Text

Refer to Section 5.2.2., Exclusion Criteria, for a list of prohibited medications, including antibiotics, concurrent medications that may affect the course of asthma or interact with sympathomimetic amines, systemic corticosteroids, asthma medications other than study drugs taken during the study, immunosuppressive medications, and investigational medications other than those used in this study.

- In addition, ipratropium bromide and albuterol should be withheld for at least 6 hours prior to pulmonary function testing.

Amended Text

Concurrent use of any of the following medications that may affect the course of asthma or interact with sympathomimetic amines will not be allowed. Specifically:

- beta blockers
- polycyclic antidepressants
- monoamine oxidase inhibitors
- phenobarbital

- rifampin
- methotrexate, gold, cyclosporine and azathioprine
- ritonavir

Also see Section 5.2.2. Exclusion Criteria for anti-asthma medications that must not be taken during the conduct of this study. Exception: a short course of an oral corticosteroid is allowed for the treatment of an exacerbation during the open-label period.

Section 9.1 Subject Completion

Original Text

A subject who completes the 16-week double-blind treatment period and undergoes all Visit 10 evaluations has completed the study. Following Visit 11, alternative asthma medication will be prescribed, and the subject will be followed as judged to be medically appropriate by the investigator.

Amended Text

A subject who completes the 16-week double-blind treatment period and undergoes all Visit **11** evaluations has completed the study. **At the conclusion of Visit 11, each subject will be provided with instructions on continued self-monitoring of pulmonary function, medications, and timely communication with a healthcare provider to help assure informed management of his/her asthma.**

Section 9.2.1 Subject Withdrawal from Study

Original Text

A subject who takes double-blinded study drug, but either does not complete the 16 week treatment period or does not complete Visit 10 evaluations has **prematurely discontinued**. Prematurely discontinued subjects, who have been correctly randomized according to the Inclusion/Exclusion criteria, will not be replaced.

Subject withdrawal from the study is also required, and Discontinuation Visit procedures performed, when:

- A subject is significantly non-compliant with the requirements of the protocol
- A subject becomes pregnant
- A subject has an adverse event that would, in the investigator's judgement, make continued participation in the study an unacceptable risk
- The treatment blind is broken for a subject
- GlaxoSmithKline discontinues the study

- The subject experiences an asthma exacerbation as defined by the protocol (see Section 6.4.5 Asthma exacerbations)

A subject may voluntarily discontinue participation in this study at any time. The investigator may also, at his/her discretion, discontinue the subject from participating in this study at any time. If a subject is prematurely discontinued from participation in the study for any reason, the investigator must make every effort to perform all evaluations specified for the Discontinuation Visit (see Appendix 1, Time and Events Table). Following these procedures, alternative asthma medication will be prescribed, and the subject will be followed as judged to be medically appropriate by the investigator.

NOTE: Medications (asthma **and** non-asthma) that are prescribed at the last clinic visit will only be recorded in the subject's source documents and **not** recorded on the subject's CRF **unless** the medication is administered prior to the completion of all study procedures at the last clinic visit.

Any clinically significant adverse events or clinically significant unfavorable changes on physical examination observed during the Discontinuation Visit will necessitate that the subject be followed or treated until satisfactory resolution occurs.

In the event that a subject is prematurely discontinued from the study at any time due to an AE (as defined in Section 10.1.), or SAE (as defined in Section 10.2.), a Discontinuation Visit must be performed (see Appendix 1, Time and Events Table).

Amended Text (New text for screening period, open-label period, double-blind period and washout period)

Screening period

Subject withdrawal from the screening period (Visit 1 to Visit 2) of the study is required, when:

- A subject is significantly non-compliant with the requirements of the protocol
- A subject becomes pregnant
- A subject has an adverse event that would, in the investigator's judgement, make continued participation in the study an unacceptable risk
- The subject experiences an asthma exacerbation as defined by the protocol (see Section 6.4.5 Asthma exacerbations)
- The number of subjects per genotype required for each treatment group is met.
- GlaxoSmithKline discontinues the study.

Open-label period

A subject who takes open-label study drug, but either does not complete the 16 week open-label treatment period or does not complete Visit 6 evaluations will be considered prematurely **discontinued**.

Subject withdrawal from the open-label period of the study is required, and discontinuation procedures are performed, when:

- A subject is significantly non-compliant with the requirements of the protocol
- A subject becomes pregnant
- A subject has an adverse event that would, in the investigator's judgement, make continued participation in the study an unacceptable risk
- The subject experiences more than one asthma exacerbation as defined by the protocol (see Section 6.4.5 Asthma exacerbations)
- The number of subjects per genotype required for each treatment group is met.
- GlaxoSmithKline discontinues the study.

Double-blind Period

A subject who takes double-blinded study drug, but either does not complete the 16 week treatment period or does not complete Visit 10 evaluations will be considered **prematurely discontinued**. Prematurely discontinued subjects, who have been correctly randomized according to the Inclusion/Exclusion criteria, will not be replaced.

Subject withdrawal from the study is required, and Discontinuation Visit procedures are performed, when:

- ☐ A subject is significantly non-compliant with the requirements of the protocol
- A subject becomes pregnant
- A subject has an adverse event that would, in the investigator's judgement, make continued participation in the study an unacceptable risk
- The treatment blind is broken for a subject
- The subject experiences an asthma exacerbation as defined by the protocol (see Section 6.4.5 Asthma exacerbations)
- GlaxoSmithKline discontinues the study.

Washout Period

A subject who takes study drug during the washout period, but either does not complete the 2 week treatment period or does not complete Visit 11 evaluations will be considered **prematurely discontinued**.

Subject withdrawal from the study is required, and Discontinuation Visit procedures are performed, when:

- A subject is significantly non-compliant with the requirements of the protocol
- A subject becomes pregnant

- A subject has an adverse event that would, in the investigator's judgement, make continued participation in the study an unacceptable risk
- The treatment blind is broken for a subject
- The subject experiences an asthma exacerbation as defined by the protocol (see Section 6.4.5 Asthma exacerbations)
- GlaxoSmithKline discontinues the study.

A subject may voluntarily discontinue participation in this study at any time. The investigator may also, at his/her discretion, discontinue the subject from participating in this study at any time. If a subject is prematurely discontinued from participation in the study for any reason, the investigator must make every effort to perform all evaluations specified for the Discontinuation Visit. (See Section 6.2.12 Premature Discontinuation Visit for discontinuation procedures.) At the conclusion of the Discontinuation Visit, each subject will be provided with instructions on continued self-monitoring of pulmonary function, medications, and timely communication with a healthcare provider to help assure informed management of his/her asthma.

NOTE: Medications (asthma **and** non-asthma) that are prescribed at the last clinic visit will only be recorded in the subject's source documents and **not** recorded on the subject's CRF **unless** the medication is administered prior to the completion of all study procedures at the last clinic visit.

Any clinically significant adverse events or clinically significant unfavorable changes on physical examination observed during a discontinuation visit will necessitate that the subject be followed or treated until satisfactory resolution occurs.

In the event that a subject is prematurely discontinued from the study at any time due to an AE as defined in Section 10.1., Definition of an AE or SAE as defined in Section 10.2., Definition of a SAE, a Discontinuation Visit must be performed.

Section 9.3 Screen and Open-Label Failures

Original Text

A subject who has at least one study procedure performed (in addition to signing a consent form), and is assigned a subject number (see Section 7.5.1), but is not randomized is classified as having **failed screening**. The following information on subjects who fail screening will be collected in the CRF:

- Demographic information (including race, age and gender)
- Reason subject was not randomized
- Pulmonary Function Tests
- Reversibility assessment
- Any adverse events/SAEs that occur during the screening and open-label periods

Amended Text

A subject who has at least one study procedure performed (in addition to signing a consent form), and is assigned a subject number (see Section 7.5.1, Assignment of Study Number), but does not participate in the open-label period(s) is classified as having **failed screening (Visit 1). The following information will be collected in the CRF on subjects who fail at the Screening Visit (Visit 1) or any time prior to Visit 2. The following information will also be collected in the CRF on subjects who fail at Visit 2 or any time during the open-label periods prior to Visit 6: :**

- Demographic information (including race, age and gender)
- **Inclusion/exclusion criteria**
- **Duration of asthma**
- **Asthma concomitant medications**
- **Non-asthma concomitant medications**
- Reversibility assessment
- Pulmonary function tests **(including MADR, if applicable)**
- **Continuation criteria, if applicable**
- **Reason subject was a screening or open-label failure**
- **Pharmacogenetic (PGx) information**
- **Investigational product information**
- **Asthma exacerbation data**
- Any adverse events/SAEs that occur during the screening and open-label periods
- **Investigator comments**
- **Investigator signature**
- **Diary cards, if applicable**

Section 11.2.2 Other Comparisons of InterestOriginal Text

In order to demonstrate assay sensitivity, assessment of the change from the screening FEV₁ to the endpoint FEV₁ will be made for each treatment. Also, to address concerns regarding possible selection bias in the two prevalent genotypes, Gly/Gly and Arg/Gly, population demographic characteristics and lung function will be summarized within each of these genotypes, both for the patients selected for enrollment in the study and for those not selected for enrollment.

Amended Text (no other text revised)

In order to demonstrate assay sensitivity, comparisons of the change from the screening FEV₁ to the endpoint FEV₁ will be made for each pair of genotypes within each treatment group. Also, to address concerns regarding possible selection bias in the two prevalent genotypes, Gly/Gly and Arg/Gly, population demographic characteristics and lung function will be summarized within each of these genotypes, **for screening failures, open-label period failures, and subjects who are randomized.**

Section 11.4 Sample Size Considerations

Original Text

It is anticipated that 540 subjects will be enrolled at approximately 60-80 investigational sites to achieve an analysis population of approximately 492 evaluable subjects (82 evaluable subjects per treatment arm per genotype). A 10% drop-out rate is assumed after randomization based on the fact that the asthmatic population is stable and mild. Assuming that 15% of the general population has the Arg/Arg genotype, it is anticipated that in order to recruit 90 subjects in each of the genotypic categories, a minimum of 1,200 subjects will need to be screened. Allowing for exclusions, refusals to participate and withdrawals, as many as 1320 subjects may need to be screened.

Amended Text (number in last sentence revised)

It is anticipated that 540 subjects will be enrolled at approximately 60-80 investigational sites to achieve an analysis population of approximately 492 evaluable subjects (82 evaluable subjects per treatment arm per genotype). A 10% drop-out rate is assumed after randomization based on the fact that the asthmatic population is stable and mild. Assuming that 15% of the general population has the Arg/Arg genotype, it is anticipated that in order to recruit 90 subjects in each of the genotypic categories, a minimum of 1,200 subjects will need to be screened. Allowing for exclusions, refusals to participate and withdrawals, **approximately 1840** subjects may need to be screened.

Section 14.2 Appendix 2: Study Schematic Diagram

Original Text

Beta₂-agonist only asthma patients

Amended Text

Short-acting beta₂-agonist only asthma patients

Section 14.5 Methacholine Challenge Dilution Schedule

Original Text

Appendix 5: Methacholine Challenge Dilution schedule

Before conducting the test, the vials of reconstituted methacholine should be removed from the refrigerator for at least 30 minutes to allow them to warm to room temperature. Since the temperature of the solution can affect the output of the nebulizer, they should not be administered until they are at room temperature. The vials of methacholine solution should be arranged in the order of administration starting with diluent and increasing to 16.0 mg/ml.

Amended Text

Appendix 5: Methacholine Challenge Dilution schedule

Before conducting the test, the vials of reconstituted methacholine should be removed from the refrigerator for at least 30 minutes to allow them to warm to room temperature. Since the temperature of the solution can affect the output of the nebulizer, they should not be administered until they are at room temperature. The vials of methacholine solution should be arranged in the order of administration starting with diluent and increasing to 16.0 mg/ml. **See the Manual of Procedures for complete instructions on methodology and assessments of a methacholine challenge performed during this study.**

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Retention Category: GRS019

Information Type: Protocol Amendment

Title:	A Randomized, Parallel Group, Double-Blind Comparative Trial Assessing Lung Function and Other Measures of Asthma Control in Adults and Adolescents, at Least 12 Years of Age, with Persistent Asthma, Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B-16 Arg/Gly Genotype and are Treated with Fluticasone Propionate/Salmeterol DISKUS Combination Product 100/50mcg or Salmeterol DISKUS 50mcg BID

Compound Number: CCI18781+GR33343

Effective Date: 16 February 2006

Protocol Amendment Number: 03

Description: Due to lack of availability of future supplies of open-label ipratropium bromide CFC inhalation aerosol 18mcg, each new subject and subjects already participating in the study will be dispensed ipratropium bromide HFA inhalation aerosol 21mcg at a regularly scheduled study visit as determined by depletion of the supply of ipratropium bromide CFC inhalation aerosol 18mcg at each study site.

Subject: Ipratropium bromide 18mcg, Ipratropium bromide 21mcg

Author: [REDACTED] Respiratory MDC, North America

Revision Chronology:

ZM2004/00008/00	2004-JUN-15	Original
ZM2004/00008/01	2004-NOV-17	Amendment No. 1: Includes Update sponsor contact information, removes the limitation that methacholine challenge testing can only be performed on subjects ≥ 18 yrs of age, add that historical PC20 < 8 mg/ml is acceptable, add an exercise-induced bronchospasm exclusion, modify Anti-Asthma Medications time intervals, clarify the use of corticosteroids in the exclusion criteria, add a peanut and soybean food allergy exclusion criterion, add AM PEF stability limits, add requirement to take vital signs during MADR testing, remove Appendix 5 & 7 and to correct

administrative and typographical errors.

ZM2004/00008/02

2005-MAY-20

Amendment No. 2: This amendment includes clarification and revision of the following sections: Protocol Summary, Open-Label Treatment Periods (continuation criteria added at Visit 2); Study Population (number of screened subjects); Section 5. Inclusion Criteria Nos. 3, 6 and 7 regarding pregnancy testing, historical reversibility, and pre-study anti-asthma medication use required for participation; Section 5. Exclusion Criteria Nos. 4, 5, 6, 9, and 10 regarding EIB, prohibited anti-asthma medications, prohibited concurrent medications, respiratory tract infection and antibiotic use; Section 6. Study Assessments, Rescreening (use of historical reversibility), Visit 2 continuation criteria added, premature discontinuation visit (open-label and washout periods, exacerbations (during the open-label periods), methacholine challenge testing (manual), albuterol and ipratropium bromide use (during open-label, randomization, and washout periods); Section 7. Dosage and Administration to include the washout period; Section 8. Concomitant Medications, permitted and prohibited medications to agree with Section 5, inclusion and exclusion criteria; Section 9. Subject Completion to include a discontinuation visit and Withdrawal to include screen and open-label, washout failures (data collection); Section 11. Data Analysis and Statistical Considerations, Other Comparisons of Interest and Sample Size Considerations modified; and corrections of administrative and reference errors.

ZM2004/00008/03

2006-FEB-14

Amendment No. 3: Replacement of the
investigational product open-label
ipratropium bromide CFC inhalation
aerosol 18mcg with ipratropium
bromide HFA inhalation aerosol
21mcg

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ZM2004/00008/03
SFA100062

Sponsor Signatory:

Signature:

Date:

[Redacted Signature]

2/15/06

MD

Vice President, MDC
Respiratory, North America

[Redacted Block]

[Redacted Block]

INVESTIGATOR AGREEMENT PAGE

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

Investigator Name: _____

Investigator Signature

Date

ABBREVIATIONS

CFC	Chlorofluorocarbon
HFA	HFA-134A (1,1,1,2-tetrafluoroethane)

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INTRODUCTION

Amendment 03 applies to all study sites participating in SFA100062.

BACKGROUND

Prior to approval of Amendment 03, the Protocol Summary and Protocol stated that each subject was to receive open-label ipratropium bromide CFC inhalation aerosol 18mcg for relief of acute asthma symptoms at Visit 4 and at all subsequent regularly scheduled visits during his/her participation in the study.

PROTOCOL SUMMARY AND PROTOCOL

Due to lack of availability of future supplies of ipratropium bromide CFC inhalation aerosol 18mcg, each new subject and subjects already participating in the study will receive open-label ipratropium bromide HFA inhalation aerosol 21mcg at a regularly scheduled study visit as determined by depletion of the supply of ipratropium bromide CFC inhalation aerosol 18mcg at each study site.

Sections in the Protocol Summary and Protocol affected by the change in the ipratropium bromide formulation and dose strength dispensed to each subject are as follows:

Protocol Summary

- Open-Label Treatment Periods, bullet 3
- Investigational Product(s)

Protocol

- Section 6.5.2.6, Ipratropium bromide use in the open-label, double-blind treatment and washout periods
- Section 7.1, Description of Investigational Product
- Section 7.2. Dosage and Administration

Division: World Wide Development
Retention Category: GRS019
Information Type: Reporting and Analysis Plan

Title:	Reporting and Analysis Plan for SFA100062: A Randomized, Parallel Group, Double-Blind, Comparative Trial Assessing Lung Function and Other Measures of Asthma Control in Adults and Adolescents, at least 12 Years of Age, with Persistent Asthma, Who Have Either a B16-Arg/Arg, a B16-Gly/Gly or a B-16 Arg/Gly Genotype and are Treated with Fluticasone Propionate/Salmeterol DISKUS Combination Product 100/50mcg or Salmeterol DISKUS 50mcg BID

Compound Number: CCI18781+GR33343

Effective Date: 13-Mar-2007

Description: This document details the planned statistical analyses for SFA100062 in support of the clinical study report.

Identifier/Version Number: RM2005/00799/00

Subject: Genetics, Asthma, Fluticasone propionate/salmeterol, Salmeterol

Author's Name, Title and Functional Area: [REDACTED] Manager Statistics and Programming, Respiratory Medical Development Center

Approved by:

[REDACTED] MD, ScD
Director Clinical Development
Respiratory Medical Development Center

Date

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ABBREVIATIONS**Abbreviation**

ADRB2

AE

AM

ANCOVA

Arg

ATC

AUC

AUC(bl)

BID

CRF

CSR

EM

FEV₁

FSC

GCSP

Gly

GSK

HWE

IDSL

ITT

MADR

Mcg

MedDRA

PC₂₀

PM

PEF

RAP

SAE

SNP

SOC

DefinitionAdrenergic Beta₂ receptor

Adverse event

Morning

Analysis of covariance

Arginine

Anatomical Therapeutic Chemical

Area under the curve

Area under the curve relative to baseline

Bis in die (twice daily)

Case report form

Clinical study report

Expectation-maximization

Forced expiratory volume in 1 second

Fluticasone propionate/salmeterol
combinationGlobal Clinical Safety and
Pharmacovigilance

Glycine

GlaxoSmithKline

Hardy-Weinberg equilibrium

International Data Standards Library

Intent-to-treat

Maximum albuterol dose response

Microgram

Medical Dictionary for Regulatory
ActivitiesProvocative concentration of methacholine
causing a $\geq 20\%$ decrease in FEV₁

Evening

Peak expiratory flow

Reporting and Analysis Plan

Serious adverse event

Single nucleotide polymorphism

System Organ Class

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1. INTRODUCTION

The purpose of this Reporting and Analysis Plan (RAP) is to document the planned analyses that will be conducted for SFA100062 on which the clinical study report (CSR) will be based. All decisions regarding analysis, as defined in this document, have been made prior to unblinding the study database. Any deviations from this RAP will be documented in the CSR and all study results will be included in the CSR. Refer to the protocol (ZM2004/00008/00) and amendments (ZM2004/00008/01), (ZM2004/00008/02) and (ZM2004/00008/03) for more details concerning this study.

2. STUDY OBJECTIVE(S) AND ENDPOINT(S)

2.1. Study Objective(s)

The primary objective of this study is to evaluate lung function as assessed by morning peak expiratory flow (AM PEF) area under the curve (AUC) relative to baseline [AUC(bl)] in subjects who have the B16 Arg/Arg genotype compared with that of subjects who have the B16 Gly/Gly genotype over 16 weeks of treatment with fluticasone propionate/salmeterol combination (FSC) **DISKUS** 100/50 mcg BID.

The secondary objective of this study is to evaluate lung function as assessed by AM PEF AUC(bl) and other measures in other adrenergic beta₂ receptor (*ADRB2*) genotypes in the salmeterol and FSC treatment groups over 16 weeks of treatment.

Other objectives include:

- Evaluation by genotype of lung function as assessed by AM PEF AUC and other measures during the last four weeks of open-label treatment with *prn* albuterol versus that during the last four weeks of open-label treatment with *prn* ipratropium bromide
- Evaluation of maximum albuterol dose response (MADR) by genotype
- Evaluation of lung function as assessed by AM PEF AUC(bl) in other *ADRB2* haplotype pairs in the salmeterol and FSC treatment groups over 16 weeks of treatment
- Evaluation of assay sensitivity
- Evaluation of screen and open-label failures to address concerns regarding possible selection bias in the two prevalent genotypes

2.2. Study Endpoint(s)

The primary measure of efficacy is mean AM PEF change from baseline as characterized by the area under the AM PEF curve relative to baseline AUC(bl) over the 16-week

double-blind treatment period. The primary comparison of interest will be between the Arg/Arg and Gly/Gly genotypes in the FSC treatment group.

Secondary measures of efficacy are mean PM PEF change from baseline and mean forced expiratory volume in one second (FEV₁) change from baseline over the 16-week double-blind treatment period, as characterized by the area under the PM PEF and FEV₁ by-time curves relative to baseline, respectively. Other secondary efficacy measures are mean change from baseline in percent of symptom-free days and mean change from baseline in supplemental ipratropium use over the 16-week double-blind treatment period. Baseline values for the diary efficacy measures and FEV₁ are defined in Section 9.2 (Derived and Transformed Data) and Section 11.2 (Secondary Efficacy Analysis(es)) of this RAP.

Other measures of efficacy are the proportion of subjects requiring supplemental albuterol during the 16-week double-blind treatment period and MADR evaluated at the end of each treatment period (open-label albuterol, open-label ipratropium and double-blind).

Other evaluations will compare mean AM PEF during the last 4 weeks of open-label treatment with as needed albuterol versus that during the last 4 weeks of open-label treatment with as needed ipratropium within each genotype. Assay sensitivity will be evaluated with FEV₁ measured at the beginning and end of the study. Summaries for screen and open label failures will be generated to address concerns regarding possible selection bias in the 3 genotypes (Gly/Gly, Arg/Gly and Arg/Arg). Evaluation of lung function in other *ADRB2* haplotype pairs is addressed in Section 11.3 (Other Efficacy Analysis(es)) of this RAP.

Safety measures are adverse events and asthma exacerbations.

2.3. Statistical Hypotheses

The study is designed to show that FSC treatment response in the Arg/Arg genotype is non-inferior to FSC treatment response in the Gly/Gly genotype. The statistical hypotheses associated with the primary comparison of the Arg/Arg and Gly/Gly genotypes within the FSC treatment group are

$$H_0: \text{AUC}(\text{bl})_{\text{Arg/Arg}} - \text{AUC}(\text{bl})_{\text{Gly/Gly}} \leq -\Delta$$

$$H_A: \text{AUC}(\text{bl})_{\text{Arg/Arg}} - \text{AUC}(\text{bl})_{\text{Gly/Gly}} > -\Delta$$

where $\text{AUC}(\text{bl})_{\text{Arg/Arg}}$ and $\text{AUC}(\text{bl})_{\text{Gly/Gly}}$ are the mean change from baseline values as characterized by the area under the AM PEF curve relative to baseline over the 16-week treatment period for the Arg/Arg and Gly/Gly genotypes, respectively, and where Δ is the acceptable difference for equivalence. The value of Δ has been set as 28.5 L/min for AM PEF in this study.

If the lower bound of the 95% 2-sided confidence interval for the mean difference in AM PEF (calculated as Arg/Arg minus Gly/Gly) should fall above -28.5 L/min then FSC

treatment response in the Arg/Arg genotype with respect to AM PEF AUC(bl) will be considered no worse than FSC treatment response in the Gly/Gly genotype.

3. STUDY DESIGN

This is a multi-center, randomized, double-blind, parallel-group, active comparator-controlled design. Eligible subjects must have reported short-acting beta₂-agonist use on an as needed or scheduled basis prior to Screening (Visit 1) and were to remain on their pre-study short-acting beta₂-agonist until Visit 2. Eligible subjects were 12 years of age or older with a diagnosis of persistent asthma for at least 3 months, a FEV₁ that is $\geq 70\%$ and $\leq 100\%$ of predicted normal, with a current or 1-year historical reversibility component (either albuterol reversibility ($\geq 12\%$ and $\geq 200\text{mL}$) or methacholine challenge ($\text{PC}_{20} < 8\text{mg/mL}$)).

The study includes a screening period, followed by two 8-week open-label treatment periods followed by a double-blind treatment period of 16 weeks. The double-blind treatment period is followed by a 2-week washout period.

Screening

At Screening (Visit 1), subjects who qualify for the study have a blood sample drawn and enter the 2-4 week screening period.

Open-Label Albuterol Treatment Period

At Visit 2, subjects return to the clinic for assessment of study continuation criteria. Subjects are to stop their pre-study short-acting beta₂-agonist and receive open-label albuterol 90mcg to be used as needed to relieve acute asthma symptoms for the first 8-week open-label treatment period. Subjects are to return to the clinic in 4 weeks (Visit 3) for study continuation assessment and then continue in the open-label albuterol treatment period for 4 additional weeks.

Open-Label Ipratropium Treatment Period

Following the open-label albuterol treatment period, subjects are to return to the clinic for Visit 4 for study continuation assessment and eligible subjects are to begin the second 8-week open-label treatment period. Subjects are to receive open-label ipratropium 18mcg to be used as needed to relieve acute asthma symptoms. Subjects also are to receive open-label albuterol 90mcg for as needed use in the event that asthma symptoms respond incompletely to ipratropium, in which case albuterol will be used as a superceding medication. Subjects are to return to the clinic in 4 weeks (Visit 5) for assessment of study continuation criteria and then continue in the open-label ipratropium treatment period for 4 additional weeks.

Double-Blind Treatment Period

Following the open-label ipratropium period, subjects are to return to the clinic for Visit 6 (Randomization). Eligible subjects are randomly assigned in a 1:1 ratio to either FSC 100/50mcg BID or salmeterol 50mcg BID for the 16-week double-blind treatment period. During the 16-week double-blind treatment period, clinic visits occur at Randomization (Visit 6), and after 4, 8, 12 and 16 weeks of treatment (Visits 7-10, respectively).

Washout Period

Following Visit 10, subjects are to receive open-label ipratropium 18mcg to be used as needed to relieve acute asthma symptoms for the 2-week washout period. Subjects also are to receive open-label albuterol 90mcg for as needed use in the event that asthma symptoms respond incompletely to ipratropium, in which case albuterol will be used as a superceding medication. Subjects are to return to the clinic in 2 weeks (Visit 11) for the final study visit.

Subjects who fail to meet the eligibility criteria at Visit 1 or the continuation criteria during the 2 open-label treatment periods will be withdrawn from the study as screen or open-label failures (See Section 6.2 Screen Failure Population and Open-Label Failure Population below). Study completers will participate in the study for approximately 36-38 weeks. Subjects are treated on an out-patient basis.

During the study, FEV₁ measures are collected at every visit. MADR is evaluated at the end of each of the open-label and double-blind treatment periods (at Visits 4, 6 and 10, respectively). Diaries are given to subjects beginning at Visit 2 for the recording of daily AM and PM PEF measures, rescue medication use and asthma symptom scores throughout the study. Refer to the protocol for more details concerning the procedures performed at each visit.

The randomization schedule for this study was generated for a stratified, parallel group study design using RandALL (an intranet based clinical trials randomization system used at GSK for the generation of randomization codes). Assignment to blinded study drug is stratified based on genotype and ethnicity with strata determined as:

Arg/Arg genotype, Black ethnicity
Arg/Arg genotype, Hispanic or Latino ethnicity
Arg/Arg genotype, Caucasian or Other ethnicity
Arg/Gly genotype, Black ethnicity
Arg/Gly genotype, Hispanic or Latino ethnicity
Arg/Gly genotype, Caucasian or Other ethnicity
Gly/Gly genotype, Black ethnicity
Gly/Gly genotype, Hispanic or Latino ethnicity
Gly/Gly genotype, Caucasian or Other ethnicity

Each treatment number is allocated to a blinded treatment group (FSC or salmeterol) using appropriate blocking within each stratum.

4. PLANNED ANALYSES

4.1. Interim Analyses

No interim analyses will be performed.

4.2. Final Analysis

Final statistical analysis will be conducted after the RAP has been finalized, all protocol deviations have been identified, all data queries have been resolved and the study database has been locked by GSK Data Management, and treatment assignments have been unblinded.

Once the study database is locked by GSK Data Management, the treatment allocations will be unblinded in RandALL. A SAS® data set will be generated that includes treatment number and the corresponding unblinded treatment assignment and randomization stratum (genotype and ethnicity stratum). This data set will then become part of the reporting database for the study. Treatment number will serve as the link between a subject's treatment assignment and genotype and his/her study data.

5. SAMPLE SIZE CONSIDERATIONS

The sample size calculation for this study is based on the primary efficacy measure of AM PEF, recorded by the subject in a daily diary over the course of the study.

It is estimated that the standard deviation of mean change from baseline in AM PEF over the 16-week double-blind treatment period in subjects randomized to the FSC treatment group will be 50 L/min. Using 28.5 L/min as the non-inferiority criterion bound (lower confidence interval limit of -28.5 L/min), a sample size of 82 subjects per group (per genotype per treatment group) will provide >90% power to demonstrate non-inferiority of the Arg/Arg genotype to the Gly/Gly genotype within the FSC treatment group in terms of AM PEF mean change from baseline over the 16-week treatment period, based on a 2-sided significance level of 0.05.

It is anticipated that approximately 540 subjects will be randomized to achieve an analysis population of approximately 492 evaluable subjects (82 evaluable subjects per genotype per treatment group). An evaluable subject is defined as a subject that completes at least 2 weeks of double-blind treatment, as documented in the subject diary. A 10% drop-out rate is assumed after randomization based on the fact that the asthmatic population is stable and mild. Assuming that 15% of the general population has the Arg/Arg genotype, it is anticipated that in order to randomize 90 subjects in each of the genotype and treatment groups, a minimum of 1,200 subjects will need to be screened. Allowing for exclusions, refusals to participate and withdrawals, approximately 2,000 subjects may need to be screened.

6. ANALYSIS POPULATIONS

The following populations will be identified for this study: Total Population, Screen Failure Population, Open-Label Failure Population, Intent-to-Treat (ITT) Population and Per Protocol population.

6.1. Total Population

The Total population will include all subjects screened in the study (i.e., assigned a subject number and performed at least one study procedure). This population will include both screen and open-label failures and randomized subjects. This population will be used for listings of serious adverse events and for summarization of the analysis populations.

6.2. Screen Failure Population and Open-Label Failure Population

The Screen Failure population will include all subjects screened for inclusion in the study but who were discontinued from the study at Visit 1 or during the screening period prior to Visit 2. The Open-Label Failure population will include subjects who entered the first open-label treatment period at Visit 2 but who were discontinued from the study prior to randomization to blinded study drug at Visit 6 (Randomization). Reasons for screen/open-label failure (including violations of inclusion/exclusion and study continuation criteria), demographics, asthma duration, concomitant medications, pulmonary function measures, diary data, adverse events and asthma exacerbations were to be collected for subjects in the Screen and Open-Label Failure populations as described in Section 9.3 (Screen and Open-label Failures) of the protocol. Data collected until study discontinuation, as appropriate (i.e., dictated by what data is available), will be summarized for these populations and by period of withdrawal (screening, open-label albuterol, and open-label ipratropium).

6.3. Intent-to-Treat Population

The ITT population will include all subjects who have been randomized to blinded study drug. Treatment group assignment will be based only on randomization (regardless of any inadvertent errors in dispensing of study drug that may occur during the study). The ITT population will be the primary analysis population for summaries and analyses of demographic/background, efficacy and safety data.

During the conduct of the study, one investigative site [REDACTED] was closed due to the result of audit findings or other information which implied that the integrity of the data had been compromised. Subjects randomized at this site (10 subjects) will not be included in the ITT efficacy analyses. Safety data collected at this site will be included in the ITT safety summaries. All subjects from this site will be included in the Total population and all screen and open-label failures will be included in the Screen Failure and Open-Label Failure populations, respectively.

6.4 Per Protocol Population

The Per Protocol population will include all subjects in the ITT population with no protocol deviations that may impact treatment response or the primary efficacy endpoint. These deviations are defined below in Section 10.2 (Protocol Deviations) of this RAP. The decision to exclude a subject from the Per Protocol population will be made prior to unblinding the study. Also, subjects randomized at the investigative site [REDACTED] closed to the result of audit findings will not be included in the Per Protocol population. As this trial is designed to show non-inferiority, analysis of the Per Protocol population is of importance and will serve as a supporting analysis for the primary analysis of the ITT population [EMA, 1998]. Analysis of the primary efficacy measure will be conducted for this population to assess sensitivity of the trial.

7. TREATMENT COMPARISONS

The primary comparisons of interest in this study are between genotypes within a given treatment group.

7.1. Primary Treatment Comparisons of Interest

The primary comparison of interest will be that of non-inferiority between the Arg/Arg and Gly/Gly genotypes in the FSC treatment group assessed in terms of overall mean AM PEF change from baseline for the 16-week double-blind treatment period.

7.2. Other Treatment Comparisons of Interest

Other comparisons will include the following:

- Arg/Arg and Gly/Gly genotypes in the salmeterol treatment group
- Arg/Arg and Arg/Gly genotypes in the FSC treatment group
- Arg/Arg and Arg/Gly genotypes in the salmeterol treatment group
- Gly/Gly and Arg/Gly genotypes in the FSC treatment group
- Gly/Gly and Arg/Gly genotypes in the salmeterol treatment group

These comparisons will also assess non-inferiority with 95% 2-sided confidence intervals and the same non-inferiority criterion bound as the primary comparison in terms of overall mean AM PEF change from baseline for the 16-week double-blind treatment period.

In addition, there is clinical interest in the comparison of lung function and symptoms (AM PEF, PM PEF and percentage of symptom-free days) as demonstrated at the end of each open-label treatment period. This comparison (between open-label treatment periods) will be made within each genotype separately as outlined below:

- The as needed albuterol open-label period versus the as needed ipratropium open-label period in the Arg/Arg genotype

- The as needed albuterol open-label period versus the as needed ipratropium open-label period in the Gly/Gly genotype
- The as needed albuterol open-label period versus the as needed ipratropium open-label period in the Arg/Gly genotype

In order to demonstrate assay sensitivity, assessment of the change from screening FEV₁ to endpoint FEV₁ will be made for each treatment group. Also, to address concerns regarding possible selection bias across the genotypes, (Gly/Gly, Arg/Gly, Arg/Arg), population demographic characteristics and lung function will be summarized by genotype for screen and open-label failures and randomized subjects.

7.3. Data Display Treatment and Other Sub-group Descriptors

The following set of treatment and genotype descriptions will be used on data displays (summaries and listings):

Treatment / genotype group	Data display descriptor
FSC 100/50mcg BID	FSC100/50, FSC
Salmeterol 50mcg BID	Salmeterol, SAL
Arg/Arg genotype	Arg/Arg
Gly/Gly genotype	Gly/Gly
Arg/Gly genotype	Arg/Gly

8. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Statistical programming and reporting will be performed in a UNIX environment using SAS® Version 8.2 and the GSK HARP (Harmonization for Analysis and Reporting Program) reporting environment. Reporting conventions will follow the GSK International Data Standards Library (IDSL) guidelines. In general, categorical measures will be summarized using frequency distributions (n, %) and continuous measures will be summarized with descriptive statistics including the number of observations, mean, standard deviation or standard error, median, minimum and maximum. Other descriptive statistics such as the upper and lower quartiles may be included, if appropriate.

8.1. Multicentre Studies

This is a multi-center study; however, a term for investigative site will not be included as a covariate in statistical models. The primary efficacy endpoint is a subject-recorded assessment (daily AM PEF) compared between blinded genotypes. Investigative site is not expected to influence the primary efficacy measure.

8.2. Other Strata and Covariates

Randomization to blinded study drug is stratified by genotype as well as by ethnicity (Black; Hispanic or Latino; Caucasian or Other) to ensure that ethnic groups are equally

represented across treatment groups. All analyses will include a term for ethnicity stratum as a covariate. In general, the baseline value of a continuous efficacy measure will also serve as a covariate in analyses of change from baseline values of that measure.

8.3. Examination of Subgroups

For the primary efficacy measure of AM PEF mean change from baseline for the overall 16-week double-blind treatment period, the extent to which the treatment response varies across the levels of genotype and ethnicity groups will be examined through interaction tests for exploratory purposes only. An exploratory statistical model will include the interaction term (genotype by ethnicity group) with all main effects in the model to explore the significance of the interaction. Any interaction term found to be statistically significant at the 0.10 significance level will be explored further by presenting summaries for the subgroups.

8.4. Multiple Comparisons and Multiplicity

A single primary comparison to assess non-inferiority between the Arg/Arg and Gly/Gly genotypes in the FSC treatment group for overall AM PEF mean change from baseline during the double-blind treatment period is defined for this study.

Non-inferiority in terms of overall AM PEF mean change from baseline will also be assessed between the other genotypes within the FSC and salmeterol treatment groups. These genotype comparisons as well as those from the secondary and other efficacy measures will be interpreted as supporting the primary comparison, secondary or other, respectively. No adjustment for multiplicity is planned.

9. DATA HANDLING CONVENTIONS

9.1. Premature Withdrawal and Missing Data

Data collected up to the time of study discontinuation for subjects who withdraw from the study prematurely will be included in analyses. A subject will be included in ITT analyses wherever his/her data is available. Therefore, the number of subjects evaluated at each visit and time point, as well as across demographic/background, efficacy and safety measures, will vary.

9.2. Derived and Transformed Data

Primary and secondary efficacy measures derived from the subject-recorded daily diaries are AM PEF, PM PEF, percentage of symptom-free days and supplemental ipratropium use.

For the 16-week double-blind treatment period, diary measures will be summarized at baseline, each 4-week interval of the double-blind treatment period and for the overall 16-week treatment period. Each set of 28 days during the double-blind treatment period will be defined as a 4-week interval.

Baseline week will be determined from the 7-day period immediately prior to Randomization (Visit 6). For AM PEF, baseline will be defined as the average of the AM PEF values recorded on the day of Visit 6 plus the 6 preceding days since AM PEF is measured in the morning (and prior to blinded study drug administration at Randomization (Visit 6)). For PM PEF, percentage of symptom-free days and supplemental ipratropium use, baseline will be defined as the average of the values from the 7 days preceding Visit 6 since these measures are derived from data collected in the evening.

Diary measures will also be summarized for the overall 2-week washout period and for each 4-week interval, for the overall 8-week interval, as well as weekly, for each of the open-label (albuterol and ipratropium) treatment periods.

A subject must have at least 3 days of diary data in any time interval to contribute a non-missing mean of daily values for that time interval. Otherwise, the mean value for that time interval will be considered missing. Also, obvious errors (rescue medication use >50 puffs/day and PEF values of 0 or >2000) included in the diary data due to subject entry error (e.g., switching the PEF and rescue medication recordings in the daily diary) will be excluded from analysis. No other diary values falling out of expected range will be excluded from analysis. If duplicate diary data is collected (i.e., 2 diary records with the same diary date in the database), then the most conservative value for this date will be included in data analysis. The most conservative AM PEF and PM PEF values are defined as the minimum AM PEF and PM PEF recordings and the most conservative symptom score and supplemental ipratropium and albuterol use values are defined as the maximum from the values recorded.

A symptom-free day will be defined as a day with no symptoms (i.e., a score of 0, indicating no asthma symptoms during the day or previous night, recorded in the daily diary). Percent of symptom-free days will be calculated as the number of symptom-free days divided by the total number of days in the assessment period, multiplied by 100 for each subject. Supplemental ipratropium use will be analyzed as the number of puffs taken per day.

9.3. Assessment Windows

Study visits during the 2 open-label treatment periods, double-blind treatment period and washout period are scheduled to take place within the following timeframes with visit windows calculated from Visit 6 (Randomization) as:

Period	Visit Number	Scheduled Time
Screening	Visit 1 (Screening)	
Open-label albuterol	Visit 2	Week -16
Open-label albuterol	Visit 3	Week -12
Open-label ipratropium	Visit 4	Week -8
Open-label ipratropium	Visit 5	Week -4
Double-blind treatment	Visit 6 (Randomization)	Day 1
Double-blind treatment	Visit 7	Week 4 $\pm$ 2 days
Double-blind treatment	Visit 8	Week 8 $\pm$ 2 days

Double-blind treatment	Visit 9	Week 12 $\pm$ 2 days
Double-blind treatment	Visit 10	Week 16 $\pm$ 2 days
Washout (Open-label ipratropium)	Visit 11	Week 18 $\pm$ 2 days

Efficacy data collected during a clinic visit (e.g., FEV₁) will be reported by visit at which the data are collected in the CRF. Data collected during a clinic visit will not be excluded from analysis for being collected outside of an assessment window. Clinic visit data will be referenced with the Scheduled Time that corresponds to the study visit on data displays (e.g., Week 4).

10. STUDY POPULATION

10.1. Disposition of Subjects

The disposition of all subjects in the Total Population will be tabulated. The Total Population includes screen and open-label failures as well as randomized subjects. Subject disposition in the Total Population will be summarized in terms of:

- the number of subjects screened (Total population)
- the number (%) of screen failures (Screen Failure population)
- the number (%) of subjects per screen failure reason
- the number (%) of open-label failures (Open-Label Failure population)
- the number (%) of subjects per open-label failure reason
- the number (%) of subjects randomized (ITT population)
- the number (%) of subjects with no major protocol deviation(s) (as described below in Section 10.2) (Per Protocol population)

Subject disposition in the ITT population will be summarized by treatment group and genotype in terms of:

- the number (%) of subjects randomized at each investigative site
- the number (%) of subjects who complete the study
- the number (%) of subjects who withdraw prematurely from the study
- the number (%) of subjects per primary reason for withdrawal

A subject listing of premature study withdrawals, including reasons for study withdrawal and days on blinded study drug will also be provided for the ITT population.

10.2. Protocol Deviations

Protocol deviations will be determined prior to unblinding treatment assignments. Data supporting the determinations of protocol deviations will be collected in the CRF and included in the study database. Protocol deviations will include the following:

- violation of inclusion/exclusion criteria
- use of prohibited medications

- unblinding of the study drug
- dispensing of incorrect blinded study drug
- incorrect randomization stratum of blinded study drug

Violations of inclusion/exclusion criteria will be obtained from the inclusion and exclusion responses from Screening (Visit 1). Use of prohibited medications will be obtained from the concomitant medication logs of the CRF. Prohibited medications are excluded asthma medications determined from those specified in the protocol (Section 8.2 Prohibited Medications) and by the Clinical study team before the data are unblinded. Any unblinding of study drug and dispensing of incorrect blinded study drug was to be collected in the CRF.

Protocol deviations will be tabulated by treatment group and genotype in a summary table as well as reported in a listing. A separate summary and listing of subjects violating the inclusion/exclusion criteria and a separate listing of subjects for whom the treatment blind was broken during the study will also be provided per IDSL standards. Protocol deviations will be summarized for subjects in the ITT population.

10.3. Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized for the ITT and Screen and Open-Label Failure populations. Since subjects in the Screen and Open-Label Failure populations discontinue the study at Visit 1 (Screening), during the screening period, or during either the open-label albuterol or open-label ipratropium treatment periods, reporting of demographic/background and baseline characteristics will be limited to the data actually collected, and as appropriate. For the ITT population, summaries will be generated by treatment group and genotype. For the Open-Label Failure population, summaries will be generated by genotype. For the Screen Failure population, summaries will be generated for the overall Screen Failure population. (Summaries for the Screen Failure population may be tabulated by genotype for the subgroup of screen failures that have genotyping data, as appropriate, as subjects could discontinue the study at Visit 1 prior to providing a blood sample for genotyping).

Demographic characteristics of age, sex, ethnicity and race will be summarized. A subject listing of demographic attributes per IDSL will also be provided for the ITT population.

Disease characteristics, current medical conditions and screening pulmonary function tests will also be summarized. Disease characteristics will include asthma duration and subject and family asthma and atopy history as assessed in the CRF. The summary of screening pulmonary function measurements will include pre-bronchodilator FEV₁ and FEV₁ percent predicted, FEV₁ percent reversibility to albuterol and PC₂₀.

Prior asthma medications stopped within 30 days of Screening (Visit 1) and concomitant medications taken during the study will be assigned codes using the GSK Drug dictionary and will be reported using the Anatomical Therapeutic Chemical (ATC) Level 1 classification and drug terms. Treatment and genotype groups will be summarized by reporting the number (%) of subjects taking any medication, the number (%) of subjects

taking a medication by ATC classification, and the number (%) of subjects taking a medication by each drug term. Combination medications will be summarized as combined drugs. A listing will be provided to outline the relationship between GSK Drug dictionary terms and verbatim drug text. Summaries will be generated for prior asthma medication use, asthma concomitant medications and non-asthma concomitant medications as collected in the CRF.

Other summaries for the Open-Label Failure population may include assessments of FEV₁, MADR and diary measures collected during the open-label treatment periods. These measures will be summarized with descriptive statistics. Diary assessments (AM PEF, PM PEF, percent of symptom-free days and supplemental rescue medication use) will also be summarized for each of the open-label treatment periods.

10.4. Treatment Compliance

Compliance with the blinded study drug regimen will be derived from the investigational product compliance pages of the CRF for each subject and will be summarized with descriptive statistics by treatment group and genotype for the ITT population. Treatment compliance will be expressed as an overall percentage of compliance calculated as the total number of doses taken during the treatment period divided by the total expected number of doses taken during the treatment period, multiplied by 100.

The total number of doses used will be determined from the DISKUS dose counter of each DISKUS dispensed and returned throughout the study. The total expected number of doses taken will be based on BID dosing during each subject's double-blind treatment period.

$$\text{Compliance (\%)} = \frac{\text{sum(dose counter start - dose counter stop)}}{(\text{treatment stop date} - \text{treatment start date} + 1) \times 2} \times 100$$

11. EFFICACY ANALYSES

The primary, secondary and other efficacy measures will be compared by genotype within treatment group for the ITT population. Analysis of the primary efficacy measure will also be performed as a supportive analysis for the Per Protocol population.

11.1. Primary Efficacy Analysis(es)

The primary efficacy measure is mean change from baseline in AM PEF over the 16-week double-blind treatment period, as characterized by AM PEF AUC(bl), compared between the Arg/Arg and Gly/Gly genotypes in the FSC treatment group. AM PEF measures and change from baseline values will be summarized with descriptive statistics by genotype for the overall 16-week double-blind treatment period, for each 4-week treatment period interval, as well as over the 2-week washout period. Baseline AM PEF and AM PEF for each week, for each of the 4-week intervals and for the overall 8 weeks of each open-label (albuterol and ipratropium) treatment period will also be summarized with descriptive statistics. An analysis of covariance (ANCOVA) model, including terms

for genotype, ethnicity stratum and baseline, will be used to assess non-inferiority in AM PEF mean change from baseline for the overall 16-week double-blind treatment period. Genotype differences from the ANCOVA model will be presented as least square means and standard errors with the corresponding 95% confidence intervals.

11.2. Secondary Efficacy Analysis(es)

Secondary efficacy measures are PM PEF, pre-dose FEV₁, percent of symptom-free days and supplemental ipratropium use.

PM PEF, Percent of Symptom-Free Days, Supplemental Ipratropium Use: PM PEF, percent of symptom-free days and supplemental ipratropium use will be summarized with descriptive statistics in the same manner as AM PEF. An ANCOVA model, including terms for genotype, ethnicity stratum and baseline, will be used to compare mean change from baseline values for the overall 16-week treatment period. Supplemental ipratropium and supplemental albuterol use will be summarized weekly and over each of the 4-week intervals and for the overall 8 weeks of the corresponding ipratropium or albuterol open-label treatment period, respectively. Genotype differences from the ANCOVA models will be presented as least square means and standard errors with the corresponding 95% confidence intervals.

FEV₁: FEV₁ measures and change from baseline values will be summarized with descriptive statistics by genotype for the overall 16-week double-blind treatment period, at Endpoint and for each visit (Visits 7-11, Weeks 4, 8, 12 and 16, and Washout, respectively). Endpoint will be defined as the last scheduled measurement of pre-dose FEV₁ during the 16-week double-blind treatment period and baseline will be defined as the pre-dose FEV₁ measure from Randomization (Visit 6). FEV₁ measures collected during the open-label treatment periods will also be summarized by visit with descriptive statistics. An ANCOVA model including terms for genotype, ethnicity stratum and baseline will be used to compare genotypes for the overall 16-week double-blind treatment period. Genotype differences from the ANCOVA model will be presented as least square means and standard errors with the corresponding 95% confidence intervals.

11.3. Other Efficacy Analysis(es)

Other efficacy measures include assessments of the proportion of subjects taking supplemental albuterol during the 16-week double-blind treatment period and MADR evaluated at the end of each treatment period (open-label albuterol, open-label ipratropium and double-blind).

Supplemental albuterol use: The proportion of subjects requiring supplemental albuterol during the 16-week double-blind treatment period will be summarized by genotype. Odds ratios and the corresponding 95% confidence intervals from Cochran-Mantel-Haenszel tests controlling for ethnicity will be presented for the comparisons of the genotypes.

MADR: MADR for this study is defined as the best FEV₁ recorded after 4, 6 or 8 puffs of albuterol. MADR FEV₁ values will be summarized along with the percent change in

max post albuterol FEV₁ from baseline FEV₁ recorded prior to albuterol administration. MADR is assessed at Visits 4, 6 and 10 (at the end of the open-label albuterol, open-label ipratropium and 16-week double blind treatment periods, respectively). MADR FEV₁ values will be summarized with descriptive statistics by genotype and by visit. Genotype differences from an ANCOVA model, with terms for genotype, ethnicity stratum and baseline, will be presented as least square means and standard errors with the corresponding 95% confidence intervals for each visit. Baseline will be defined as the pre-albuterol FEV₁ measure for each visit.

Other evaluations include within-group comparisons of lung function.

Mean AM PEF over the last 4 weeks of the open-label albuterol treatment period will be compared with mean AM PEF over the last 4 weeks of the open-label ipratropium period within each genotype. Mean AM PEF values over the last 4 weeks of each open-label treatment period and mean differences between the 2 periods will be summarized with descriptive statistics. Within group t-tests will be used to compare mean AM PEF values over the last 4 weeks of the 2 open-label treatment periods. Mean AM PEF over the first 4 weeks and for the overall 8 weeks of the open-label treatment periods, as well as weekly, will also be summarized. PM PEF and percent of symptom-free days will be compared in the same manner.

In order to assess assay sensitivity, mean change in FEV₁ at Endpoint from Screening FEV₁ will be summarized and compared within each treatment group using within-group t-tests. Screening FEV₁ is measured at Visit 1 and Endpoint FEV₁ is defined as the last FEV₁ measure collected at a scheduled clinic visit during the 16-week double-blind treatment period.

Haplotype Analysis: A haplotype is a specific combination of closely linked single nucleotide polymorphisms (SNPs) on the same chromosome of an individual. Using SNP-based haplotypes may yield more powerful tests of genetic association than using individual SNPs, especially when the causal variants are unknown or not measured or when there are interactions between mutations on the same chromosome. Determining the haplotypes is not easily obtained with current genotyping technology. Several methods exist to infer haplotypes or estimate haplotype frequencies from unphased genotype data. The majority of these tools assume that the sample is in Hardy-Weinberg equilibrium (HWE). Any deviation from HWE may adversely affect the validity of the estimation.

Since this study recruited specific numbers of genotypes it most likely will not be in HWE and could lead to biased estimates of genetic effects and even less control of type I error rates. In an exploratory manner, reported in a supplemental report, we will evaluate the impact of HWE on this selected population, and the possible utilization of estimation algorithms not as critically dependent on HWE.

Also included in the supplemental report, we will look at single point analyses on additional loci utilized to estimate haplotypes in this gene. These will include a panel of 11 tagging SNPs (at positions -3459, -2387, -1818, -468, -47, +46, +79, +491, +523, +659, +1053) and a poly-C repeat at position +1269 [Hawkins, 2006]. Comparisons of clinical endpoints will include those for AM PEF, percent of symptom-free days,

supplemental ipratropium use and FEV₁ as described above in Section 11 (Efficacy Analyses). Independent covariates (or stratification variables) including age, sex, ethnic origin, percent albuterol reversibility, baseline severity (baseline FEV₁ % predicted) and baseline value for the ANCOVA models may be included in the statistical models used to describe the association between haplotypes and clinical endpoints.

12. SAFETY ANALYSES

12.1. Extent of Exposure

The extent of exposure to blinded study drug, calculated as treatment stop date - treatment start date + 1, will be summarized by treatment group and genotype using summary statistics. A subject listing of double-blind treatment exposure will also be provided. Extent of exposure to blinded study drug will be summarized for the ITT population.

12.2. Adverse Events

Adverse events (AEs) will be coded and grouped by primary system organ class (SOC) and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). The relationship of primary SOC, preferred term and verbatim adverse event text will be outlined in a listing.

The number and percentage of subjects with AEs will be summarized. Adverse events will be sorted by SOC with SOC presented in descending order of total AE incidence. Within each SOC, preferred terms will be presented in descending order of total incidence. Where 2 or more preferred terms within a SOC have the same total incidence they will be sorted alphabetically.

Adverse event summaries will be provided for both the ITT and Open-Label Failure populations. Summaries of all adverse events occurring during the study will be reported by treatment group and genotype for the ITT population. Separate summaries will be generated for adverse events occurring pre-treatment (during the screening and open-label treatment periods), during treatment (during the double-blind treatment period), and post-treatment (during the 2-week follow-up period). The summary of adverse events for the Open-Label Failure population will be reported by genotype.

The following summaries of all adverse events and drug-related adverse events (those with a reasonable possibility that they may have been caused by study drug as assessed by the investigator) will be provided:

- All Adverse Events Prior to Treatment (ITT population)
- All Adverse Events During Treatment (ITT population)
- Most Common (>3%) Adverse Events During Treatment (ITT population)
- All Adverse Events Post-Treatment (ITT population)
- Drug-Related Adverse Events During Treatment (ITT population)
- All Adverse Events (Open-Label Failure population)

The summary of most common adverse events will report events experienced by >3% (after rounding) of subjects in any genotype group. A subject listing of all reported adverse events (those reported pre-treatment, during treatment and post-treatment) will be provided. In addition, an adverse event listing will be generated for each reported adverse event and the corresponding subjects who experienced the event during the study. These listings will be provided for the ITT population.

12.3. Deaths and Serious Adverse Events

The number and percentage of subjects with serious adverse events (SAEs) occurring during the treatment period will be tabulated (by genotype by treatment group) for the ITT population. Listings of all fatal SAEs and all non-fatal SAEs (pre, during and post-treatment) will be generated using the Total population. Case narratives for all SAEs will be written by Global Clinical Safety and Pharmacovigilance (GCSP).

12.4. Device Incidents and Near Incidents

Any device incidents or near incidents reported during this study will be summarized in case narratives written by GCSP personnel.

12.5. Adverse Events Leading to Discontinuation of Investigational Product and/or Withdrawal from the Study and Other Significant Adverse Events

The number and percentage of subjects with adverse events occurring during the treatment period and leading to withdrawal from the study will be tabulated by treatment group and genotype in a summary table and listed by subject for the ITT population.

12.6. Pregnancies (as applicable)

Any positive pregnancy tests that occur during the study will be presented in a listing. Pregnancies reported during this study will also be summarized in case narratives written by GCSP personnel.

12.7. Exacerbations

An exacerbation is defined as worsening asthma requiring emergency intervention, hospitalization or treatment with asthma medication in addition to those allowed by the protocol. The proportion of subjects experiencing an exacerbation during the double-blind treatment period will be summarized by treatment group and genotype for the ITT population. Exacerbations will further be described by tabulating the number of exacerbations and the number (%) of exacerbations by suspected primary cause, outcome and severity. Exacerbations will also be tabulated for the Open-Label Failure population by genotype. All exacerbations occurring during the study will also be presented in a listing for the ITT population.

13. PHARMACOGENETIC DATA ANALYSES

Pharmacogenetic data analyses that will be presented in a CSR supplemental report (i.e., CSR amendment or attachment) will include evaluation of lung function as assessed by AM PEF AUC(bl), as well as evaluations of FEV₁, symptom scores and supplemental ipratropium use, for each of the 12 markers and haplotypes defined above in Section 11.3 (Other Efficacy Analysis(es)).

14. REFERENCES

Hawkins GA, Tantisira K, Meyers DA, Ampleford EJ, Moore WC, Klanderman B, Liggett SB, Peters SP, Weiss ST, Bleeker ER. Sequence, haplotype, and association analysis of *ADRβ2* in a multiethnic asthma case-control study. *Am J Respir Crit Care Med* 2006; 174:1101-1109.

The European Agency for the Evaluation of Medicinal Products (EMA), Note for Guidance on Statistical Principles for Clinical Trials, ICH Topic E9, (CPMP/ICH/363/96), September 1998.

15. ATTACHMENTS

15.1. Table of Contents for Data Display Specifications

Study Population (ITT Population)

(Study Population Tables (with the exception of Table #1) will be generated by genotype by treatment group).

1. Summary of Analysis Populations (Total Population)
2. Summary of Enrollment by Investigator
3. Summary of End of Study Record
4. Summary of Protocol Deviations
5. Summary of Inclusion/Exclusion Criteria Deviations
6. Summary of Demographic Characteristics
7. Summary of Disease Characteristics
8. Summary of Current Medical Conditions
9. Summary of Screening Pulmonary Function
10. Summary of Prior Asthma Medication Use
11. Summary of Asthma Concomitant Medications
12. Summary of Non-Asthma Concomitant Medications
13. Summary of Double-Blind Treatment Compliance

Efficacy (ITT Population)

(Efficacy Tables for the ITT population will be generated by genotype for each treatment group.)

1. Summary of AM PEF (L/min)
2. Analysis of AM PEF (L/min)
3. Summary of PM PEF (L/min)
4. Analysis of PM PEF (L/min)
5. Summary of Pre-dose FEV₁ (L)

6. Analysis of Pre-dose FEV₁ (L)
7. Summary of Percentage of Symptom-Free Days
8. Analysis of Percentage of Symptom-Free Days
9. Summary of Supplemental Ipratropium Use (puffs/day)
10. Analysis of Supplemental Ipratropium Use (puffs/day)
11. Summary of Maximum Albuterol Dose Response
12. Analysis of Maximum Albuterol Dose Response
13. Summary of Percentage of Subjects Requiring Albuterol
14. Analysis of Percentage of Subjects Requiring Albuterol

Efficacy (Per Protocol Population)

(Efficacy Tables for the Per Protocol population will be generated by genotype for each treatment group).

1. Summary of AM PEF (L/min)
2. Analysis of AM PEF (L/min)

Open-Label Treatment Period Comparisons (Open-Label Albuterol versus Open-Label Ipratropium ITT Population)

1. Summary of AM PEF (L/min) by Open-Label Treatment Period for Arg/Arg
2. Summary of AM PEF (L/min) by Open-Label Treatment Period for Gly/Gly
3. Summary of AM PEF (L/min) by Open-Label Treatment Period for Arg/Gly
4. Summary of PM PEF (L/min) by Open-Label Treatment Period for Arg/Arg
5. Summary of PM PEF (L/min) by Open-Label Treatment Period for Gly/Gly
6. Summary of PM PEF (L/min) by Open-Label Treatment Period for Arg/Gly
7. Summary of Percentage of Symptom-Free Days by Open-Label Treatment Period for Arg/Arg
8. Summary of Percentage of Symptom-Free Days by Open-Label Treatment Period for Gly/Gly
9. Summary of Percentage of Symptom-Free Days by Open-Label Treatment Period for Arg/Gly

Assay Sensitivity (ITT Population)

1. Summary of Pre-dose FEV₁ (L) by Treatment Group**Safety (ITT Population)**

(Safety Tables for the ITT population will be generated by genotype by treatment group).

1. Summary of Exposure to Double-Blind Study Drug
2. Summary of Asthma Exacerbations
3. Summary of All Adverse Events Prior to Treatment
4. Summary of All Adverse Events During Treatment
5. Summary of Most Common (>3%) Adverse Events During Treatment
6. Summary of All Adverse Events Post Treatment
7. Summary of Drug-Related Adverse Events During Treatment
8. Summary of Serious Adverse Events During Treatment
9. Summary of Adverse Events Leading to Withdrawal from the Study During Treatment

Open-Label Failure Population

(Open-Label Failure tables will be generated by genotype).

1. Summary of Demographic Characteristics
2. Summary of Disease Characteristics
3. Summary of Current Medical Conditions
4. Summary of Screening Pulmonary Function
5. Summary of Prior Asthma Medication Use
6. Summary of Asthma Concomitant Medications
7. Summary of Non-Asthma Concomitant Medications
8. Summary of AM PEF (L/min)
9. Summary of PM PEF (L/min)
10. Summary of Pre-dose FEV₁ (L)
11. Summary of Percentage of Symptom-Free Days
12. Summary of Rescue Medication Use (puffs/day)

13. Summary of Maximum Albuterol Dose Response
14. Summary of Adverse Events
15. Summary of Asthma Exacerbations

Screen Failure Population

(Screen Failure tables will be generated for the overall population).

1. Summary of Demographic Characteristics
2. Summary of Disease Characteristics
3. Summary of Current Medical Conditions
4. Summary of Screening Pulmonary Function

Listings (ITT Population)

1. Listing of End of Study Record
2. Listing of Protocol Deviations
3. Listing of Subjects with Inclusion/Exclusion Criteria Deviations
4. Listing of Subjects for Whom the Treatment Blind was Broken
5. Listing of Demographic Characteristics
6. Relationship of Medication Class, Dictionary Term and Verbatim Text
7. Listing of Exposure to Double-Blind Study Drug
8. Listing of All Adverse Events
9. Listing of Subject Numbers for Individual Adverse Events
10. Listing of Fatal Adverse Events (Total Population)
11. Listing of Non-Fatal Serious Adverse Events (Total Population)
12. Listing of Adverse Events Leading to Withdrawal from the Study
13. Relationship of Adverse Event System Organ Class, Preferred Term and Verbatim Text
14. Listing of Asthma Exacerbations

CONFIDENTIAL



Protocol Identifier

SFA100062

Final Protocol Amendment 2 - 27 JUN 05

Final - 26 MAY 04

DEMOGRAPHY

INVESTIGATOR INSTRUCTIONS

Note: If the subject is of mixed heritage, choose the ethnicity the subject feels is most prevalent.

- Ensure that you ✓ only one box for Ethnicity.
- **Hispanic or Latino** A person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term, "Spanish origin," can be used in addition to "Hispanic or Latino."

Note: If the subject is of mixed race, choose the race the subject feels is most prevalent or ✓ the "Other" box.

- Ensure that you ✓ only one primary box for Race.
- **Arabic/North African** A person having origins in any of the original peoples of the Middle East, or North Africa.
- **Black - African American** A person having origins within the United States of America and in any of the black racial groups of Africa residing within the United States of America.
- **Black - African Heritage** A person having origins outside of the United States of America and in any of the black racial groups of Africa residing outside of the United States of America.
- **East and South East Asian** A person having origins in any of the original peoples of the Far East, Southeast Asia including, for example, China, Korea, Malaysia, the Philippine Islands, Thailand, Cambodia and Vietnam.
- **Japanese** A person having origins in any of the original peoples of Japan.
- **South Asian** A person having origins in any of the original peoples of the Indian subcontinent including, for example, India, Pakistan and Bangladesh.
- **White/Caucasian** A person having origins in any of the original peoples of Europe.

Other:

- **Native Hawaiian** A person having origins in any of the original peoples of Hawaii.
- **Other - Pacific Islander** A person having origins in any of the original peoples of Guam, Samoa, or other Pacific Islands.
- **American Indian** A person having origins in any of the original peoples of North and South America (including Central America), and who maintains tribal affiliation or community attachment.
- **Alaska Native** A person having origins in any of the original peoples of Alaska who maintains tribal affiliation or community attachment.



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Protocol Identifier	Subject Identifier	Visit Date			Visit Description
SFA100062		Day 	Month 	Year 	Visit 1 (Screen)

DEMOGRAPHY

Date of birth

Day	Month	Year

Sex

[M] ☐ Male[F] ☐ Female

Ethnicity

*If the subject is of mixed heritage, choose the ethnicity the subject feels is most prevalent.**✓ only one:*[1] ☐ Hispanic or Latino[2] ☐ Non-Hispanic or LatinoRace¹*If the subject is of mixed race, choose the race the subject feels is most prevalent or ✓ the "Other" box.**✓ only one primary race box:*[2] ☐ Arabic/North African[3] ☐ Black[1] ☐ African American[2] ☐ African Heritage[4] ☐ East & South East Asian[5] ☐ Japanese[6] ☐ South Asian[7] ☐ White/Caucasian[2] ☐ Other[3] ☐ Native Hawaiian[4] ☐ Other Pacific Islander[5] ☐ American Indian[6] ☐ Alaska Native¹ See facing page for race definitions.



Protocol Identifier	Subject Identifier	Visit Description
SFA100062		Visit 1 (Screen)

ELIGIBILITY QUESTION

Did the subject meet all the entry criteria?

[Y] ☐ Yes [N] ☐ No

If No, ✓ all boxes corresponding to violations of any inclusion/exclusion criteria.

*Do **not** enter the subject into the study if they failed any inclusion or exclusion criteria below.*

INCLUSION CRITERIA

✓ the boxes corresponding to any of the inclusion criteria the subject failed.

1. ☐ **Type of Subject:** A subject must be treatable on an outpatient basis.

2. ☐ **Age:** A subject must be 12 years of age or older at Visit 1.

3. ☐ **Gender:** Male or Female.

Females are eligible to participate only if they are currently non-pregnant and non lactating. There are no birth control restrictions for this study. Female subjects of childbearing potential will undergo a urine pregnancy test at the beginning of the study (Visit 2) and at Visit 4, 6, 8, 10 and at the end of the study (Visit 11 or a **Premature Discontinuation Visit which may occur during the open-label periods, the double-blind treatment period, or the washout period**). Any female who becomes pregnant during the study will be withdrawn. Female subjects should not be enrolled if they plan to become pregnant during the time of study participation.

4. ☐ **Disease:** Each subject must have a diagnosis of persistent asthma for at least 3 months prior to Visit 1. Asthma is defined by the American Thoracic Society as follows:

"Asthma is a clinical syndrome characterized by increased responsiveness of the tracheobronchial tree to a variety of stimuli. The major symptoms of asthma are paroxysms of dyspnea, wheezing, and cough, which may vary from mild and almost undetectable to severe and unremitting (status asthmaticus). The primary physiological manifestation of this hyperresponsiveness is variable airways obstruction. This can take the form of spontaneous fluctuations in the severity of obstruction, substantial improvements in the severity of obstruction following bronchodilators or corticosteroids, or increased obstruction caused by drugs or other stimuli" [American Thoracic Society, 1987].

5. ☐ **FEV₁ Component:** The subject has a best FEV₁ that is $\geq 70\%$ and $\leq 100\%$ of predicted normal at Visit 1 after withholding asthma medications as detailed in the protocol. Predicted FEV₁ will be based on the **National Health and Nutrition Examination Survey (NHANES III) predicted normal values for ages 8 years and older [Hankinson, 1999]**.



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Protocol Identifier	Subject Identifier	Visit Description
SFA100062		Visit 1 (Screen)

INCLUSION CRITERIA (Continued)

6. ☐ **Reversibility Component:** The subject has reversible airways disease as demonstrated by an increase in FEV₁ of $\geq 12\%$ and 200mL over baseline within 30 minutes after the inhalation of 2-4 puffs (180µg -360µg) of albuterol (with or without a spacer) or 1-2 nebulized albuterol (2 puffs = 1 nebule) treatments at Visit 1 or at a visit that is within the 7-day period immediately following Visit 1. If the subject fails to reverse at least 12% during Visit 1, a second attempt to reverse may be scheduled within 7 days. If the second attempt to document reversibility is unsuccessful, the subject may undergo a methacholine challenge test (MCT). A PC₂₀ result of <8mg/mL obtained at an unscheduled visit prior to Visit 2 is required. An historical PC₂₀ value of <8mg/ml that has been documented at the investigative site within the past 12 months and was obtained using ATS or ACRN guidelines for MCT is also acceptable [American Thoracic Society, 2000; ACRN, 2002]. Methacholine challenge testing should be performed only at sites that have past experience performing this test.
- Note: Documentation of historical reversibility within one year of the Screening Visit demonstrating an increase in FEV₁ of $\geq 12\%$ and 200ml over baseline is acceptable and will preclude the requirement for reversibility testing at the Screening Visit.**
7. ☐ **Concurrent Anti-Asthma Therapy:** Eligible subjects must have reported **short-acting** β_2 -agonist for use on a prn (or scheduled) basis **for at least 4 weeks** prior to Visit 1. Each subject must be judged by the investigator to be able to withhold short-acting β_2 -agonist therapy for at least 6 hours prior to clinic visits when FEV₁ is performed.
8. ☐ The subject agrees to allow a venipuncture for blood draw.
9. ☐ The subject demonstrates correct use of the **DISKUS** device and a MDI, as well as correct use of a peak flow meter.
10. ☐ **Literacy:** A subject must be able to read, comprehend and record information.

EXCLUSION CRITERIA

✓ the boxes corresponding to any of the exclusion criteria that disqualified the subject from entry.

1. ☐ **Life-Threatening Asthma:** A subject may not have life-threatening asthma. Life-threatening asthma is defined for this protocol as a history of significant asthma episode(s) requiring intubation, associated with hypercapnia, respiratory arrest, hypoxic seizures, or asthma-related syncopal episode(s).
2. ☐ **Asthma instability:** A subject must not have been hospitalised due to asthma one or more times within 6 months prior to Visit 1.
3. ☐ **Respiratory Disease:** Current evidence of cystic fibrosis, pneumonia, pneumothorax, atelectasis, pulmonary fibrotic disease, chronic bronchitis or any other respiratory abnormalities other than asthma excludes a subject from participation.



Protocol Identifier	Subject Identifier	Visit Description
SFA100062		Visit 1 (Screen)

EXCLUSION CRITERIA (Continued)

4. ☐ **Anti-Asthma Medications:** Asthma medications listed below must not have been used prior to Screening (Visit 1) for the required interval indicated below, and not taken during the study.
- | | |
|--|-------------------------|
| Nebulized short-acting beta ₂ -agonists | 6 hours |
| Oral short-acting beta ₂ -agonists | 6 hours |
| Inhaled short-acting anticholinergics | 6 hours |
| Inhaled long-acting anticholinergics | 24 hours |
| Leukotriene modifiers | 4 weeks |
| Inhaled long-acting beta ₂ -agonists | 4 weeks |
| Theophylline products | 48 hours |
| Oral long-acting beta ₂ -agonists | 4 weeks |
| Inhaled corticosteroids | 4 weeks |
| Inhaled corticosteroid/Inhaled long-acting beta ₂ -agonist combination products | 4 weeks |
| Oral corticosteroids | 4 weeks ^{1, 2} |
| Parenteral corticosteroids | 4 weeks ² |
| Inhaled cromolyn sodium or nedocromil | 4 weeks |
- ¹ Any subject who has received oral corticosteroid treatment for any reason for 2 months or longer must have discontinued use for at least 6 months prior to Visit 1.
- ² A subject must not have had two courses of oral or parenteral corticosteroids for any reason in the 6 months prior to Visit 1.
5. ☐ **Concurrent Medications:** Concurrent use of any of the following medications that may affect the course of asthma or interact with sympathomimetic amines will not be allowed. Specifically:
- beta blockers
 - polycyclic antidepressants
 - monoamine oxidase inhibitors
 - phenobarbital
 - rifampin
- Note: Regular use of short-acting nasal decongestants is allowed. Other intranasal medications including antihistamines and intranasal corticosteroids for the treatment of rhinitis are also allowed. Topical hydrocortisone cream or ointment (1% or less) is also allowed.*
6. ☐ **Immunosuppressive Medications:** Use of immunosuppressive medications is not allowed at any time during the study.
- Note: Immunotherapy for the treatment of allergies is allowed during the study, provided that the subject has received a constant dose for 30 days prior to Visit 1, and that the same dose will be continued throughout the study.*
7. ☐ **Other Medications:** The medications listed below must not have been used prior to Screening (Visit 1) for the required interval indicated below, and not taken during the study.
- | | |
|---|-----------|
| • Methotrexate, gold, cyclosporine and azathioprine | 12 Months |
| • Ritonavir | 12 Months |



Protocol Identifier	Subject Identifier	Visit Description
SFA100062		Visit 1 (Screen)

EXCLUSION CRITERIA (Continued)

8. ☐ **Respiratory Tract Infection:** The subject has a respiratory infection that is suspected or diagnosed within 4 weeks immediately preceding Visit 1 or during the period from Visit 1 to **Visit 2**. The subject may be re-screened one time. Rescreening must be no sooner than 4 weeks following resolution of any suspected or diagnosed respiratory infection (whether treated or not).
9. ☐ **Antibiotic Usage:** The subject used an antibiotic (or other medication) for treatment of a suspected or diagnosed upper or lower respiratory tract infection within 4 weeks of Visit 1 or during the periods from Visit 1 to **Visit 2**. The subject may be re-screened one time. Antibiotics for other infections or acne are permitted.
10. ☐ **Other Concurrent Conditions/Diseases:** Any clinically significant, uncontrolled condition or disease state that, in the opinion of the investigator, would put the safety of the subject at risk through study participation or would confound the interpretation of the results if the condition/disease exacerbated during the study excludes a subject from participation. The list of conditions/diseases that will result in exclusion if determined to be clinically significant includes, but is not limited to: cardiac arrhythmias, congestive heart failure, coronary artery disease, Cushing's or Addison's disease, diabetes mellitus, dyspnea by any cause other than asthma, hematological, hepatic, neurological, thyroid, peptic ulcer, or renal disease, uncontrolled hypertension, immunologic compromise, current malignancy, current or quiescent tuberculosis.
11. ☐ **Drug Allergy:** The subject has any adverse reaction, including immediate or delayed hypersensitivity, to study medications, severe milk protein allergy or allergies to soya lecithin or related food products such as soybeans or peanuts.
12. ☐ **Tobacco Use:** The subject has a greater than 10 pack-year history of cigarette smoking and/or use of any tobacco products within 1 year of Visit 1.
13. ☐ **Positive Pregnancy Test (for females of childbearing potential):** A current positive pregnancy test.
14. ☐ **Questionable Validity of Consent:** The subject or parent (caregiver) has a history of psychiatric disease, intellectual deficiency, poor motivation, substance abuse (including drug and alcohol), or other conditions which would limit the validity of informed consent to participate in the study.
15. ☐ **Investigational Drug:** A subject may not have been exposed to an investigational drug within 30 days prior to Visit 1.
16. ☐ **Affiliation with Investigational Site:** A subject may not participate if he/she is a participating investigator, sub-investigator, study coordinator, or employee of a participating investigator, or is an immediate family member of the aforementioned.
17. ☐ **Questionable Compliance with Medications or Visits:** A subject may not participate if he/she has an infirmity, disability or geographical location which seems likely, in the opinion of the investigator, to impair compliance with any aspect of this study protocol or scheduled visits.
18. ☐ **Exercise-Induced Bronchospasm Alone:** A subject may not have been diagnosed with exercise-induced bronchospasm alone, in the absence of a diagnosis of persistent asthma within the last 3 months prior to Visit 1.

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HISTORICAL REVERSIBILITY MONITOR DATA VALIDATION CHECKS

- Ensure that if the historical reversibility question is answered 'Yes' that the percent changed has been recorded in the space provided.

PULMONARY FUNCTION TESTING MONITOR DATA VALIDATION CHECKS

- Ensure that the appropriate test is within the protocol defined range.
- Ensure that predicted normal(s) is/are correct from the table provided.
- Ensure that % Predicted Normal(s) calculation(s) ($\frac{A}{B} \times 100$) is/are correct and within the protocol specified range(s).
- Ensure that the % Reversibility calculation ($\frac{C - A}{A} \times 100$) is correct.
- Ensure that % Predicted Normal has been rounded accurately to 1 decimal place.
- Ensure that % Reversibility has been rounded accurately to 1 decimal place.
- Ensure that 3 Pre-dose and Post-dose measurements were taken and only the highest of the 3 technically acceptable measurements was recorded where indicated.
- Ensure that FEV₁ has been rounded accurately to 2 decimal places.
- Ensure that all spirometry printouts are signed and dated by the responsible person and clearly indicate the clinic visit, the date of the visit, and the GlaxoSmithKline subject number.
- The spirometry printouts must be stored in the CRF Binder.
- If spirometry printouts are on thermal paper the pages must be copied.

HISTORICAL METHACHOLINE CHALLENGE MONITOR DATA VALIDATION CHECKS

- Ensure that if the historical methacholine challenge question is answered 'Yes' that a value has been recorded in the space provided.

METHACHOLINE CHALLENGE

INVESTIGATOR INSTRUCTIONS

- The subject may undergo methacholine challenge testing (MCT) once if the second attempt to document reversibility is unsuccessful. See Section 6.5.1.3 of the protocol.
- The testing should be performed between 6 AM and 11 AM.

MONITOR DATA VALIDATION CHECKS

Ensure that PC₂₀ is correctly recorded and is within protocol specifications.



GlaxoSmithKline



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Protocol Identifier	Subject Identifier		Visit Description
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HISTORICAL REVERSIBILITYDoes the subject have historical reversibility of $\geq 12\%$ and 200 mL over baseline?[Y] ☐ Yes [N] ☐ NoIf Yes, record percent changed %**PULMONARY FUNCTION TESTING**

Test	Actual Measurement Pre-Bronchodilator (highest of 3 technically acceptable measurements)	Predicted Normal	% Predicted Normal	Actual Measurement 30 minutes Post-Bronchodilator (highest of 3 technically acceptable measurements)	% Reversibility
	A	B	$\frac{A}{B} \times 100$	C	$(\frac{C-A}{A} \times 100)$
e.g., FEV ₁ (L)	1.75	3.25	53.8	1.82	2.2
FEV ₁ (L)	.	.	.	.	.

HISTORICAL METHACHOLINE CHALLENGEDoes the subject have historical methacholine challenge MCT with a PC₂₀ result of less than 8 mg/mL?[Y] ☐ Yes [N] ☐ NoIf Yes, record value mg/mL**METHACHOLINE CHALLENGE****Note:** If a PC₂₀ <8mg/mL is documented during an unscheduled visit prior to Visit 2, the subject is eligible.PC₂₀ mg/mL✓ if Methacholine Challenge not done/not needed ☐

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SCREEN / OPEN-LABEL FAILURE MONITOR DATA VALIDATION CHECKS

- A subject who has at least one study procedure performed (in addition to signing a consent form), and is assigned a subject number (see Section 7.5.1 of the protocol 'Assignment of Subject Number'), but does not participate in the open-label period(s) is classified as having **failed screening (Visit 1)**. The following information will be collected in the CRF on subjects who fail at the Screening Visit (Visit 1) or any time prior to Visit 2.

The following information will also be collected in the CRF on subjects who fail at Visit 2 or any time during the open-label periods prior to Visit 6:

- Demographic information (including race, age and gender)
- Inclusion/exclusion criteria
- Duration of asthma
- Asthma concomitant medications
- Non-asthma concomitant medications
- Reversibility assessment
- Pulmonary function tests (including MADR), if applicable
- Continuation criteria, if applicable
- Reason subject was a screening or open-label failure
- Pharmacogenetic (PGx) information
- Investigational product information
- Asthma exacerbation data
- Any adverse events/SAEs that occur during the screening and open-label periods
- Investigator comments
- Investigator signature
- Diary cards, if applicable
- Complete and transmit those CRF pages to GSK.
- Refer to Section 9.3 of the protocol to evaluate subject screen or open-label failures from the study.
- If the subject is a screen or open-label failure, ensure that at least one reason has been ✓.
- Check that either 'Yes' or 'No' box at the top of the page has been completed. If 'Yes' is ✓, ensure that a complete failure date is present.
- Ensure that at least one box is ✓ for screen or open-label failure reason.
- Ensure that if 'Other, specify' is ✓ a reason is provided on the specify line.

Note: All pharmacogenetic samples from screen or open-label failures are to be destroyed. Therefore, if a blood sample was collected for a screen or open-label failure, complete the PGx-Pharmacogenetic destruction form and fax it to the GSK Study Manager.



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SCREEN / OPEN-LABEL FAILUREWas this subject a screen or open-label failure?¹[Y] ☐ Yes [N] ☐ No

If Yes, record the screen or open-label failure date

Day		Month		Year	

If Yes, ✓ *primary reason:*[1] ☐ Adverse event →*Record details on Non-Serious Adverse Events or Serious Adverse Event page(s) as appropriate.*[2] ☐ Lost to follow-up[4] ☐ Subject decided to withdraw from study[5] ☐ Prohibited medication use[6] ☐ Did not fulfil eligibility criteria[7] ☐ Exacerbation of medical condition →
under investigation*Exacerbations will not be classified as adverse events unless the exacerbation meets the definition of a serious adverse event as defined in the protocol.*[9] ☐ Genotype quota filled[10] ☐ Did not fulfil continuation criteria[OT] ☐ Other, specify _____

¹ **All pharmacogenetic samples from screen or open-label failures are to be destroyed. Therefore, if a blood sample was collected for a screen or open-label failure, complete the PGx-Pharmacogenetic destruction form and fax it to the GSK Study Manager.**

PREGNANCY INFORMATION

Did the subject become pregnant during the study?

[Y] ☐ Yes [N] ☐ No [X] ☐ Not Applicable (not of childbearing potential or male)

If Yes, complete Pregnancy Notification form.

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Final Protocol Amendment 2 - 27 JUN 05
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Perform a urine pregnancy test on all females of childbearing potential.

CONCOMITANT MEDICATIONS

Record any changes to the subject's concomitant medications or any new medications taken since the last visit in the appropriate Concomitant Medications section.

ADVERSE EVENTS

Record details of any new non-serious adverse events/serious adverse events observed or reported by the subject or any changes to ongoing non-serious adverse events in the appropriate Non-Serious Adverse Events/ Serious Adverse Event section.

CONTINUATION CRITERIA

- Ensure that the Continuation Criterion has been completed and subject is eligible to continue in the study.
- Ensure that the subject has a best $FEV_1 \geq 70\%$ of predicted at Visit 2.

 **FEV_1
MONITOR DATA VALIDATION CHECKS**

- Ensure that the correct FEV_1 measurement has been recorded.
- Ensure that the FEV_1 is within the protocol defined inclusion/continuation range.
- Ensure that the FEV_1 is rounded accurately to 2 decimal places.
- Ensure that all spirometry printouts are signed and dated by the responsible person and clearly indicate the clinic visit, the date of the visit, and the GlaxoSmithKline subject number.
- The spirometry printouts must be stored in the CRF binder.
- If spirometry printouts are on thermal paper the pages must be copied.



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Protocol Identifier	Subject Identifier	Visit Date			Visit Description
SFA100062		Day 	Month 	Year 	Visit 2

CONTINUATION CRITERION

Did the subject meet the following continuation criterion?

1. A best
- $FEV_1 \geq 70\%$
- of predicted.

[Y] ☐ Yes [N] ☐ No*If No, **do not** continue the subject in the study.* **FEV_1** *Record the highest of 3 technically acceptable measurements.* FEV_1 . (L)

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Final Protocol Amendment 2 - 27 JUN 05
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INSTRUCTIONS TO INVESTIGATOR**

Note: If the subject discontinues the study ANYTIME at or after Visit 2, complete the Premature Discontinuation Visit section.

PREGNANCY TEST

Perform a urine pregnancy test on all females of childbearing potential.

PHYSICAL EXAMINATION

Perform a physical examination including vital signs. Record physical exam findings and vital signs in subject's source documents.

CONCOMITANT MEDICATIONS

Record any changes to the subject's concomitant medications or any new medications taken since the last visit in the appropriate Concomitant Medications section.

ADVERSE EVENTS

Record details of any new non-serious adverse events/serious adverse events observed or reported by the subject or any changes to ongoing non-serious adverse events in the appropriate Non-Serious Adverse Events/Serious Adverse Event section.

**FEV₁
MONITOR DATA VALIDATION CHECKS**

- Ensure that the correct FEV₁ measurement has been recorded.
- Ensure that the FEV₁ is within the protocol defined inclusion/continuation range.
- Ensure that the FEV₁ is rounded accurately to 2 decimal places.
- Ensure that all spirometry printouts are signed and dated by the responsible person and clearly indicate the clinic visit, the date of the visit, and the GlaxoSmithKline subject number.
- The spirometry printouts must be stored in the CRF binder.
- If spirometry printouts are on thermal paper the pages must be copied.

PGx-PHARMACOGENETIC RESEARCH

Ask subject whether they want their pharmacogenetic sample destroyed or stored. Document answer on the PGx-Pharmacogenetic Research page.

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ASTHMA EXACERBATIONS

INVESTIGATOR INSTRUCTIONS

Note: A subject who experiences an exacerbation during the screening period between Visit 1 and Visit 2 must be discontinued. For purposes of this study, a subject may experience one exacerbation during the 16 week combined open-label period that is successfully treated within 10 days and remain in the study, predicated on consultation with GSK. If a subject experiences more than one exacerbation during the open-label treatment periods the subject must be discontinued. Any subject who experiences an exacerbation at or following Visit 6 must be discontinued from the study.

- For the purposes of this protocol, a clinical exacerbation is defined as worsening asthma requiring emergency intervention, hospitalization, or treatment with asthma medication in addition to those allowed by the protocol.
If a subject is withdrawn for a clinical exacerbation based upon the above definition, the reason for withdrawal noted on the Study Conclusion page of the CRF should be recorded as "Exacerbation".
- For the purposes of this study, a subject will be withdrawn due to worsening asthma if he/she experiences an exacerbation during the double-blind treatment period or the washout period. In addition, the investigator may discontinue a subject at any time, if the investigator believes that the subject is at risk by remaining in the study.
- For subjects who enter the screening period between Visit 1 and Visit 2 and experience an exacerbation, worsening asthma data will be recorded only in the source documents. For all subjects who are in the open-label, double-blind, and washout treatment periods, asthma exacerbation data will be recorded in the source documents and the Asthma Exacerbation section of the CRF.
- If an exacerbation meets the definition of an SAE (Section 10.2 of the protocol 'Definition of a SAE'), worsening asthma data must be collected as a SAE for all subjects who sign an Informed consent and participate in this study.
- Ensure that you answer the leading question 'Was there an asthma exacerbation?' either Yes or No.
- Do not leave any items on this page blank.
- Dates must be complete dates recorded in DD MMM YY format (18 AUG 04). If Date of Resolution is unknown, enter 'UNK'.
 - If the exacerbation resulted in death, the Date of Death must be provided.

Primary Cause of Exacerbation Codes

Cold air / Cold weather	1
Tobacco smoke	2
Upper respiratory infection	3
Air pollution	4
Allergy	5
Exercise	6
Stress / Emotions	7
Beta-blockers	8

Aspirin	9
Other NSAIDS	10
Withholding or reducing asthma medication	11
Unknown etiology	13
Lack of efficacy	14
Lower respiratory infection	15
Other	OT

ASTHMA EXACERBATION

MONITOR DATA VALIDATION CHECKS

- Ensure that the leading question 'Was there an asthma exacerbation?' has been answered either Yes or No.



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ASTHMA EXACERBATIONS

Was there an asthma exacerbation? [Y] ☐ Yes [N] ☐ No <i>If Yes, record below:¹</i>				
Date of Onset	Outcome	Date of Resolution or Death	Severity	Primary Cause of Exacerbation
Day Month Year	1 = Resolved 2 = Fatal 3 = Not resolved	Day Month Year	1 = Mild 2 = Moderate 3 = Severe	(See facing page for codes)
<i>e.g., 08 AUG 04</i>	1	18 AUG 04	2	6
1.				
2.				
3.				
¹ Record all medications used to treat an asthma exacerbation on the Asthma Concomitant Medications page.				

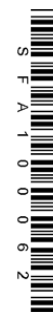
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NON-ASTHMA CONCOMITANT MEDICATIONS (Continued)

Drug Name ^{1,2} (Trade Name preferred)	Reason for Medication	Start Date Day Month Year	Taken Prior to Study? Y=Yes N=No	Stop Date Day Month Year	Ongoing Medi- cation? Y=Yes N=No
e.g., Tylenol	Headache	31 MAY 04	N	31 MAY 04	N
19.					
20.					
21.					
22.					
23.					
24.					
25.					
26.					
27.					
28.					
29.					

¹ Record details of asthma concomitant medications on the Asthma Concomitant Medications page.

² Do not record Investigational Product or supplemental albuterol or ipratropium bromide use on this page.



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MEDICAL DEVICE INCIDENT REPORT FORM INVESTIGATOR INSTRUCTIONS

Complete the Medical Device Incident Report Form for each subject who has an incident¹ or near-incident² with GlaxoSmithKline (GSK) medical devices provided for use during the study period. Send a copy of the form to GSK (GSK will provide separately a list of contact names and information) by **fax or mail (fax preferred)** within 24 hours. Original pages must remain with the subject's Case Report Form (CRF).

A copy of the form must be sent to the nominated GSK monitor for the study.

In addition, for incidents and near incidents fulfilling the definition of an Adverse Event (AE) or a Serious Adverse Event (SAE), the appropriate pages of the CRF must be completed as described in the protocol. If there is a SAE, the completed CRF pages should be sent together with this report form. If the subject is withdrawn due to this incident/near-incident, ensure the Study Conclusion page is completed.

Note: If a copy of the SAE page is sent with this form, this does not replace the procedure to report a SAE.

¹ Incident **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 fulfil 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.

² Near-incident **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 **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 **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.



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MEDICAL DEVICE INCIDENT REPORT FORM

Date of birth				Sex	☐ Male	☐ Female			
	Day	Month	Year						
DEVICE DETAILS (complete all applicable details)									
Manufacturer name _____									
Medical device (commercial name) _____									
Type of device _____									
Model number _____									
Catalogue number _____									
Serial number(s) _____									
Lot number(s) _____									
Accessories/Associated device _____									
Software version _____									
Did the incident/near-incident fulfil the definition of an AE or SAE? ☐ Yes ☐ No									
If Yes, complete Non-Serious AE or SAE page(s) as appropriate.									
INVESTIGATIONAL PRODUCT AND CONCOMITANT MEDICATIONS									
Enter the investigational product details on the first line (if the investigational product is blinded, enter "Investigational Product" on this line). List the relevant concomitant medications the subject received during the study period. If there are extensive concomitant medications, attach a copy of the Concomitant Medications page (where applicable).									
Drug Name (Trade Name preferred)	Dose	Unit	Frequency	Route	Date Started Day Month Year	Taken Prior to Study? Y=Yes N=No	Date Stopped Day Month Year	Ongoing Medication? Y=Yes N=No	Reason for Medication
e.g., Zantac	150	mg	BID	PO	05 AUG 03	N	07 AUG 03	N	Gastric ulcer
1.									
2.									
3.									
4.									
5.									



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MEDICAL DEVICE INCIDENT REPORT FORM (continued)**DETAILS OF INCIDENT OR NEAR-INCIDENT**

✓ one: ☐ Incident Onset date
Day Month Year

☐ Near-incident

Incident/near-incident description

Treatment given

Outcome, ✓ one:

- ☐ Recovered/Resolved
- ☐ Recovering/Resolving (*leave outcome date blank*)
- ☐ Not recovered/Not resolved (*leave outcome date blank*)
- ☐ Recovered/Resolved with sequelae
- ☐ Fatal (*complete SAE form*)

Outcome date

Day
Month
Year

Corrective action (e.g., adjustment to device, return of device to manufacturer for investigation, including any device decontamination procedures necessary)

Was the subject withdrawn from the study as a result of this incident/near-incident?

☐ Yes ☐ No

Is there a reasonable possibility that the incident/near-incident was caused by the medical device?

☐ Yes ☐ No

Investigator's signature

(confirming that the data on these pages are accurate and complete)

Date

Day
Month
Year

Investigator's name (print)



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PREGNANCY NOTIFICATION FORM (SUBJECT)

This form should be completed according to the protocol reporting requirements.

Complete this form for each subject who becomes pregnant during the study period. Send a copy of the form to GlaxoSmithKline (GSK will provide separately a list of contact names and information) by mail or fax (fax preferred) within two weeks of learning of the pregnancy. Original pages should remain with the subject's Case Report Form.

Note: This form does not routinely need to be completed for subject's partner pregnancy unless there is specific instruction to do so stated in the protocol.

MOTHER'S RELEVANT MEDICAL/FAMILY HISTORY

Mother's date of birth Day Month Year Date of last menstrual period Day Month Year

Estimated date of delivery Day Month Year

Was the mother using a method of contraception?

☐ Yes ☐ No

If Yes, specify _____

Type of conception, ✓one: ☐ Normal (includes use of fertility drugs)
☐ IVF (in vitro fertilisation)

Relevant laboratory tests and procedures (e.g., ultrasound, amniocentesis and chorionic villi sampling, including dates of tests and procedures).

Number of previous pregnancies Pre-term Full-term

If applicable, record the number in the appropriate categories below:

Normal births	Spontaneous abortion
Stillbirths	Elective abortion
Children born with defects	Other

Record details of children born with defects _____

Are there any additional factors that may have an impact on the outcome of this pregnancy?

☐ Yes ☐ No

If Yes, specify _____



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PREGNANCY NOTIFICATION FORM (SUBJECT) (Continued)**FATHER'S RELEVANT MEDICAL/FAMILY HISTORY**

(Include habitual exposures such as alcohol/substance abuse, chronic illnesses, familial birth defects/genetic/chromosomal disorders and medication use)

DRUG EXPOSURES

In the following table, list **all** medications (including study medications) the subject received during the study period (e.g. prescription, OTC, vaccines, recreational, alcohol, etc.). **Enter the investigational product details on the first line** (if the investigational product is blinded, enter 'Investigational Product' on this line). If there are extensive concomitant medications, attach a copy of the Concomitant Medications CRF page.

Drug Name (Trade Name preferred)	Route of Admin. or For- mulation	Total Daily Dose	Units	Started Pre- Study Y=Yes N=No	Start Date Day Month Year	Stop Date Day Month Year	Ongoing Med- ication Y=Yes N=No	Reason for Medication

Was the subject withdrawn from the study as a result of this pregnancy?

☐ Yes ☐ No

REPORTING INVESTIGATOR INFORMATION (Forward to a more appropriate physician if needed)

Name _____ Title _____ Speciality _____

Address _____

City or State/Province _____

Country _____

Post or Zip Code _____

Telephone No _____

Fax No _____

Investigator's signature _____ Date
(confirming that the data on these pages are accurate and complete)

Investigator's name (print) _____

INSTRUCTIONS FOR COMPLETING SERIOUS ADVERSE EVENT FORMS (SAE)

SECTION 12 SAE Additional/Follow-up Information	On receipt of follow-up information, the appropriate section(s) on the SAE form must be amended/updated with any changes (i.e., diagnosis, end date or death, change in intensity, or causality). These changes must be initialled and dated with confirmation by the investigator with his/her re-signing the form and forwarded to GCSP within 24 hours. The investigator and others responsible for subject care should institute any supplementary investigations of SAEs based on their clinical judgement of the likely causative factors. This may include seeking a further opinion from a specialist in the field of the AE. GSK may also request extra tests or extra follow-up information. If a subject dies, any post-mortem/autopsy findings, including histopathology, must be provided to GSK.



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Protocol Identifier SFA100062	Subject Identifier 	Centre Number 	Randomisation Number 	

SERIOUS ADVERSE EVENT (SAE) - ADDITIONAL/FOLLOW-UP INFORMATION (Continued)

SECTION 12 SAE Additional/Follow-up Information (use this page to provide any additional details on the SAE not already captured on the previous pages)

Investigator's signature _____
(confirming that the data on this page is accurate and complete)

Investigator's name (print) _____

Date

Day	Month	Year

Page 9999. _____



Case Report Form

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Subject Identifier

SFA100062

A Randomized, Parallel Group, Double-Blind, Comparative Trial Assessing Lung Function and Other Measures of Asthma Control in Adults and Adolescents, at Least 12 Years of Age, with Persistent Asthma, Who Have Either a B16-Arg/Arg, a B16-Gly/Gly or a B-16 Arg/Gly Genotype and are Treated With Fluticasone Propionate/Salmeterol DISKUS® Combination Product 100/50mcg or Salmeterol DISKUS 50mcg BID



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Protocol Identifier	Subject Identifier	Centre Number
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COVER SHEET - TRACKING DETAILS

A Randomized, Parallel Group, Double-Blind, Comparative Trial Assessing Lung Function and Other Measures of Asthma Control in Adults and Adolescents, at Least 12 Years of Age, with Persistent Asthma, Who Have Either a B16-Arg/Arg, a B16-Gly/Gly or a B-16 Arg/Gly Genotype and are Treated With Fluticasone Propionate/Salmeterol DISKUS® Combination Product 100/50mcg or Salmeterol DISKUS 50mcg BID

Module Number 1

Visits included in this Module: Visit 1 (Screen), Pharmacogenetics, Screen Failures, Visits 2 - 11, Premature Discontinuation Visit, Investigational Product, Investigational Product Compliance, Status of Treatment Blind, Asthma Exacerbations, Asthma Concomitant Medications, Non-Asthma Concomitant Medications, Non-Serious Adverse Events, Serious Adverse Events, Study Conclusion, Investigator Comment Log, Investigator's Signature.

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COMPLETION GUIDELINES FOR CASE REPORT FORMS (CRFS)

GENERAL INSTRUCTIONS FOR CRF COMPLETION

- Complete CRFs in English; answer all questions on every page unless directed otherwise.
- Print neatly and legibly; use a black ballpoint pen and press firmly so that all copies are legible.
- Do not write information on page margins.
- Avoid use of abbreviations and acronyms whenever possible. If abbreviations must be used, use only clear abbreviations that are in standard medical use, or those supplied on instructional pages in this CRF.
- Enter Subject Identifier in the space provided at the top of each CRF page.
- Do not write the Subject's name or initials anywhere inside the CRF.
- Record all values in the units indicated on the CRF (e.g., Height in centimetres, Weight in kilograms).
- Where boxes are provided in the CRF to record numbers, complete as follows, using leading zeroes if necessary: 6 recorded as

0	6

.
- Ensure that information classified as "Other, specify" does not fit into one of the listed categories. Record a concise reason in the "specify" field that accompanies "Other", if "Other" is ✓.
- If extra pages need to be inserted between numbered CRF pages, do the following: insert the first extra page after the last numbered page in the section of the CRF affected (e.g., Concomitant Medications) and number the extra page as nn.01. Subsequent extra pages are then numbered nn.02, nn.03 etc.

DATE

- If the CRF is not completed at time of subject assessment, record date of assessment, not date of CRF completion.
- Use the first three letters of each month as the abbreviation for the months (e.g., JAN, FEB, MAR).

0	1	J	A	N	0	4
Day		Month			Year	

 = 1st January 2004

TIME

- Record time in 24-hour clock format unless specified otherwise, per conversion chart below.

a.m.		p.m.	
Midnight = 00:00	6:00 = 06:00	Noon = 12:00	6:00 = 18:00
1:00 = 01:00	7:00 = 07:00	1:00 = 13:00	7:00 = 19:00
2:00 = 02:00	8:00 = 08:00	2:00 = 14:00	8:00 = 20:00
3:00 = 03:00	9:00 = 09:00	3:00 = 15:00	9:00 = 21:00
4:00 = 04:00	10:00 = 10:00	4:00 = 16:00	10:00 = 22:00
5:00 = 05:00	11:00 = 11:00	5:00 = 17:00	11:00 = 23:00

Note: Midnight = 00:00 is the start of the new day, not the end of the previous day.

MISSING INFORMATION

- Use the following abbreviations for missing information.
 - NA not available/not applicable
 - ND not done
 - UNK unknown
 - NR no result (to be used only for missing data recorded on Local Lab pages)

CRF CORRECTION PROCESS

- Draw a single line through an incorrect entry and write the correct information nearby.
- Initial and date all corrections, additions or deletions.
- DO NOT erase, write over, use correction fluid or tape, or re-copy the original page to correct errors.

TIME AND EVENTS TABLE

Screening, Open-label, and Blinded Treatment Periods	Screen	Open-Label	Open-Label	Open-Label	Open-Label	Blinded	Blinded	Blinded	Blinded	Blinded	Washout	Pre-mature Discontinuation
Visit	1	2	3	4	5	6	7	8	9	10	11	
Week		-16	-12	-8	-4	0	4	8	12	16	18	
Number of Days from Visit 6						0	28±2	56±2	84±2	112±2	126±2	
Informed Consent	x ^a											
Medical History	x											
Physical Examination	x									x		x
Adverse Event Assessment	x ^b	x ^b	x	x	x	x	x	x	x	x	x	x
Concomitant Medication Assess-	x	x	x	x	x	x	x	x	x	x	x	x
Vital Signs	x									x		x
Venipuncture	x ^c											
Urinalysis for Pregnancy		x		x		x		x		x	x	x
Clinic FEV ₁	x ^d	x	x ^f	x ^f	x ⁱ	x ^f	x	x	x	x	x	x
Reversibility	x ^e											
Maximum Albuterol Dose Response Assessment (MADR)				x ^g		x ^g				x ^g		
Dispense Peak Flow Meter		x										
Dispense Study Medication (rescue, open-label, blinded)		x	x	x	x	x	x	x	x	x		
Collect Study Medication (rescue, open-label, blinded)			x	x	x	x	x	x	x	x	x	x
Dispense Diary Card		x	x	x	x	x	x	x	x	x		
Collect / Review Diary Data			x	x	x	x	x	x	x	x	x	x
^a Consent must be signed prior to the withholding of any medication ^b Study participation events only ^c Take 2 tubes of blood at Visit 1, one for genotyping and one for pharmacogenetics ^d Visit 1 FEV ₁ percent predicted assessment ^e If reversibility assessment is failed twice, site can perform methacholine challenge testing ^f Continuation assessment ^g Take vital signs before MADR and at least once after each dose of albuterol is administered												

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**GENERAL CRF
MONITOR DATA VALIDATION CHECKS**

All CRF pages must be reviewed for consistency, completeness, logic and legibility in line with SOP-WWD –1103, Section 6.3 and ICH GCP E6 5.18.4 to include:

- Accurate identifier information completed on every CRF page.
- Identification & completion of missing CRF pages and blank data fields in line with the instructions pre-printed in the CRF.
- Validity and chronology of recorded dates and times.
- Ensuring only one ✓ box response is completed in response to a given question (unless otherwise indicated on the CRF).
- Review of free text fields for spelling and translation errors.
- Where an option of Other; *specify* is provided, specify text should only be completed when the 'Other' option is ✓. A concise text entry, which does not match one of the alternative specified options, should be present in the space provided.
- Data is placed at the correct visit and on the correct CRF page.

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DEMOGRAPHY

INVESTIGATOR INSTRUCTIONS

Note: If the subject is of mixed heritage, choose the ethnicity the subject feels is most prevalent.

- Ensure that you ✓ only one box for Ethnicity.
- **Hispanic or Latino** A person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term, "Spanish origin," can be used in addition to "Hispanic or Latino."

Note: If the subject is of mixed race, choose the race the subject feels is most prevalent or ✓ the "Other" box.

- Ensure that you ✓ only one primary box for Race.
- **Arabic/North African** A person having origins in any of the original peoples of the Middle East, or North Africa.
- **Black - African American** A person having origins within the United States of America and in any of the black racial groups of Africa residing within the United States of America.
- **Black - African Heritage** A person having origins outside of the United States of America and in any of the black racial groups of Africa residing outside of the United States of America.
- **East and South East Asian** A person having origins in any of the original peoples of the Far East, Southeast Asia including, for example, China, Korea, Malaysia, the Philippine Islands, Thailand, Cambodia and Vietnam.
- **Japanese** A person having origins in any of the original peoples of Japan.
- **South Asian** A person having origins in any of the original peoples of the Indian subcontinent including, for example, India, Pakistan and Bangladesh.
- **White/Caucasian** A person having origins in any of the original peoples of Europe.

Other:

- **Native Hawaiian** A person having origins in any of the original peoples of Hawaii.
- **Other - Pacific Islander** A person having origins in any of the original peoples of Guam, Samoa, or other Pacific Islands.
- **American Indian** A person having origins in any of the original peoples of North and South America (including Central America), and who maintains tribal affiliation or community attachment.
- **Alaska Native** A person having origins in any of the original peoples of Alaska who maintains tribal affiliation or community attachment.



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Protocol Identifier	Subject Identifier	Visit Date			Visit Description
SFA100062		Day 	Month 	Year 	Visit 1 (Screen)

DEMOGRAPHY

Date of birth
Day Month Year

Sex [M] ☐ Male
 [F] ☐ Female

Ethnicity *If the subject is of mixed heritage, choose the ethnicity the subject feels is most prevalent.*
✓ only one:
 [1] ☐ Hispanic or Latino
 [2] ☐ Non-Hispanic or Latino

Race¹ *If the subject is of mixed race, choose the race the subject feels is most prevalent or ✓ the "Other" box.*
✓ only one primary race box:
 [2] ☐ Arabic/North African
 [3] ☐ Black
 [1] ☐ African American
 [2] ☐ African Heritage
 [4] ☐ East & South East Asian
 [5] ☐ Japanese
 [6] ☐ South Asian
 [7] ☐ White/Caucasian
 [2] ☐ Other
 [3] ☐ Native Hawaiian
 [4] ☐ Other Pacific Islander
 [5] ☐ American Indian
 [6] ☐ Alaska Native

¹ See facing page for race definitions.

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***SUBJECT RECRUITMENT
INVESTIGATOR INSTRUCTIONS*****PRIMARY METHOD DEFINITION**

Primary method should be the reason that prompted subject's interest in the study.

For example:

The Investigator provided a clinic patient with information about a study and the patient decided to participate but mentioned that he/she heard about the study on the radio. Clinic patient would be the reason ✓. However, if a clinic patient heard about a study on a local radio show and initiated contact with the clinic for information then Local radio advertisement would be ✓.

- Indicate the **primary method** for subject recruitment into the study by placing a ✓ in the appropriate box.
- Ensure that you ✓ **only one** box.

***SUBJECT RECRUITMENT
MONITOR DATA VALIDATION CHECKS***

- Ensure that page has been completed and only one 'primary method' has been ✓.



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Protocol Identifier	Subject Identifier	Visit Description
SFA100062		Visit 1 (Screen)

SUBJECT RECRUITMENT

What is the **primary method** that prompted the subject's interest in the study?

✓ *only one:*

- [1] ☐ Clinic patient (site actively reviews patient charts and/or databases and initiates contact with patient.)
- [2] ☐ Physician referral (e.g., lunch-n-learn, letter to colleagues, etc.)
- [3] ☐ Referred by family member
- [4] ☐ Referred by study participant
- [5] ☐ Subject-initiated internet search (e.g., discovered findclinicalstudy.com)
- [6] ☐ Other internet provider paid by GSK (e.g., harrisinteractive.com), *specify*
- [7] ☐ Information in clinic (e.g., posters, brochures, etc.)
- [8] ☐ Community outreach (e.g., healthfair, advocacy groups, support groups, etc.)
- [9] ☐ Local newspaper advertisement
- [10] ☐ Local radio advertisement
- [11] ☐ Other local paid advertisement (e.g., local television, local direct mail, etc.)
- [12] ☐ Information at daycare
- [13] ☐ National radio campaign
- [14] ☐ National television campaign
- [15] ☐ Other national campaign (e.g., national magazine, national direct mail, etc.)
- [16] ☐ Call center
- [OT] ☐ Other, *specify* _____

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**INCLUSION AND EXCLUSION CRITERIA
MONITOR DATA VALIDATION CHECK**

- Confirm that the subject is eligible to participate in the study and if not, that all the failed criteria have been marked.

PHYSICAL EXAMINATION

Perform a physical examination including current measurements of height, weight, and vital signs. Record physical exam findings and vital signs in subject's source documents.

CONCOMITANT MEDICATIONS

Record details of the subject's ongoing concomitant medications in the appropriate Concomitant Medications section.

CLINICAL LABORATORY TESTS

Collect (2) blood samples from the subject for genotyping and pharmacogenetic analysis.



Protocol Identifier	Subject Identifier	Visit Description
SFA100062		Visit 1 (Screen)

ELIGIBILITY QUESTION

Did the subject meet all the entry criteria?

[Y] ☐ Yes [N] ☐ No

If No, ✓ all boxes corresponding to violations of any inclusion/exclusion criteria.

*Do **not** enter the subject into the study if they failed any inclusion or exclusion criteria below.*

INCLUSION CRITERIA

✓ the boxes corresponding to any of the inclusion criteria the subject failed.

1. ☐ **Type of Subject:** A subject must be treatable on an outpatient basis.

2. ☐ **Age:** A subject must be 12 years of age or older at Visit 1.

3. ☐ **Gender:** Male or Female.

Females are eligible to participate only if they are currently non-pregnant and non lactating. There are no birth control restrictions for this study. Female subjects of childbearing potential will undergo a urine pregnancy test at the beginning of the study (Visit 2) and at Visit 4, 6, 8, 10 and at the end of the study (Visit 11 or a **Premature Discontinuation Visit which may occur during the open-label periods, the double-blind treatment period, or the washout period**). Any female who becomes pregnant during the study will be withdrawn. Female subjects should not be enrolled if they plan to become pregnant during the time of study participation.

4. ☐ **Disease:** Each subject must have a diagnosis of persistent asthma for at least 3 months prior to Visit 1. Asthma is defined by the American Thoracic Society as follows:

"Asthma is a clinical syndrome characterized by increased responsiveness of the tracheobronchial tree to a variety of stimuli. The major symptoms of asthma are paroxysms of dyspnea, wheezing, and cough, which may vary from mild and almost undetectable to severe and unremitting (status asthmaticus). The primary physiological manifestation of this hyperresponsiveness is variable airways obstruction. This can take the form of spontaneous fluctuations in the severity of obstruction, substantial improvements in the severity of obstruction following bronchodilators or corticosteroids, or increased obstruction caused by drugs or other stimuli" [American Thoracic Society, 1987].

5. ☐ **FEV₁ Component:** The subject has a best FEV₁ that is $\geq 70\%$ and $\leq 100\%$ of predicted normal at Visit 1 after withholding asthma medications as detailed in the protocol. Predicted FEV₁ will be based on the **National Health and Nutrition Examination Survey (NHANES III) predicted normal values for ages 8 years and older [Hankinson, 1999]**.



Protocol Identifier	Subject Identifier	Visit Description
SFA100062		Visit 1 (Screen)

INCLUSION CRITERIA (Continued)

6. ☐ **Reversibility Component:** The subject has reversible airways disease as demonstrated by an increase in FEV₁ of $\geq 12\%$ and 200mL over baseline within 30 minutes after the inhalation of 2-4 puffs (180µg -360µg) of albuterol (with or without a spacer) or 1-2 nebulized albuterol (2 puffs = 1 nebule) treatments at Visit 1 or at a visit that is within the 7-day period immediately following Visit 1. If the subject fails to reverse at least 12% during Visit 1, a second attempt to reverse may be scheduled within 7 days. If the second attempt to document reversibility is unsuccessful, the subject may undergo a methacholine challenge test (MCT). A PC₂₀ result of <8mg/mL obtained at an unscheduled visit prior to Visit 2 is required. An historical PC₂₀ value of <8mg/ml that has been documented at the investigative site within the past 12 months and was obtained using ATS or ACRN guidelines for MCT is also acceptable [American Thoracic Society, 2000; ACRN, 2002]. Methacholine challenge testing should be performed only at sites that have past experience performing this test.
- Note: Documentation of historical reversibility within one year of the Screening Visit demonstrating an increase in FEV₁ of $\geq 12\%$ and 200ml over baseline is acceptable and will preclude the requirement for reversibility testing at the Screening Visit.**
7. ☐ **Concurrent Anti-Asthma Therapy:** Eligible subjects must have reported **short-acting** β_2 -agonist for use on a prn (or scheduled) basis **for at least 4 weeks** prior to Visit 1. Each subject must be judged by the investigator to be able to withhold short-acting β_2 -agonist therapy for at least 6 hours prior to clinic visits when FEV₁ is performed.
8. ☐ The subject agrees to allow a venipuncture for blood draw.
9. ☐ The subject demonstrates correct use of the **DISKUS** device and a MDI, as well as correct use of a peak flow meter.
10. ☐ **Literacy:** A subject must be able to read, comprehend and record information.

EXCLUSION CRITERIA

✓ the boxes corresponding to any of the exclusion criteria that disqualified the subject from entry.

1. ☐ **Life-Threatening Asthma:** A subject may not have life-threatening asthma. Life-threatening asthma is defined for this protocol as a history of significant asthma episode(s) requiring intubation, associated with hypercapnia, respiratory arrest, hypoxic seizures, or asthma-related syncopal episode(s).
2. ☐ **Asthma instability:** A subject must not have been hospitalised due to asthma one or more times within 6 months prior to Visit 1.
3. ☐ **Respiratory Disease:** Current evidence of cystic fibrosis, pneumonia, pneumothorax, atelectasis, pulmonary fibrotic disease, chronic bronchitis or any other respiratory abnormalities other than asthma excludes a subject from participation.



Protocol Identifier	Subject Identifier	Visit Description
SFA100062		Visit 1 (Screen)

EXCLUSION CRITERIA (Continued)

4. ☐ **Anti-Asthma Medications:** Asthma medications listed below must not have been used prior to Screening (Visit 1) for the required interval indicated below, and not taken during the study.
- | | |
|--|-------------------------|
| Nebulized short-acting beta ₂ -agonists | 6 hours |
| Oral short-acting beta ₂ -agonists | 6 hours |
| Inhaled short-acting anticholinergics | 6 hours |
| Inhaled long-acting anticholinergics | 24 hours |
| Leukotriene modifiers | 4 weeks |
| Inhaled long-acting beta ₂ -agonists | 4 weeks |
| Theophylline products | 48 hours |
| Oral long-acting beta ₂ -agonists | 4 weeks |
| Inhaled corticosteroids | 4 weeks |
| Inhaled corticosteroid/Inhaled long-acting beta ₂ -agonist combination products | 4 weeks |
| Oral corticosteroids | 4 weeks ^{1, 2} |
| Parenteral corticosteroids | 4 weeks ² |
| Inhaled cromolyn sodium or nedocromil | 4 weeks |
- ¹ Any subject who has received oral corticosteroid treatment for any reason for 2 months or longer must have discontinued use for at least 6 months prior to Visit 1.
- ² A subject must not have had two courses of oral or parenteral corticosteroids for any reason in the 6 months prior to Visit 1.
5. ☐ **Concurrent Medications:** Concurrent use of any of the following medications that may affect the course of asthma or interact with sympathomimetic amines will not be allowed. Specifically:
- beta blockers
 - polycyclic antidepressants
 - monoamine oxidase inhibitors
 - phenobarbital
 - rifampin
- Note: Regular use of short-acting nasal decongestants is allowed. Other intranasal medications including antihistamines and intranasal corticosteroids for the treatment of rhinitis are also allowed. Topical hydrocortisone cream or ointment (1% or less) is also allowed.*
6. ☐ **Immunosuppressive Medications:** Use of immunosuppressive medications is not allowed at any time during the study.
- Note: Immunotherapy for the treatment of allergies is allowed during the study, provided that the subject has received a constant dose for 30 days prior to Visit 1, and that the same dose will be continued throughout the study.*
7. ☐ **Other Medications:** The medications listed below must not have been used prior to Screening (Visit 1) for the required interval indicated below, and not taken during the study.
- | | |
|---|-----------|
| • Methotrexate, gold, cyclosporine and azathioprine | 12 Months |
| • Ritonavir | 12 Months |



Protocol Identifier	Subject Identifier	Visit Description
SFA100062		Visit 1 (Screen)

EXCLUSION CRITERIA (Continued)

8. ☐ **Respiratory Tract Infection:** The subject has a respiratory infection that is suspected or diagnosed within 4 weeks immediately preceding Visit 1 or during the period from Visit 1 to **Visit 2**. The subject may be re-screened one time. Rescreening must be no sooner than 4 weeks following resolution of any suspected or diagnosed respiratory infection (whether treated or not).
9. ☐ **Antibiotic Usage:** The subject used an antibiotic (or other medication) for treatment of a suspected or diagnosed upper or lower respiratory tract infection within 4 weeks of Visit 1 or during the periods from Visit 1 to **Visit 2**. The subject may be re-screened one time. Antibiotics for other infections or acne are permitted.
10. ☐ **Other Concurrent Conditions/Diseases:** Any clinically significant, uncontrolled condition or disease state that, in the opinion of the investigator, would put the safety of the subject at risk through study participation or would confound the interpretation of the results if the condition/disease exacerbated during the study excludes a subject from participation. The list of conditions/diseases that will result in exclusion if determined to be clinically significant includes, but is not limited to: cardiac arrhythmias, congestive heart failure, coronary artery disease, Cushing's or Addison's disease, diabetes mellitus, dyspnea by any cause other than asthma, hematological, hepatic, neurological, thyroid, peptic ulcer, or renal disease, uncontrolled hypertension, immunologic compromise, current malignancy, current or quiescent tuberculosis.
11. ☐ **Drug Allergy:** The subject has any adverse reaction, including immediate or delayed hypersensitivity, to study medications, severe milk protein allergy or allergies to soya lecithin or related food products such as soybeans or peanuts.
12. ☐ **Tobacco Use:** The subject has a greater than 10 pack-year history of cigarette smoking and/or use of any tobacco products within 1 year of Visit 1.
13. ☐ **Positive Pregnancy Test (for females of childbearing potential):** A current positive pregnancy test.
14. ☐ **Questionable Validity of Consent:** The subject or parent (caregiver) has a history of psychiatric disease, intellectual deficiency, poor motivation, substance abuse (including drug and alcohol), or other conditions which would limit the validity of informed consent to participate in the study.
15. ☐ **Investigational Drug:** A subject may not have been exposed to an investigational drug within 30 days prior to Visit 1.
16. ☐ **Affiliation with Investigational Site:** A subject may not participate if he/she is a participating investigator, sub-investigator, study coordinator, or employee of a participating investigator, or is an immediate family member of the aforementioned.
17. ☐ **Questionable Compliance with Medications or Visits:** A subject may not participate if he/she has an infirmity, disability or geographical location which seems likely, in the opinion of the investigator, to impair compliance with any aspect of this study protocol or scheduled visits.
18. ☐ **Exercise-Induced Bronchospasm Alone:** A subject may not have been diagnosed with exercise-induced bronchospasm alone, in the absence of a diagnosis of persistent asthma within the last 3 months prior to Visit 1.

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**MEDICAL CONDITIONS
DEFINITIONS****CURRENT MEDICAL CONDITIONS**

Conditions from which the subject is currently suffering, regardless of how long they have been present. If the subject has had a recurring condition that is not present at the time of the assessment, it can be classed as current if, in the Investigator's opinion it is likely to recur during the study.

- Record the subject's asthma and allergy history/information on the Subject and Family Asthma / Atopy History page.

NO MEDICAL HISTORY

No history of any medical conditions.



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Protocol Identifier	Subject Identifier	Visit Description
SFA100062		Visit 1 (Screen)

MEDICAL CONDITIONS

MedDRA System Organ Class ✓ only one response for each system organ class	Current [1]	No Medical History [3]
1. Blood and lymphatic system disorders		
2. Cardiac disorders		
3. Ear and labyrinth disorders		
4. Endocrine disorders		
5. Eye disorders		
6. Gastrointestinal disorders		
7. Hepatobiliary disorders		
8. Immune system disorders		
9. Metabolism and nutrition disorders		
10. Musculoskeletal and connective tissue disorders		
11. Neoplasms benign, malignant and unspecified (including cysts and polyps)		
12. Nervous system disorders		
13. Psychiatric disorders		
14. Renal and urinary disorders		
15. Reproductive system and breast disorders		
16. Skin and subcutaneous tissue disorders		
17. Vascular disorders		
18. Infections and infestations		
19. Congenital, familial and genetic disorders		
20. General disorders and administration site conditions		

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DURATION OF ASTHMA MONITOR DATA VALIDATION CHECKS

- Ensure that the Duration is not greater than the subject's age.
- Ensure that both years and months boxes have been recorded, including leading zeros where applicable.
- Ensure that months are in the range of 0-11.

*Note: 12 months must be entered as 1 year. If only years are known enter months as 00.
(e.g., 24 months should be entered as 2 years 00 months, 35 months should be entered as 2 years 11 months).*

SUBJECT AND FAMILY ASTHMA / ATOPY HISTORY

INVESTIGATOR INSTRUCTIONS

- Ask the subject's parent/guardian the three questions regarding exposure to passive smoke, pets, and school settings and place a ✓ in either the YES or NO box for each question.
- Determine if the subject or any of the subject's family members listed have a history of any of the conditions listed in the table. Place a ✓ in the appropriate space for all conditions that are known to exist for each family member.

MONITOR DATA VALIDATION CHECKS

- Check that the questions regarding exposure to passive smoke, pets, and school settings have been ✓ either YES or NO.
- Check that a ✓ has been placed in the appropriate space(s) for all conditions that are known to exist for each family member.



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Protocol Identifier	Subject Identifier		Visit Description
SFA100062			Visit 1 (Screen)

DURATION OF ASTHMA

Duration		years		months

SUBJECT AND FAMILY ASTHMA / ATOPY HISTORY

Is the subject exposed to passive smoke in the home or school environment?	[Y] ☐ Yes	[N] ☐ No							
Is the subject exposed to pets in the home or school environment?	[Y] ☐ Yes	[N] ☐ No							
Does the subject attend school?	[Y] ☐ Yes	[N] ☐ No							
Does the subject or any of the subject's immediate family have a history of any of the following?	[Y] ☐ Yes	[N] ☐ No							
If Yes, ✓ all that are known to apply:									
	Asthma	Croup	Eczema	Food allergy	Hives	Pet allergy	Sinus infection(s)	Seasonal allergies or hay fever ¹	Year-round hay fever
e.g., Subject	✓					✓		✓	
Subject (SB)									
Father (F)									
Mother (M)									
Sibling(s) (S)									
Maternal grandparent(s) (MG)									
Paternal grandparent(s) (PG)									

¹ Allergies to pollens, grasses, etc.

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Protocol Identifier

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HISTORICAL REVERSIBILITY MONITOR DATA VALIDATION CHECKS

- Ensure that if the historical reversibility question is answered 'Yes' that the percent changed has been recorded in the space provided.

PULMONARY FUNCTION TESTING MONITOR DATA VALIDATION CHECKS

- Ensure that the appropriate test is within the protocol defined range.
- Ensure that predicted normal(s) is/are correct from the table provided.
- Ensure that % Predicted Normal(s) calculation(s) ($\frac{A}{B} \times 100$) is/are correct and within the protocol specified range(s).
- Ensure that the % Reversibility calculation ($\frac{C - A}{A} \times 100$) is correct.
- Ensure that % Predicted Normal has been rounded accurately to 1 decimal place.
- Ensure that % Reversibility has been rounded accurately to 1 decimal place.
- Ensure that 3 Pre-dose and Post-dose measurements were taken and only the highest of the 3 technically acceptable measurements was recorded where indicated.
- Ensure that FEV₁ has been rounded accurately to 2 decimal places.
- Ensure that all spirometry printouts are signed and dated by the responsible person and clearly indicate the clinic visit, the date of the visit, and the GlaxoSmithKline subject number.
- The spirometry printouts must be stored in the CRF Binder.
- If spirometry printouts are on thermal paper the pages must be copied.

HISTORICAL METHACHOLINE CHALLENGE MONITOR DATA VALIDATION CHECKS

- Ensure that if the historical methacholine challenge question is answered 'Yes' that a value has been recorded in the space provided.

METHACHOLINE CHALLENGE

INVESTIGATOR INSTRUCTIONS

- The subject may undergo methacholine challenge testing (MCT) once if the second attempt to document reversibility is unsuccessful. See Section 6.5.1.3 of the protocol.
- The testing should be performed between 6 AM and 11 AM.

MONITOR DATA VALIDATION CHECKS

Ensure that PC₂₀ is correctly recorded and is within protocol specifications.



GlaxoSmithKline



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Protocol Identifier	Subject Identifier		Visit Description
SFA100062			Visit 1 (Screen)

HISTORICAL REVERSIBILITYDoes the subject have historical reversibility of $\geq 12\%$ and 200 mL over baseline?[Y] ☐ Yes [N] ☐ NoIf Yes, record percent changed %**PULMONARY FUNCTION TESTING**

Test	Actual Measurement Pre-Bronchodilator (highest of 3 technically acceptable measurements)	Predicted Normal	% Predicted Normal	Actual Measurement 30 minutes Post-Bronchodilator (highest of 3 technically acceptable measurements)	% Reversibility
	A	B	$\frac{A}{B} \times 100$	C	$(\frac{C-A}{A} \times 100)$
e.g., FEV ₁ (L)	1.75	3.25	53.8	1.82	2.2
FEV ₁ (L)	.	.	.	.	.

HISTORICAL METHACHOLINE CHALLENGEDoes the subject have historical methacholine challenge MCT with a PC₂₀ result of less than 8 mg/mL?[Y] ☐ Yes [N] ☐ NoIf Yes, record value mg/mL**METHACHOLINE CHALLENGE****Note:** If a PC₂₀ <8mg/mL is documented during an unscheduled visit prior to Visit 2, the subject is eligible.PC₂₀ mg/mL✓ if Methacholine Challenge not done/not needed ☐

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SCREEN / OPEN-LABEL FAILURE MONITOR DATA VALIDATION CHECKS

- A subject who has at least one study procedure performed (in addition to signing a consent form), and is assigned a subject number (see Section 7.5.1 of the protocol 'Assignment of Subject Number'), but does not participate in the open-label period(s) is classified as having **failed screening (Visit 1)**. The following information will be collected in the CRF on subjects who fail at the Screening Visit (Visit 1) or any time prior to Visit 2.

The following information will also be collected in the CRF on subjects who fail at Visit 2 or any time during the open-label periods prior to Visit 6:

- Demographic information (including race, age and gender)
- Inclusion/exclusion criteria
- Duration of asthma
- Asthma concomitant medications
- Non-asthma concomitant medications
- Reversibility assessment
- Pulmonary function tests (including MADR), if applicable
- Continuation criteria, if applicable
- Reason subject was a screening or open-label failure
- Pharmacogenetic (PGx) information
- Investigational product information
- Asthma exacerbation data
- Any adverse events/SAEs that occur during the screening and open-label periods
- Investigator comments
- Investigator signature
- Diary cards, if applicable
- Complete and transmit those CRF pages to GSK.
- Refer to Section 9.3 of the protocol to evaluate subject screen or open-label failures from the study.
- If the subject is a screen or open-label failure, ensure that at least one reason has been ✓.
- Check that either 'Yes' or 'No' box at the top of the page has been completed. If 'Yes' is ✓, ensure that a complete failure date is present.
- Ensure that at least one box is ✓ for screen or open-label failure reason.
- Ensure that if 'Other, specify' is ✓ a reason is provided on the specify line.

Note: All pharmacogenetic samples from screen or open-label failures are to be destroyed. Therefore, if a blood sample was collected for a screen or open-label failure, complete the PGx-Pharmacogenetic destruction form and fax it to the GSK Study Manager.



Protocol Identifier	Subject Identifier
SFA100062	

SCREEN / OPEN-LABEL FAILUREWas this subject a screen or open-label failure?¹[Y] ☐ Yes [N] ☐ No

If Yes, record the screen or open-label failure date

Day	Month	Year			

If Yes, ✓ *primary reason:*[1] ☐ Adverse event →*Record details on Non-Serious Adverse Events or Serious Adverse Event page(s) as appropriate.*[2] ☐ Lost to follow-up[4] ☐ Subject decided to withdraw from study[5] ☐ Prohibited medication use[6] ☐ Did not fulfil eligibility criteria[7] ☐ Exacerbation of medical condition →
under investigation*Exacerbations will not be classified as adverse events unless the exacerbation meets the definition of a serious adverse event as defined in the protocol.*[9] ☐ Genotype quota filled[10] ☐ Did not fulfil continuation criteria[OT] ☐ Other, specify _____

¹ **All pharmacogenetic samples from screen or open-label failures are to be destroyed. Therefore, if a blood sample was collected for a screen or open-label failure, complete the PGx-Pharmacogenetic destruction form and fax it to the GSK Study Manager.**

PREGNANCY INFORMATION

Did the subject become pregnant during the study?

[Y] ☐ Yes [N] ☐ No [X] ☐ Not Applicable (not of childbearing potential or male)

If Yes, complete Pregnancy Notification form.

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Final Protocol Amendment 2 - 27 JUN 05
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Perform a urine pregnancy test on all females of childbearing potential.

CONCOMITANT MEDICATIONS

Record any changes to the subject's concomitant medications or any new medications taken since the last visit in the appropriate Concomitant Medications section.

ADVERSE EVENTS

Record details of any new non-serious adverse events/serious adverse events observed or reported by the subject or any changes to ongoing non-serious adverse events in the appropriate Non-Serious Adverse Events/ Serious Adverse Event section.

CONTINUATION CRITERIA

- Ensure that the Continuation Criterion has been completed and subject is eligible to continue in the study.
- Ensure that the subject has a best $FEV_1 \geq 70\%$ of predicted at Visit 2.

 **FEV_1
MONITOR DATA VALIDATION CHECKS**

- Ensure that the correct FEV_1 measurement has been recorded.
- Ensure that the FEV_1 is within the protocol defined inclusion/continuation range.
- Ensure that the FEV_1 is rounded accurately to 2 decimal places.
- Ensure that all spirometry printouts are signed and dated by the responsible person and clearly indicate the clinic visit, the date of the visit, and the GlaxoSmithKline subject number.
- The spirometry printouts must be stored in the CRF binder.
- If spirometry printouts are on thermal paper the pages must be copied.



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Protocol Identifier	Subject Identifier	Visit Date			Visit Description
SFA100062		Day 	Month 	Year 	Visit 2

CONTINUATION CRITERION

Did the subject meet the following continuation criterion?

1. A best
- $FEV_1 \geq 70\%$
- of predicted.

[Y] ☐ Yes [N] ☐ No*If No, **do not** continue the subject in the study.* **FEV_1** *Record the highest of 3 technically acceptable measurements.* FEV_1 . (L)

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Protocol Identifier

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CONTINUATION CRITERIA

- Ensure that the Continuation Criterion has been completed and subject is eligible to continue in the study.
- Ensure that the subject has a best $FEV_1 \geq 70\%$ of predicted and <56 puffs per week of rescue medication, for all of the previous 4 weeks since the last visit.

CONCOMITANT MEDICATIONS

Record any changes to the subject's concomitant medications or any new medications taken since the last visit in the appropriate Concomitant Medications section.

ADVERSE EVENTS

Record details of any new non-serious adverse events/serious adverse events observed or reported by the subject or any changes to ongoing non-serious adverse events in the appropriate Non-Serious Adverse Events/ Serious Adverse Event section.

 **FEV_1
MONITOR DATA VALIDATION CHECKS**

- Ensure that the correct FEV_1 measurement has been recorded.
- Ensure that the FEV_1 is within the protocol defined inclusion/continuation range.
- Ensure that the FEV_1 is rounded accurately to 2 decimal places.
- Ensure that all spirometry printouts are signed and dated by the responsible person and clearly indicate the clinic visit, the date of the visit, and the GlaxoSmithKline subject number.
- The spirometry printouts must be stored in the CRF binder.
- If spirometry printouts are on thermal paper the pages must be copied.



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Protocol Identifier	Subject Identifier	Visit Date			Visit Description
SFA100062		Day 	Month 	Year 	Visit 3

CONTINUATION CRITERION

Did the subject meet the following continuation criterion?

1. A best $FEV_1 \geq 70\%$ of predicted **and** < 56 puffs per week of rescue medication.

[Y] ☐ Yes [N] ☐ No

*If No, **do not** continue the subject into the study.*

 FEV_1

Record the highest of 3 technically acceptable measurements.

FEV_1 . (L)

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Protocol Identifier

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CONTINUATION CRITERIA

- Ensure that the Continuation Criterion has been completed and subject is eligible to continue in the study.
- Ensure that the subject has a best FEV₁ ≥70% of predicted and <56 puffs per week of rescue medication, for all of the previous 4 weeks since the last visit (rescue medications = albuterol + ipratropium bromide).

PREGNANCY TEST

Perform a urine pregnancy test on all females of childbearing potential.

CONCOMITANT MEDICATIONS

Record any changes to the subject's concomitant medications or any new medications taken since the last visit in the appropriate Concomitant Medications section.

ADVERSE EVENTS

Record details of any new non-serious adverse events/serious adverse events observed or reported by the subject or any changes to ongoing non-serious adverse events in the appropriate Non-Serious Adverse Events/ Serious Adverse Event section.

MAXIMUM ALBUTEROL DOSE ASSESSMENT (MADR)**SAMPLE CALCULATIONS****Sample 1:**

$$\% \Delta = \frac{(\text{current amount} - \text{original amount})}{\text{original amount}} \times 100 \quad \longrightarrow \quad \% \Delta = \frac{(2.92 - 2.65)}{2.65} \times 100 = 10.19\%$$

Cumulative Puffs of Albuterol	FEV ₁ (L)	% Δ From 4 Puffs	If % Δ is >5%, administer 2 more doses of albuterol and repeat spirometry.
0 puffs	2.45	.	
4 puff	2.65	.	
6 puffs	2.92	10.19	
8 puffs	2.95	.	

Sample 2:

$$\% \Delta = \frac{(\text{current amount} - \text{original amount})}{\text{original amount}} \times 100 \quad \longrightarrow \quad \% \Delta = \frac{(2.72 - 2.65)}{2.65} \times 100 = 2.64\%$$

Cumulative Puffs of Albuterol	FEV ₁ (L)	% Δ From 4 Puffs	If % Δ is ≤5%, do not administer any more albuterol or take spirometry again.
0 puffs	2.45	.	
4 puff	2.65	.	
6 puffs	2.72	2.64	
8 puffs	NA	.	



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Protocol Identifier	Subject Identifier	Visit Date			Visit Description
SFA100062		Day 	Month 	Year 	Visit 4

CONTINUATION CRITERION

Did the subject meet the following continuation criterion?

1. A best FEV₁ $\geq$ 70% of predicted **and** <56 puffs per week of rescue medication (rescue medications = albuterol + ipratropium bromide).

[Y] ☐ Yes [N] ☐ No

If No, **do not** continue the subject in the study.

MAXIMUM ALBUTEROL DOSE ASSESSMENT (MADR)

Cumulative Puffs of Albuterol	FEV ₁ (L)	% Δ From 4 Puffs	If % Δ is $\leq$ 5%, do not administer any more albuterol. If % Δ is $>$ 5%, administer 2 more doses of albuterol and repeat spirometry.
0 puffs	.	.	
4 puff	.	.	
6 puffs	.	.	
8 puffs	.	.	

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Final Protocol Amendment 1 - 15 DEC 04
Final - 26 MAY 04**CONTINUATION CRITERIA**

- Ensure that the Continuation Criterion has been completed and subject is eligible to continue in the study.
- Ensure that the subject has a best $FEV_1 \geq 70\%$ of predicted and <56 puffs per week of rescue medication, for all of the previous 4 weeks since the last visit (rescue medications = albuterol + ipratropium bromide).

CONCOMITANT MEDICATIONS

Record any changes to the subject's concomitant medications or any new medications taken since the last visit in the appropriate Concomitant Medications section.

ADVERSE EVENTS

Record details of any new non-serious adverse events/serious adverse events observed or reported by the subject or any changes to ongoing non-serious adverse events in the appropriate Non-Serious Adverse Events/ Serious Adverse Event section.

 **FEV_1
MONITOR DATA VALIDATION CHECKS**

- Ensure that the correct FEV_1 measurement has been recorded.
- Ensure that the FEV_1 is within the protocol defined inclusion/continuation range.
- Ensure that the FEV_1 is rounded accurately to 2 decimal places.
- Ensure that all spirometry printouts are signed and dated by the responsible person and clearly indicate the clinic visit, the date of the visit, and the GlaxoSmithKline subject number.
- The spirometry printouts must be stored in the CRF binder.
- If spirometry printouts are on thermal paper the pages must be copied.



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Protocol Identifier	Subject Identifier	Visit Date			Visit Description
SFA100062		Day 	Month 	Year 	Visit 5

CONTINUATION CRITERION

Did the subject meet the following continuation criterion?

1. A best $FEV_1 \geq 70\%$ of predicted **and** < 56 puffs per week of rescue medication (rescue medications = albuterol + ipratropium bromide).

[Y] ☐ Yes [N] ☐ No

*If No, **do not** continue the subject in the study.*

 FEV_1

Record the highest of 3 technically acceptable measurements.

FEV_1 (L)

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CONTINUATION CRITERIA

- Ensure that the Continuation Criterion has been completed and subject is eligible to continue in the study.
- Ensure that the subject has a best FEV₁ ≥70% of predicted and <56 puffs per week of rescue medication, for all of the previous 4 weeks since the last visit (rescue medications = albuterol + ipratropium bromide).

PREGNANCY TEST

Perform a urine pregnancy test on all females of childbearing potential.

CONCOMITANT MEDICATIONS

Record any changes to the subject's concomitant medications or any new medications taken since the last visit in the appropriate Concomitant Medications section.

ADVERSE EVENTS

Record details of any new non-serious adverse events/serious adverse events observed or reported by the subject or any changes to ongoing non-serious adverse events in the appropriate Non-Serious Adverse Events/ Serious Adverse Event section.

MAXIMUM ALBUTEROL DOSE ASSESSMENT (MADR)**SAMPLE CALCULATIONS****Sample 1:**

$$\% \Delta = \frac{(\text{current amount} - \text{original amount})}{\text{original amount}} \times 100 \quad \longrightarrow \quad \% \Delta = \frac{(2.92 - 2.65)}{2.65} \times 100 = 10.19\%$$

Cumulative Puffs of Albuterol	FEV ₁ (L)	% Δ From 4 Puffs	If % Δ is >5%, administer 2 more doses of albuterol and repeat spirometry.
0 puffs	2.45	.	
4 puff	2.65	.	
6 puffs	2.92	10.19	
8 puffs	2.95	.	

Sample 2:

$$\% \Delta = \frac{(\text{current amount} - \text{original amount})}{\text{original amount}} \times 100 \quad \longrightarrow \quad \% \Delta = \frac{(2.72 - 2.65)}{2.65} \times 100 = 2.64\%$$

Cumulative Puffs of Albuterol	FEV ₁ (L)	% Δ From 4 Puffs	If % Δ is ≤5%, do not administer any more albuterol or take spirometry again.
0 puffs	2.45	.	
4 puff	2.65	.	
6 puffs	2.72	2.64	
8 puffs	NA	.	



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Protocol Identifier	Subject Identifier	Visit Date			Visit Description
SFA100062		Day	Month	Year	Visit 6 (Randomisation Visit)

CONTINUATION CRITERION

Did the subject meet the following continuation criterion?

1. A best Visit 6 FEV₁ $\geq$ 70% of predicted **and** <56 puffs per week of rescue medication (rescue medications = albuterol + ipratropium bromide).

[Y] ☐ Yes [N] ☐ No

If No, **do not** continue the subject in the study.

MAXIMUM ALBUTEROL DOSE ASSESSMENT (MADR)

Cumulative Puffs of Albuterol	FEV ₁ (L)	% Δ From 4 Puffs	If % Δ is $\leq$ 5%, do not administer any more albuterol. If % Δ is $>$ 5%, administer 2 more doses of albuterol and repeat spirometry.
0 puffs	.	.	
4 puff	.	.	
6 puffs	.	.	
8 puffs	.	.	

RANDOMISATION NUMBER

Record randomisation number.

TREATMENT CONFIRMATION

Did the subject receive the correct treatment (e.g., treatment which the subject was randomised to) during this dosing interval?

[Y] ☐ Yes [N] ☐ No

If No, record reason(s)

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CONCOMITANT MEDICATIONS

Record any changes to the subject's concomitant medications or any new medications taken since the last visit in the appropriate Concomitant Medications section.

ADVERSE EVENTS

Record details of any new non-serious adverse events/serious adverse events observed or reported by the subject or any changes to ongoing non-serious adverse events in the appropriate Non-Serious Adverse Events/ Serious Adverse Event section.

**FEV₁
MONITOR DATA VALIDATION CHECKS**

- Ensure that the correct FEV₁ measurement has been recorded.
- Ensure that the FEV₁ is within the protocol defined inclusion/continuation range.
- Ensure that the FEV₁ is rounded accurately to 2 decimal places.
- Ensure that all spirometry printouts are signed and dated by the responsible person and clearly indicate the clinic visit, the date of the visit, and the GlaxoSmithKline subject number.
- The spirometry printouts must be stored in the CRF binder.
- If spirometry printouts are on thermal paper the pages must be copied.



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Protocol Identifier	Subject Identifier	Visit Date			Visit Description
SFA100062		Day 	Month 	Year 	Visit 7

FEV₁*Record the highest of 3 technically acceptable measurements.*FEV₁ (L)**TREATMENT CONFIRMATION**

Did the subject receive the correct treatment (e.g., treatment which the subject was randomised to) during this dosing interval?

[Y] ☐ Yes [N] ☐ No*If No, record reason(s)*

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PREGNANCY TEST

Perform a urine pregnancy test on all females of childbearing potential.

CONCOMITANT MEDICATIONS

Record any changes to the subject's concomitant medications or any new medications taken since the last visit in the appropriate Concomitant Medications section.

ADVERSE EVENTS

Record details of any new non-serious adverse events/serious adverse events observed or reported by the subject or any changes to ongoing non-serious adverse events in the appropriate Non-Serious Adverse Events/ Serious Adverse Event section.

**FEV₁
MONITOR DATA VALIDATION CHECKS**

- Ensure that the correct FEV₁ measurement has been recorded.
- Ensure that the FEV₁ is within the protocol defined inclusion/continuation range.
- Ensure that the FEV₁ is rounded accurately to 2 decimal places.
- Ensure that all spirometry printouts are signed and dated by the responsible person and clearly indicate the clinic visit, the date of the visit, and the GlaxoSmithKline subject number.
- The spirometry printouts must be stored in the CRF binder.
- If spirometry printouts are on thermal paper the pages must be copied.



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Protocol Identifier	Subject Identifier	Visit Date			Visit Description
SFA100062		Day 	Month 	Year 	Visit 8

FEV₁

Record the highest of 3 technically acceptable measurements.

FEV₁ (L)**TREATMENT CONFIRMATION**

Did the subject receive the correct treatment (e.g., treatment which the subject was randomised to) during this dosing interval?

[Y] ☐ Yes [N] ☐ No

If No, record reason(s)

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CONCOMITANT MEDICATIONS

Record any changes to the subject's concomitant medications or any new medications taken since the last visit in the appropriate Concomitant Medications section.

ADVERSE EVENTS

Record details of any new non-serious adverse events/serious adverse events observed or reported by the subject or any changes to ongoing non-serious adverse events in the appropriate Non-Serious Adverse Events/ Serious Adverse Event section.

**FEV₁
MONITOR DATA VALIDATION CHECKS**

- Ensure that the correct FEV₁ measurement has been recorded.
- Ensure that the FEV₁ is within the protocol defined inclusion/continuation range.
- Ensure that the FEV₁ is rounded accurately to 2 decimal places.
- Ensure that all spirometry printouts are signed and dated by the responsible person and clearly indicate the clinic visit, the date of the visit, and the GlaxoSmithKline subject number.
- The spirometry printouts must be stored in the CRF binder.
- If spirometry printouts are on thermal paper the pages must be copied.



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Protocol Identifier	Subject Identifier	Visit Date			Visit Description
SFA100062		Day 	Month 	Year 	Visit 9

FEV₁

Record the highest of 3 technically acceptable measurements.

FEV₁ (L)**TREATMENT CONFIRMATION**

Did the subject receive the correct treatment (e.g., treatment which the subject was randomised to) during this dosing interval?

[Y] ☐ Yes [N] ☐ No

If No, record reason(s)

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PREGNANCY TEST

Perform a urine pregnancy test on all females of childbearing potential.

PHYSICAL EXAMINATION

Perform a physical examination including vital signs. Record physical exam findings and vital signs in subject's source documents.

CONCOMITANT MEDICATIONS

Record any changes to the subject's concomitant medications or any new medications taken since the last visit in the appropriate Concomitant Medications section.

ADVERSE EVENTS

Record details of any new non-serious adverse events/serious adverse events observed or reported by the subject or any changes to ongoing non-serious adverse events in the appropriate Non-Serious Adverse Events/Serious Adverse Event section.

MAXIMUM ALBUTEROL DOSE ASSESSMENT (MADR)**SAMPLE CALCULATIONS****Sample 1:**

$$\% \Delta = \frac{(\text{current amount} - \text{original amount})}{\text{original amount}} \times 100 \quad \longrightarrow \quad \% \Delta = \frac{(2.92 - 2.65)}{2.65} \times 100 = 10.19\%$$

Cumulative Puffs of Albuterol	FEV ₁ (L)	% Δ From 4 Puffs	If % Δ is >5%, administer 2 more doses of albuterol and repeat spirometry.
0 puffs	2.45	.	
4 puff	2.65	.	
6 puffs	2.92	10.19	
8 puffs	2.95	.	

Sample 2:

$$\% \Delta = \frac{(\text{current amount} - \text{original amount})}{\text{original amount}} \times 100 \quad \longrightarrow \quad \% \Delta = \frac{(2.72 - 2.65)}{2.65} \times 100 = 2.64\%$$

Cumulative Puffs of Albuterol	FEV ₁ (L)	% Δ From 4 Puffs	If % Δ is ≤5%, do not administer any more albuterol or take spirometry again.
0 puffs	2.45	.	
4 puff	2.65	.	
6 puffs	2.72	2.64	
8 puffs	NA	.	



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Protocol Identifier	Subject Identifier	Visit Date			Visit Description
SFA100062		Day 	Month 	Year 	Visit 10

MAXIMUM ALBUTEROL DOSE ASSESSMENT (MADR)

Cumulative Puffs of Albuterol	FEV ₁ (L)	% Δ From 4 Puffs	If % Δ is ≤5%, do not administer any more albuterol. If % Δ is >5%, administer 2 more doses of albuterol and repeat spirometry.
0 puffs	.	.	
4 puff	.	.	
6 puffs	.	.	
8 puffs	.	.	

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PREGNANCY TEST

Perform a urine pregnancy test on all females of childbearing potential.

CONCOMITANT MEDICATIONS

Record any changes to the subject's concomitant medications or any new medications taken since the last visit in the appropriate Concomitant Medications section.

ADVERSE EVENTS

Record details of any new non-serious adverse events/serious adverse events observed or reported by the subject or any changes to ongoing non-serious adverse events in the appropriate Non-Serious Adverse Events/ Serious Adverse Event section.

**FEV₁
MONITOR DATA VALIDATION CHECKS**

- Ensure that the correct FEV₁ measurement has been recorded.
- Ensure that the FEV₁ is within the protocol defined inclusion/continuation range.
- Ensure that the FEV₁ is rounded accurately to 2 decimal places.
- Ensure that all spirometry printouts are signed and dated by the responsible person and clearly indicate the clinic visit, the date of the visit, and the GlaxoSmithKline subject number.
- The spirometry printouts must be stored in the CRF binder.
- If spirometry printouts are on thermal paper the pages must be copied.



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FEV₁*Record the highest of 3 technically acceptable measurements.*FEV₁ . (L)

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**PGx-PHARMACOGENETIC RESEARCH
INVESTIGATOR INSTRUCTIONS****WITHDRAWAL OF CONSENT**

The question "Has the subject withdrawn consent for PGx-Pharmacogenetic research?" **must be completed immediately** if the subject withdraws consent. Otherwise, it must be completed when the subject leaves the study. It must be completed for all subjects for whom informed consent was obtained for PGx-Pharmacogenetic research.

- If consent is withdrawn, a request for destruction must be made and Blood Sample Destruction section completed.

BLOOD SAMPLE DESTRUCTION

Do **not** complete this section if a blood sample was not collected.

The question "Has a request been made for sample destruction?" must be completed immediately if there is a request for sample destruction. Otherwise, it must be completed when the subject leaves the study. It must be completed for all subjects for whom a blood sample was obtained for PGx-Pharmacogenetic research.

- If the question is answered Yes, ✓ one box for reason.
- If consent is withdrawn and sample destruction has been requested, complete the PGx-Pharmacogenetic destruction form and fax it to the GSK Study Manager.



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Protocol Identifier SFA100062	Subject Identifier <table border="1"><tr><td></td><td></td><td></td><td></td><td></td><td></td></tr></table>							

PGx-PHARMACOGENETIC RESEARCH**WITHDRAWAL OF CONSENT**

Has subject withdrawn consent for PGx-Pharmacogenetic research?

[Y] ☐ Yes [N] ☐ No**BLOOD SAMPLE DESTRUCTION**

Has a request been made for sample destruction?

[Y] ☐ Yes [N] ☐ No

If Yes, ✓ one reason:

[1] ☐ Subject requested[2] ☐ Screen failure[z] ☐ Other, specify _____

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Final Protocol Amendment 2 - 27 JUN 05
Final - 26 MAY 04**PREMATURE DISCONTINUATION VISIT
INSTRUCTIONS TO INVESTIGATOR**

Note: If the subject discontinues the study ANYTIME at or after Visit 2, complete the Premature Discontinuation Visit section.

PREGNANCY TEST

Perform a urine pregnancy test on all females of childbearing potential.

PHYSICAL EXAMINATION

Perform a physical examination including vital signs. Record physical exam findings and vital signs in subject's source documents.

CONCOMITANT MEDICATIONS

Record any changes to the subject's concomitant medications or any new medications taken since the last visit in the appropriate Concomitant Medications section.

ADVERSE EVENTS

Record details of any new non-serious adverse events/serious adverse events observed or reported by the subject or any changes to ongoing non-serious adverse events in the appropriate Non-Serious Adverse Events/ Serious Adverse Event section.

**FEV₁
MONITOR DATA VALIDATION CHECKS**

- Ensure that the correct FEV₁ measurement has been recorded.
- Ensure that the FEV₁ is within the protocol defined inclusion/continuation range.
- Ensure that the FEV₁ is rounded accurately to 2 decimal places.
- Ensure that all spirometry printouts are signed and dated by the responsible person and clearly indicate the clinic visit, the date of the visit, and the GlaxoSmithKline subject number.
- The spirometry printouts must be stored in the CRF binder.
- If spirometry printouts are on thermal paper the pages must be copied.

PGx-PHARMACOGENETIC RESEARCH

Ask subject whether they want their pharmacogenetic sample destroyed or stored. Document answer on the PGx-Pharmacogenetic Research page.



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Protocol Identifier	Subject Identifier	Visit Date			Visit Description
SFA100062		Day 	Month 	Year 	Premature Discontinuation Visit

FEV₁*Record the highest of 3 technically acceptable measurements.*FEV₁ . (L)

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***INVESTIGATIONAL PRODUCT
MONITOR DATA VALIDATION CHECKS***

- Ensure that the Investigational Product Start Date and Stop Dates have been recorded.

***INVESTIGATIONAL PRODUCT COMPLIANCE
MONITOR DATA VALIDATION CHECKS***

- Ensure that the Dose Counter Stop numbers have been recorded for each visit.



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INVESTIGATIONAL PRODUCT

Investigational Product	Start Date	Stop Date
	Day Month Year	Day Month Year
<i>e.g., Open-Label Treatment Period 1 (Albuterol)</i>	05 JUN 04	10 JUL 04
Open-Label Treatment Period 1 (Albuterol)		
Open-Label Treatment Period 2 (Ipratropium Bromide)		
Double-Blind Treatment Period		
Wash-Out Period		

INVESTIGATIONAL PRODUCT COMPLIANCE

Investigational Product	Visit Investigational Product Dispensed	Dose Counter Start	Dose Counter Stop
<i>e.g., [1] Double-Blind DISKUS</i>	6	60	32
[1] Double-Blind DISKUS	6	60	
		60	
[1] Double-Blind DISKUS	7	60	
		60	
[1] Double-Blind DISKUS	8	60	
		60	
[1] Double-Blind DISKUS	9	60	
		60	
[1] Double-Blind DISKUS	Unscheduled	60	
		60	
[1] Double-Blind DISKUS	Unscheduled	60	
		60	



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STATUS OF TREATMENT BLIND

Was the treatment blind broken during the study?

[Y] ☐ Yes [N] ☐ No*If Yes, complete the following*Date blind broken

Day		Month		Year	

Reason blind broken, ✓ one:

[1] ☐ Medical emergency requiring identification of investigational product for further treatment[z] ☐ Other, specify _____*Complete Non-Serious Adverse Event, Serious Adverse Event and/or Investigational Product pages, as appropriate.*

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ASTHMA EXACERBATIONS

INVESTIGATOR INSTRUCTIONS

Note: A subject who experiences an exacerbation during the screening period between Visit 1 and Visit 2 must be discontinued. For purposes of this study, a subject may experience one exacerbation during the 16 week combined open-label period that is successfully treated within 10 days and remain in the study, predicated on consultation with GSK. If a subject experiences more than one exacerbation during the open-label treatment periods the subject must be discontinued. Any subject who experiences an exacerbation at or following Visit 6 must be discontinued from the study.

- For the purposes of this protocol, a clinical exacerbation is defined as worsening asthma requiring emergency intervention, hospitalization, or treatment with asthma medication in addition to those allowed by the protocol.
If a subject is withdrawn for a clinical exacerbation based upon the above definition, the reason for withdrawal noted on the Study Conclusion page of the CRF should be recorded as "Exacerbation".
- For the purposes of this study, a subject will be withdrawn due to worsening asthma if he/she experiences an exacerbation during the double-blind treatment period or the washout period. In addition, the investigator may discontinue a subject at any time, if the investigator believes that the subject is at risk by remaining in the study.
- For subjects who enter the screening period between Visit 1 and Visit 2 and experience an exacerbation, worsening asthma data will be recorded only in the source documents. For all subjects who are in the open-label, double-blind, and washout treatment periods, asthma exacerbation data will be recorded in the source documents and the Asthma Exacerbation section of the CRF.
- If an exacerbation meets the definition of an SAE (Section 10.2 of the protocol 'Definition of a SAE'), worsening asthma data must be collected as a SAE for all subjects who sign an Informed consent and participate in this study.
- Ensure that you answer the leading question 'Was there an asthma exacerbation?' either Yes or No.
- Do not leave any items on this page blank.
- Dates must be complete dates recorded in DD MMM YY format (18 AUG 04). If Date of Resolution is unknown, enter 'UNK'.
 - If the exacerbation resulted in death, the Date of Death must be provided.

Primary Cause of Exacerbation Codes

Cold air / Cold weather	1
Tobacco smoke	2
Upper respiratory infection	3
Air pollution	4
Allergy	5
Exercise	6
Stress / Emotions	7
Beta-blockers	8

Aspirin	9
Other NSAIDS	10
Withholding or reducing asthma medication	11
Unknown etiology	13
Lack of efficacy	14
Lower respiratory infection	15
Other	OT

ASTHMA EXACERBATION

MONITOR DATA VALIDATION CHECKS

- Ensure that the leading question 'Was there an asthma exacerbation?' has been answered either Yes or No.



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ASTHMA EXACERBATIONS

Was there an asthma exacerbation? [Y] ☐ Yes [N] ☐ No <i>If Yes, record below:¹</i>				
Date of Onset	Outcome	Date of Resolution or Death	Severity	Primary Cause of Exacerbation
Day Month Year <i>e.g., 08 AUG 04</i>	1 = Resolved 2 = Fatal 3 = Not resolved	Day Month Year <i>18 AUG 04</i>	1 = Mild 2 = Moderate 3 = Severe	(See facing page for codes)
	1	18 AUG 04	2	6
1.				
2.				
3.				
¹ Record all medications used to treat an asthma exacerbation on the Asthma Concomitant Medications page.				

ASTHMA CONCOMITANT MEDICATIONS INVESTIGATOR INSTRUCTIONS

- Record unknown months as UNK.

UNITS

Abbreviation

Label

TAB	=	Tablet
MCL	=	Microlitre
ML	=	Millilitre
L	=	Litre
MCG	=	Microgram
MG	=	Milligram
G	=	Gram

FREQUENCY

Abbreviation

Label

OD/QD	=	1 x Daily
BID	=	2 x Daily
TID	=	3 x Daily
QID	=	4 x Daily
PRN	=	As required

ROUTE

Abbreviation

Label

IM	=	Intramuscular
IH	=	Inhaled
IN	=	Intranasal
INJ	=	Injection
IV	=	Intravenous
NS	=	Nasal spray
OTH	=	Other - Miscellaneous
PO	=	Oral
SC	=	Subcutaneous
SR	=	Sustained release
TP	=	Topical
UNK	=	Unknown

**ASTHMA CONCOMITANT MEDICATIONS
MONITOR DATA VALIDATION CHECKS**

- Ensure that either the Yes or No box is checked for the leading question
"Were any asthma concomitant medications taken by the subject 30 days prior to and/or during the study?" If Yes, check that at least one drug is recorded.
- Ensure that the spelling of the Drug Name(s) is correct (use of Trade Names is preferred).
- Ensure that the Unit Dose is recorded as a single unit.
- Ensure that the Units, Frequency, and Route are correctly abbreviated.
- Ensure that Start Date is accurate and complete.
- Ensure that Taken Prior to Study is answered Yes or No.
- Ensure that Stop Date is accurate and complete.
- Ensure that Ongoing Medication? is answered Yes or No.
- Ensure that the question "Was drug administered for an exacerbation?" is answered Yes or No. If Yes, check that a corresponding exacerbation is recorded on the Asthma Exacerbation page or, the appropriate Non-Serious Adverse Events or Serious Adverse Event page(s) if applicable.

Protocol Identifier	Subject Identifier						
SFA100062	<table><tr><td></td><td></td><td></td><td></td><td></td><td></td></tr></table>						

ASTHMA CONCOMITANT MEDICATIONS

Were any asthma concomitant medications taken by the subject 30 days prior to and/or during the study?

[Y] ☐ Yes [N] ☐ No

if Yes, record each medication on a separate line using Trade Names where possible. If the medication is related to a Non-Serious Adverse Event or Serious Adverse Event, details should be expressed using the same terminology.

Drug Name ¹ (Trade Name preferred)	Unit Dose	Units ²	Freq- uency ²	Route ²	Start Date Day Month Year	Taken Prior to Study? Y = Yes N = No	Stop Date Day Month Year	Ongoing Medi- cation? Y = Yes N = No	Was drug administered for an exacerbation? Y = Yes N = No
e.g., DUOVENT (100 / 40 mcg)	1	PUFF	BID	IH		Y	07 AUG 04	N	Y
4.									
5.									
6.									
7.									
8.									
9.									
10.									
11.									

¹ Record details of asthma exacerbations on the Asthma Exacerbation page as appropriate.

² For Units, Frequency, and Route see facing page for examples of acceptable abbreviations.



NON-ASTHMA CONCOMITANT MEDICATIONS
MONITOR DATA VALIDATION CHECKS

- Check that either 'Yes' or 'No' box at the top of the page has been completed.
- Check that either medication start date is completed or 'Taken Prior to Study?' is 'Yes'.
 - It is acceptable for start date to be missing if 'Taken Prior to Study?' is 'Yes'.
 - It is acceptable if 'Taken Prior to Study?' is 'Yes' and a start date is present, as long as the start date is prior to the date of the subject's initial visit.
- Check that either medication stop date is completed or 'Ongoing Medication?' is 'Yes'.
 - It is acceptable for stop date to be missing if 'ongoing Medication?' is 'Yes'.
 - It is acceptable if 'Ongoing medication?' is 'Yes' and an end date is present, as long as the stop date is after the date of the subject's final visit.

Protocol Identifier	Subject Identifier
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NON-ASTHMA CONCOMITANT MEDICATIONS

Were any non-asthma concomitant medications taken by the subject prior to and/or during the study?

[Y] ☐ Yes [N] ☐ No

If Yes, record each medication on a separate line using Trade Names where possible. If the medication is related to a Non-Serious Adverse Event or Serious Adverse Event, details should be expressed using the same terminology.

Drug Name ^{1,2} (Trade Name preferred)	Reason for Medication	Start Date Day Month Year	Taken Prior to Study? Y=Yes N=No	Stop Date Day Month Year	Ongoing Medi- cation? Y=Yes N=No
e.g., Tylenol	Headache	31 MAY 03	N	31 MAY 03	N
1.					
2.					
3.					
4.					
5.					
6.					
7.					

¹ Record details of asthma concomitant medications on the Asthma Concomitant Medications page.

² Do not record Investigational Product or supplemental albuterol or ipratropium bromide use on this page.



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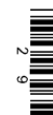
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NON-ASTHMA CONCOMITANT MEDICATIONS (Continued)

Drug Name ^{1, 2} (Trade Name preferred)	Reason for Medication	Start Date Day Month Year	Taken Prior to Study? Y=Yes N=No	Stop Date Day Month Year	Ongoing Medi- cation? Y=Yes N=No
e.g., Tylenol	Headache	31 MAY 03	N	31 MAY 03	N
8.					
9.					
10.					
11.					
12.					
13.					
14.					
15.					
16.					
17.					
18.					

¹ Record details of asthma concomitant medications on the Asthma Concomitant Medications page.

² Do not record Investigational Product or supplemental albuterol or ipratropium bromide use on this page.



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DEFINITION OF A NON-SERIOUS ADVERSE EVENT (AE) (Page 1 of 3)

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 condition(s) 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).

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). See protocol for clarification.

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.

IF THIS EVENT MEETS THE DEFINITION OF SERIOUS, COMPLETE THE SERIOUS ADVERSE EVENT SECTION

NON-SERIOUS ADVERSE EVENTS (AE) (Page 2 of 3)
MONITOR DATA VALIDATION CHECKS

- Check that either 'Yes' or 'No' box at the top of the page has been completed.
- Start dates must be provided for the reporting of adverse event data. If the exact date is not known, liaise with the investigator to ensure that a best estimate is provided.
- Ensure that **no** medical or investigational procedures are captured on Non-Serious Adverse Events pages.
- Non-serious adverse event terms should be reviewed for potential SAEs per protocol.
- Confirm that any adverse events marked as **Recovering/Resolving** or **Not recovered/Not resolved** have been followed up for details of resolution.
- If the subject was withdrawn from the study due to an adverse event, confirm that the following variables are consistent for the adverse event which resulted in withdrawal:
 - If investigational product was permanently withdrawn due to an adverse event ...
 - 'Primary Reason for Withdrawal' on the Study Conclusion page is recorded as 'Adverse Event'
 - If the subject was withdrawn from the study for an adverse event ...
 - 'Withdrawal' on the Non-Serious Adverse Events page is recorded as 'Yes'.

INSTRUCTIONS FOR COMPLETING NON-SERIOUS ADVERSE EVENTS (AE) (Page 3 of 3)

Diagnosis	Enter only the diagnosis (if known); otherwise enter sign or symptom. If a diagnosis subsequently becomes available, then this should be entered and the sign or symptom crossed out, initialled and dated by the investigator.
Start Date	Record the start date of the first occurrence of the AE.
Outcome	All AEs must be followed until the events are resolved, the condition stabilises, the events are otherwise explained, or the subject is lost to follow-up. Indicate if the event was 'Recovered/Resolved' or 'Recovered/Resolved with sequelae'. If the AE is ongoing at the time the subject completes the study or becomes lost to follow-up, the outcome must be recorded as 'Not recovered/Not resolved' or 'Recovering/Resolving'. Also enter 'Not recovered/Not resolved' if the AE was ongoing at the time of death, but was not the cause of death.
End Date	Record the end date. This is the date the AE Recovered/Resolved. If the event Recovered/Resolved with sequelae, enter the date the subject's medical condition resolved or stabilised. Leave blank if the AE is 'Not recovered/Not resolved' or 'Recovering/Resolving'.
Frequency	Select either single episode or intermittent. Intermittent should be used if the subject experiences the same AE on multiple occasions over a period of time (e.g., dizziness). In these circumstances, the start date will be the start date of the first episode and the end date will be the date of resolution.
Maximum Intensity	Record the maximum intensity that occurred over the duration of the event. Amend the intensity if it increases. 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. Not applicable = those event(s) where intensity is meaningless or impossible to determine (i.e., blindness and coma).
Action Taken with Investigational Product(s) as a Result of the Non-Serious AE	Investigational product(s) withdrawn = Administration of investigational product(s) was permanently discontinued. Dose reduced = Dose is reduced for one or more investigational product(s). Dose increased = Dose increased for one or more investigational product(s). Dose not changed = Investigational product(s) continues even though an adverse event has occurred. Dose interrupted = Administration of one or more investigational product(s) was stopped temporarily but then restarted. Not applicable = Subject was not receiving investigational product(s) when the event occurred (e.g., pre- or post-dosing).
Withdrawal	Indicate 'Yes' if the event(s) were directly responsible for the subject's withdrawal as indicated on the Study Conclusion page, otherwise indicate 'No'.
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 or arguments that may support 'a reasonable possibility' include, e.g., a temporal relationship, a pharmacologically-predicted event, or positive dechallenge or rechallenge. Confounding factors, such as concomitant medication, a concurrent illness, or relevant medical history, should also be considered.

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NON-SERIOUS ADVERSE EVENTS (AE)

Note: If this is a **Serious Adverse Event (SAE)**, do not complete this form, go to the SAE section and complete the SAE form.

Did the subject experience any non-serious adverse events during the study? [Y] ☐ Yes [N] ☐ No If Yes, record details below.

Event	Start Date	Outcome	End Date	Frequency	Maximum Intensity	Action Taken with Investigational Product(s) as a Result of the Non-Serious AE	Withdrawal	Relationship to Investigational Product(s)
Diagnosis Only (if known) Otherwise Sign/Symptom	Day Month Year	1=Recovered/ Resolved 2=Recovering/ Resolving 3=Not recovered/ Not resolved 4=Recovered/ Resolved with sequelae	Day Month Year	1=Single episode 2=Intermit- tent	1=Mild 2=Moderate 3=Severe X=Not applicable	1=Investigational product(s) withdrawn 2=Dose reduced 3=Dose increased 4=Dose not changed 5=Dose interrupted X=Not applicable	Did the subject withdraw from study as a result of this AE? Y=Yes ¹ N=No	Is there a reasonable possibility that the AE may have been caused by the investigational product? Y=Yes N=No
e.g., Headache	25 JUN 03	1	27 JUN 03	1	1	4	Y	Y
1.								
2.								
3.								
4.								
5.								
6.								

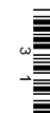
¹ Complete Study Conclusion page and ✓ Adverse event as reason for withdrawal.



Protocol Identifier	Subject Identifier						
SFA100062	<table><tr><td></td><td></td><td></td><td></td><td></td><td></td></tr></table>						

NON-SERIOUS ADVERSE EVENTS (AE) (Continued)

Event	Start Date	Outcome	End Date	Frequency	Maximum Intensity	Action Taken with Investigational Product(s) as a Result of the Non-Serious AE	Withdrawal	Relationship to Investigational Product(s)
Diagnosis Only (if known) Otherwise Sign/Symptom	Day Month Year	1=Recovered/ Resolved 2=Recovering/ Resolving 3=Not recovered/ Not resolved 4=Recovered/ Resolved with sequelae	Day Month Year	1=Single episode 2=Intermit- tent	1=Mild 2=Moderate 3=Severe X=Not applicable	1=Investigational product(s) withdrawn 2=Dose reduced 3=Dose increased 4=Dose not changed 5=Dose interrupted X=Not applicable	Did the subject withdraw from study as a result of this AE? Y=Yes ¹ N=No	Is there a reasonable possibility that the AE may have been caused by the investigational product? Y=Yes N=No
e.g., Headache	25 JUN 03	1	27 JUN 03	1	1	4	Y	Y
7.								
8.								
9.								
10.								
11.								
12.								
13.								
14.								
¹ Complete Study Conclusion page and ✓ Adverse event as reason for withdrawal.								



DEFINITION OF A SERIOUS ADVERSE EVENT (SAE) (Page 1 of 5)

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 hospitalisation or prolongation of existing hospitalisation.

Note: In general, hospitalisation 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-patient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is 'serious'.

When in doubt as to whether 'hospitalisation' occurred or was necessary, the AE should be considered 'serious'. Hospitalisation 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, diarrhoea, 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) 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 hospitalisation but may jeopardise 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 hospitalisation, or development of drug dependency or drug abuse.

SERIOUS ADVERSE EVENTS (SAE) (Page 2 of 5)
MONITOR DATA VALIDATION CHECKS

- Check that either 'Yes' or 'no' box at the top of the page has been completed.
- Start dates must be provided for the reporting of serious adverse event data. If the exact date is not known, liaise with the investigator to ensure that a best estimate is provided.
- Ensure that **no** medical or investigational procedures are captured on Serious Adverse Events pages.
- **Death** should not be recorded as an SAE but should be recorded as the outcome of an SAE. The condition that resulted in the death should be recorded as the SAE.
- Confirm that any SAEs marked as **Recovering/Resolving** or **Not recovered/Not resolved** have been followed up for details of resolution.
- If the subject was withdrawn from the study due to an SAE, confirm that the following variables are consistent for the SAE which resulted in withdrawal:
 - If investigational product was permanently withdrawn due to an adverse event ...
 - 'Primary Reason for Withdrawal' on the Study Conclusion page is recorded as 'Adverse Event'
 - If the subject was withdrawn from the study for an adverse event ...
 - 'Withdrawal' on the SAE page is recorded as 'Yes'.

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 pages must remain in the Case Report Form)

INSTRUCTIONS FOR COMPLETING SERIOUS ADVERSE EVENT FORMS (SAE) (Page 3 of 5)

Diagnosis	Record one SAE diagnosis per line, or a sign/symptom if the diagnosis is not available. If a diagnosis subsequently becomes available, this then should be entered and the sign/symptom crossed out, initialled and dated by the investigator. A separate form should be used for each SAE however if multiple SAEs which are temporally or clinically related are apparent at the time of initial reporting then these may be reported on the same page.
Start Date	Record the start date of the first occurrence of the SAE.
Outcome	All SAEs must be followed until the events are resolved, the condition stabilises, the events are otherwise explained, or the subject is lost to follow-up. Indicate if the event was 'Recovered/Resolved' or 'Recovered/Resolved with sequelae'. 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 recovered/Not resolved' or 'Recovering/Resolving'. Also enter 'Not recovered/Not resolved' if the SAE was ongoing at the time of death, but was not the cause of death, enter fatal for the SAE which was the direct cause of death.
End Date	Record the end date. This is the date the SAE Recovered/Resolved, or if the outcome was fatal, record the date the subject died. If the event Recovered/Resolved with sequelae, enter the date the subject's medical condition resolved or stabilised. Leave blank if the SAE is 'Not recovered/Not resolved' or 'Recovering/Resolving'.
Maximum Intensity	Record the maximum intensity that occurred over the duration of the event. Amend the intensity if it increases. 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 everyday activities. Severe = An event that prevents normal everyday activities. Not applicable = Those event(s) where intensity is meaningless or impossible to determine (i.e., blindness and coma).
Action Taken with Investigational Product(s) as a Result of the SAE	Investigational product(s) withdrawn = Administration of investigational product(s) was permanently discontinued. Dose reduced = Dose is reduced for one or more investigational product(s). Dose increased = Dose increased for one or more investigational product(s). Dose not changed = Investigational product(s) continues even though an adverse event has occurred. Dose interrupted = Administration of one or more investigational product(s) was temporarily interrupted but then restarted. Not applicable = Subject was not receiving investigational product(s) when the event occurred (e.g., pre- or post-dosing) or the subject died and there was no prior decision to discontinue IP(s).
Withdrawal	Indicate 'Yes' if the event(s) were directly responsible for the subject's withdrawal as indicated on the Study Conclusion page, otherwise indicate 'No'.
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 or arguments that may support 'a reasonable possibility' include, e.g., a temporal relationship, a pharmacologically-predicted event, or positive dechallenge or rechallenge. Confounding factors, such as concomitant medication, a concurrent illness, or relevant medical history, should also be considered.

Protocol Identifier SFA100062	Subject Identifier 	Centre Number 	Randomisation Number

SERIOUS ADVERSE EVENT (SAE)Did the subject experience a serious adverse event during the study? [Y] ☐ Yes [N] ☐ No If Yes, record details below.**SECTION 1**

Event	Start Date	Outcome	End date	Maximum Intensity	Action Taken with Investigational Product(s) as a Result of the SAE	Withdrawal	Relationship to Investigational Product(s)
Diagnosis Only (if known) Otherwise Sign/Symptom		1=Recovered/ Resolved 2=Recovering/ Resolving 3=Nct recovered/ Nct resolved 4=Recovered/ Resolved with sequelae 5=Fatal	If fatal, record date of death.	1=Mild 2=Moderate 3=Severe X=Not applicable	1=Investigational product(s) withdrawn 2=Dose reduced 3=Dose increased 4=Dose not changed 5=Dose interrupted X=Not applicable	Did the subject withdraw from study as a result of this SAE? Y=Yes ¹ N=No	Is there a reasonable possibility the SAE may have been caused by the investi- gational product? Y=Yes N=No
e.g., <i>Anaphylaxis</i>	Day Month Year 25 JUN 03	1	Day Month Year 27 JUN 03	1	4	Y	Y

¹ Complete Study Conclusion page and ✓ Adverse event as reason for withdrawal.If fatal, was a post-mortem/autopsy performed? [Y] ☐ Yes [N] ☐ No If Yes, summarise findings in Section 11 Narrative Remarks of this SAE form.**SECTION 2 Seriousness** (specify reason(s) for considering this a SAE, ✓ all that apply:

[A] ☐ Results in death	[D] ☐ Results in disability/incapacity
[B] ☐ Is life-threatening	[E] ☐ Congenital anomaly/birth defect
[C] ☐ Requires hospitalisation or prolongation of existing hospitalisation	[F] ☐ Other, specify _____ (see definition of SAE)



INSTRUCTIONS FOR COMPLETING SERIOUS ADVERSE EVENT FORMS (SAE) (Page 4 of 5)

SECTION 4 If Investigational Product was Stopped, Did the Reported Event(s) Recur After Further Investigational Product(s) Were Administered?	If deliberate or inadvertent administration of further dose(s) of investigational product(s) to the subject occurred, did the reported adverse event recur?

Protocol Identifier	Subject Identifier
SFA100062	

SERIOUS ADVERSE EVENT (SAE) (Continued)

SECTION 3 Demography Data

Date of birth Sex ☐ Male ☐ Female Weight kg

Day Month Year

SECTION 4 If Investigational Product(s) was Stopped, Did the Reported Event(s) Recur After Further Investigational Product(s) were Administered?

☐ Yes ☐ No ☐ Unknown at this time ☐ Not applicable

SECTION 5 Possible Causes of SAE Other Than Investigational Product(s), ✓ all that apply:

☐ Disease under study	☐ Concomitant medication (record in Section 8)
☐ Medical condition(s) (record in Section 6)	☐ Activity related to study participation (e.g., procedures)
☐ Lack of efficacy	☐ Other, specify _____
☐ Withdrawal of investigational product(s)	

SECTION 6 RELEVANT Medical Conditions

<i>Specify any RELEVANT past or current medical disorders, allergies, surgeries, etc. that can help explain the SAE</i>	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





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INSTRUCTIONS FOR COMPLETING SERIOUS ADVERSE EVENT FORMS (SAE) (Page 5 of 5)

SECTION 9 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 Section 11 Narrative Remarks if the subject has taken an overdose of investigational product(s), including whether it was accidental or intentional.

Protocol Identifier	Subject Identifier						
SFA100062	<table><tr><td></td><td></td><td></td><td></td><td></td><td></td></tr></table>						

SERIOUS ADVERSE EVENT (SAE) (Continued)**SECTION 7 Other RELEVANT Risk Factors** (provide any family or social history (e.g., smoking, alcohol, diet, drug abuse, occupational hazard) relevant to the SAE)

SECTION 8 RELEVANT Concomitant Medications (include details of any concomitant medication(s) which may have contributed to the event)

Drug Name (Trade Name preferred)	Dose	Unit	Frequency	Route	Taken Prior to Study? Y=Yes N=No	Start Date Day Month Year	Stop Date Day Month Year	Ongoing Medication? Y=Yes N=No	Reason for Medication
e.g., Zantac	150	mg	BID	PO	N	25 JUN 03	27 JUN 03	N	Gastric ulcer

SECTION 9 Details of Investigational Product(s)

Investigational Product	Start Date	Stop Date
Open-Label Treatment Period 1 (Albuterol)		
Open-Label Treatment Period 2 (Ipratropium Bromide)		
Double-Blind Treatment Period		
Wash-Out Period		
Was randomisation code broken at investigational site? ☐ Yes ☐ No ☐ Not applicable		



Protocol Identifier	Subject Identifier
SFA100062	

SERIOUS ADVERSE EVENT (SAE) (Continued)

SECTION 10 Details of RELEVANT Assessments (provide details of any other tests/procedures which were carried out to diagnose or confirm the SAE e.g., laboratory data with units and normal range)

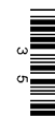
SECTION 11 Narrative Remarks (provide a brief narrative description of the SAE and details of treatment given)

Investigator's signature _____
(confirming that the data on the SAE pages are accurate and complete)

Date

Day		Month		Year	

Investigator's name (print) _____



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Protocol Identifier

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**STUDY CONCLUSION
INVESTIGATOR INSTRUCTIONS**

- Refer to protocol section(s) 9.1 and 9.2 to evaluate subject completion or withdrawal from the study.
- If subject completed study:
Date of subject completion or withdrawal must match the last scheduled study visit date.
- If subject withdrew and a withdrawal visit was conducted:
Date of subject completion or withdrawal must match the date of subject withdrawal.
- If subject lost to follow-up:
Date of subject completion or withdrawal must match the last actual contact with the subject whether or not the contact was a clinic visit. Do not record dates of unsuccessful attempts to contact the subject.
- *Exacerbations will not be classified as adverse events unless the exacerbation meets the definition of a "serious" adverse event as defined in Section 10.2 of the protocol.*

Note: An 'actual contact' is defined as an interaction between the subject and the investigator or investigator's designee, where the investigator/designee has the opportunity to query the subject about the subject's status. This would include clinic visits and telephone contacts, but normally would not include mail correspondence or third party reports.

MONITOR DATA VALIDATION CHECKS

- If the investigational product was discontinued at the same time as the subject was withdrawn from the study, ensure the reasons for the two discontinuations are consistent.
- If the subject was withdrawn due to an adverse event, confirm that details recorded correspond with details on the Adverse Event page(s):
 - 'Withdrawal' on the AE/SAE page is recorded as 'Yes'.
 - 'Action Taken with Investigational Product(s) as a Result of the Non-Serious AE' on the AE/SAE page is recorded as 'Investigational Product Withdrawn'.
 - 'Primary Reason for Withdrawal' on the Study Conclusion page is recorded as 'Adverse Event'.



Protocol Identifier	Subject Identifier
SFA100062	

STUDY CONCLUSION

Date of subject completion or withdrawal		Day Month Year
Was the subject withdrawn from the study?		
[Y] ☐ Yes [N] ☐ No		
If Yes, ✓ the primary reason for withdrawal:		
[1] ☐	Adverse event	(Record details on the Non-Serious Adverse Event or Serious Adverse Event pages as appropriate.)
[2] ☐	Lost to follow-up	
[3] ☐	Protocol violation	
[4] ☐	Subject decided to withdraw from the study	Ask subject whether they want their pharmacogenetic sample destroyed or stored. Document answer on PGx-Pharmacogenetic Research page.
[6] ☐	Sponsor terminated study	
[14] ☐	Exacerbation	
[z] ☐	Other, specify _____	

PREGNANCY INFORMATION

Did the subject become pregnant during the study?		
[Y] ☐ Yes [N] ☐ No [x] ☐ Not Applicable (not of childbearing potential or male)		
If Yes, complete Pregnancy Notification form.		



Protocol Identifier	Subject Identifier							
SFA100062	<table border="1"><tr><td></td><td></td><td></td><td></td><td></td><td></td></tr></table>							

Only use this form to record explanatory information on anomalies such as missing data, sponsor waiver of inclusion/exclusion criteria, departures from planned investigational product administration or missed visits.

[illegible]



Protocol Identifier	Subject Identifier						
SFA100062	<table border="1"><tr><td></td><td></td><td></td><td></td><td></td></tr></table>						

Only use this form to record explanatory information on anomalies such as missing data, sponsor waiver of inclusion/exclusion criteria, departures from planned investigational product administration or missed visits.

[illegible]

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Protocol Identifier

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INVESTIGATOR'S SIGNATURE
INVESTIGATOR INSTRUCTIONS

The Investigator is accountable for CRF data. However, the Principal Investigator may delegate CRF signature authority to a medically qualified Sub-investigator (as indicated on the Site Staff Signature Sheet).



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Protocol Identifier SFA100062	Subject Identifier 	

INVESTIGATOR'S SIGNATURE

I confirm that I have reviewed the data in this Case Report Form for this subject. All information entered by myself or my colleagues is, to the best of my knowledge, complete and accurate, as of the date below.

Investigator's signature _____ Date

Day	Month	Year

Investigator's name (print) _____

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Treatment Period 1 (Open-Label Albuterol) Diary Visit 2

Subject Identifier

SFA100062

Date of Next Clinic Visit

Day		Month		Year	

Study contact's name: _____

Clinic telephone number: _____

Reminders:

- Bring this diary, your peak flow meter, and all study medications to your next clinic visit.
- Do not take any new medications, other than the study medication provided for this study, without first contacting the study doctor.

*(For site use only; subjects **do not** complete this section.)*

I have examined all yellow copies of the diary pages in this booklet and certify by my signature that they are legible, exact copies of the original white pages. The yellow copies are now certified copies.

Signature: _____

Day		Month		Year	

Name (printed): _____

US:ENG (USA/English)

TREATMENT PERIOD 1 (OPEN-LABEL ALBUTEROL) DIARY INSTRUCTIONS

Reminders: - Bring this diary, your peak flow meter, and all study medications to each clinic visit. - Do not take any new medications, other than the study medication provided for this study, without first contacting the study doctor. General rules for diary completion: - Print neatly and legibly using only black ballpoint pen. Do NOT use pencil. - Draw one line through any changes or mistakes and re-enter the correct information above/beside. DO NOT use correction fluid. - Place the (front cover) flap between each set of daily diary pages to prevent overwriting on or smudging subsequent pages. DO NOT write your name anywhere on this diary. IF YOU NEED ALBUTEROL, RECORD THE FOLLOWING INFORMATION IN THIS DIARY EVERY MORNING BEFORE TAKING IT: Date. Record dates in DD MMM YY format (for example: 15 JUN 04). Morning Peak Flow Readings. Perform 3 peak flow measurements in the morning of each day during the study. Write down the results of your peak flow readings on a separate piece of paper before writing the highest measurement (reading) in this diary.	IF YOU NEED ALBUTEROL, RECORD THE FOLLOWING INFORMATION IN THIS DIARY EVERY EVENING BEFORE TAKING IT: 24 Hour Asthma Symptom Score. Circle the (one) asthma symptom score that best describes the asthma symptoms (wheeze, shortness of breath, or chest tightness) that bothered you over the past 24 hours. Do before performing the evening peak flow readings. 0 = No symptoms during the day or previous night 1 = Symptoms for one short period during the day or previous night 2 = Symptoms for two or more short periods during the day or previous night 3 = Symptoms for most of the day or previous night which did not affect my normal daily activities 4 = Symptoms for most of the day or previous night which did affect my normal daily activities 5 = Symptoms so severe that I could not go to school or perform normal daily activities Daily Albuterol Use. If you required albuterol for asthma symptoms during the past 24 hour period, record the total number of puffs administered. If none, enter zero (0). Evening Peak Flow Readings. Perform 3 peak flow measurements in the evening of each day during the study. Write down the results of your peak flow readings on a separate piece of paper before writing the highest measurement (reading) in this diary. Medical Problems/Medications Taken. Record all medical problems which may have occurred on that date, AND all medication(s) you took on that date to treat the problem. Do not include study-related medications.

US:ENG (USA/English)

Protocol Identifier	Subject Identifier	TREATMENT PERIOD 1 (OPEN-LABEL ALBUTEROL) DIARY	Visit Description
SFA100062			Visit 2

Complete this section every morning before taking any medications.		Complete this section every evening before taking any medications.			
Date	Morning peak flow reading	Asthma symptoms score over the past 24 hours	Number of puffs of albuterol taken during the past 24 hours	Evening peak flow reading	Record any:
Day Month Year	(highest of 3 readings)	(circle one)		(highest of 3 readings)	- medical problems experienced - medications taken (other than study medication)
e.g., 15 JUN 04	380	0 1 2 (3) 4 5	0	400	headache, took 2 Tylenol
1.		0 1 2 3 4 5			
2.		0 1 2 3 4 5			
3.		0 1 2 3 4 5			
4.		0 1 2 3 4 5			
5.		0 1 2 3 4 5			
6.		0 1 2 3 4 5			
7.		0 1 2 3 4 5			
8.		0 1 2 3 4 5			
9.		0 1 2 3 4 5			
10.		0 1 2 3 4 5			
11.		0 1 2 3 4 5			
12.		0 1 2 3 4 5			

US:ENG (USA/English)



Protocol Identifier	Subject Identifier	TREATMENT PERIOD 1 (OPEN-LABEL ALBUTEROL) DIARY	Visit Description
SFA100062			Visit 2

Complete this section every morning before taking any medications.		Complete this section every evening before taking any medications.			
Date	Morning peak flow reading	Asthma symptoms score over the past 24 hours	Number of puffs of albuterol taken during the past 24 hours	Evening peak flow reading	Record any:
Day Month Year	(highest of 3 readings)	(circle one)		(highest of 3 readings)	- medical problems experienced - medications taken (other than study medication)
e.g., 15 JUN 04	380	0 1 2 (3) 4 5	0	400	headache, took 2 Tylenol
13.		0 1 2 3 4 5			
14.		0 1 2 3 4 5			
15.		0 1 2 3 4 5			
16.		0 1 2 3 4 5			
17.		0 1 2 3 4 5			
18.		0 1 2 3 4 5			
19.		0 1 2 3 4 5			
20.		0 1 2 3 4 5			
21.		0 1 2 3 4 5			
22.		0 1 2 3 4 5			
23.		0 1 2 3 4 5			
24.		0 1 2 3 4 5			

US:ENG (USA/English)



Protocol Identifier	Subject Identifier	TREATMENT PERIOD 1 (OPEN-LABEL ALBUTEROL) DIARY	Visit Description
SFA100062			Visit 2

Complete this section every morning before taking any medications.		Complete this section every evening before taking any medications.			
Date	Morning peak flow reading	Asthma symptoms score over the past 24 hours	Number of puffs of albuterol taken during the past 24 hours	Evening peak flow reading	Record any:
Day Month Year	(highest of 3 readings)	(circle one)		(highest of 3 readings)	- medical problems experienced - medications taken (other than study medication)
e.g., 15 JUN 04	380	0 1 2 (3) 4 5	0	400	headache, took 2 Tylenol
25.		0 1 2 3 4 5			
26.		0 1 2 3 4 5			
27.		0 1 2 3 4 5			
28.		0 1 2 3 4 5			
29.		0 1 2 3 4 5			
30.		0 1 2 3 4 5			
31.		0 1 2 3 4 5			
32.		0 1 2 3 4 5			
33.		0 1 2 3 4 5			
34.		0 1 2 3 4 5			
35.		0 1 2 3 4 5			
36.		0 1 2 3 4 5			



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Treatment Period 1 (Open-Label Albuterol) Diary Visit 3

Subject Identifier

SFA100062

Date of Next Clinic Visit

Day		Month		Year	

Study contact's name: _____

Clinic telephone number: _____

Reminders:

- Bring this diary, your peak flow meter, and all study medications to your next clinic visit.
- Do not take any new medications, other than the study medication provided for this study, without first contacting the study doctor.

*(For site use only; subjects **do not** complete this section.)*

I have examined all yellow copies of the diary pages in this booklet and certify by my signature that they are legible, exact copies of the original white pages. The yellow copies are now certified copies.

Signature: _____

Day		Month		Year	

Name (printed): _____

US:ENG (USA/English)

TREATMENT PERIOD 1 (OPEN-LABEL ALBUTEROL) DIARY INSTRUCTIONS

Reminders: • Bring this diary, your peak flow meter, and all study medications to each clinic visit. • Do not take any new medications, other than the study medication provided for this study, without first contacting the study doctor. General rules for diary completion: • Print neatly and legibly using only black ballpoint pen. Do NOT use pencil. • Draw one line through any changes or mistakes and re-enter the correct information above/beside. • DO NOT use correction fluid. • Place the (front cover) flap between each set of daily diary pages to prevent overwriting on or smudging subsequent pages. • DO NOT write your name anywhere on this diary. IF YOU NEED ALBUTEROL, RECORD THE FOLLOWING INFORMATION IN THIS DIARY EVERY MORNING BEFORE TAKING IT: 1. Date. Record dates in DD MMM YY format (for example: 15 JUN 04). 2. Morning Peak Flow Readings. Perform 3 peak flow measurements in the morning of each day during the study. Write down the results of your peak flow readings on a separate piece of paper before writing the highest measurement (reading) in this diary.	IF YOU NEED ALBUTEROL, RECORD THE FOLLOWING INFORMATION IN THIS DIARY EVERY EVENING BEFORE TAKING IT: 3. 24 Hour Asthma Symptom Score. Circle the (one) asthma symptom score that best describes the asthma symptoms (wheeze, shortness of breath, or chest tightness) that bothered you over the past 24 hours. Do before performing the evening peak flow readings. 0 = No symptoms during the day or previous night 1 = Symptoms for one short period during the day or previous night 2 = Symptoms for two or more short periods during the day or previous night 3 = Symptoms for most of the day or previous night which did not affect my normal daily activities 4 = Symptoms for most of the day or previous night which did affect my normal daily activities 5 = Symptoms so severe that I could not go to school or perform normal daily activities 4. Daily Albuterol Use. If you required albuterol for asthma symptoms during the past 24 hour period, record the total number of puffs administered. If none, enter zero (0). 5. Evening Peak Flow Readings. Perform 3 peak flow measurements in the evening of each day during the study. Write down the results of your peak flow readings on a separate piece of paper before writing the highest measurement (reading) in this diary. 6. Medical Problems/Medications Taken. Record all medical problems which may have occurred on that date, AND all medication(s) you took on that date to treat the problem. Do not include study-related medications.

US:ENG (USA/English)

Protocol Identifier	Subject Identifier	TREATMENT PERIOD 1 (OPEN-LABEL ALBUTEROL) DIARY	Visit Description
SFA100062			Visit 3

Complete this section every morning before taking any medications.		Complete this section every evening before taking any medications.			
Date	Morning peak flow reading	Asthma symptoms score over the past 24 hours	Number of puffs of albuterol taken during the past 24 hours	Evening peak flow reading	Record any:
Day Month Year	(highest of 3 readings)	(circle one)		(highest of 3 readings)	- medical problems experienced - medications taken (other than study medication)
e.g., 15 JUN 04	380	0 1 2 (3) 4 5	0	400	headache, took 2 Tylenol
1.		0 1 2 3 4 5			
2.		0 1 2 3 4 5			
3.		0 1 2 3 4 5			
4.		0 1 2 3 4 5			
5.		0 1 2 3 4 5			
6.		0 1 2 3 4 5			
7.		0 1 2 3 4 5			
8.		0 1 2 3 4 5			
9.		0 1 2 3 4 5			
10.		0 1 2 3 4 5			
11.		0 1 2 3 4 5			
12.		0 1 2 3 4 5			

US:ENG (USA/English)



Protocol Identifier	Subject Identifier	TREATMENT PERIOD 1 (OPEN-LABEL ALBUTEROL) DIARY	Visit Description
SFA100062			Visit 3

Complete this section every morning before taking any medications.		Complete this section every evening before taking any medications.			
Date	Morning peak flow reading	Asthma symptoms score over the past 24 hours	Number of puffs of albuterol taken during the past 24 hours	Evening peak flow reading	Record any:
Day Month Year	(highest of 3 readings)	(circle one)		(highest of 3 readings)	- medical problems experienced - medications taken (other than study medication)
e.g., 15 JUN 04	380	0 1 2 (3) 4 5	0	400	headache, took 2 Tylenol
13.		0 1 2 3 4 5			
14.		0 1 2 3 4 5			
15.		0 1 2 3 4 5			
16.		0 1 2 3 4 5			
17.		0 1 2 3 4 5			
18.		0 1 2 3 4 5			
19.		0 1 2 3 4 5			
20.		0 1 2 3 4 5			
21.		0 1 2 3 4 5			
22.		0 1 2 3 4 5			
23.		0 1 2 3 4 5			
24.		0 1 2 3 4 5			



Protocol Identifier	Subject Identifier	TREATMENT PERIOD 1 (OPEN-LABEL ALBUTEROL) DIARY	Visit Description
SFA100062			Visit 3

Complete this section every morning before taking any medications.		Complete this section every evening before taking any medications.			
Date	Morning peak flow reading	Asthma symptoms score over the past 24 hours	Number of puffs of albuterol taken during the past 24 hours	Evening peak flow reading	Record any:
Day Month Year	(highest of 3 readings)	(circle one)		(highest of 3 readings)	• medical problems experienced • medications taken (other than study medication)
e.g., 15 JUN 04	380	0 1 2 (3) 4 5	0	400	headache, took 2 Tylenol
25.		0 1 2 3 4 5			
26.		0 1 2 3 4 5			
27.		0 1 2 3 4 5			
28.		0 1 2 3 4 5			
29.		0 1 2 3 4 5			
30.		0 1 2 3 4 5			
31.		0 1 2 3 4 5			
32.		0 1 2 3 4 5			
33.		0 1 2 3 4 5			
34.		0 1 2 3 4 5			
35.		0 1 2 3 4 5			
36.		0 1 2 3 4 5			



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Treatment Period 2 (Open-Label Ipratroprium Bromide) Diary Visit 4

Subject Identifier

SFA100062

Date of Next Clinic Visit

Day		Month		Year	

Study contact's name: _____

Clinic telephone number: _____

Reminders:

- Bring this diary, your peak flow meter, and all study medications to your next clinic visit.
- Do not take any new medications, other than the study medication provided for this study, without first contacting the study doctor.

*(For site use only; subjects **do not** complete this section.)*

I have examined all yellow copies of the diary pages in this booklet and certify by my signature that they are legible, exact copies of the original white pages. The yellow copies are now certified copies.

Signature: _____

Day		Month		Year	

Name (printed): _____

TREATMENT PERIOD 2 (OPEN-LABEL IPRATROPIUM BROMIDE) DIARY INSTRUCTIONS

Reminders: • Bring this diary, your peak flow meter, and all study medications to each clinic visit. • Do not take any new medications, other than the study medication provided for this study, without first contacting the study doctor. General rules for diary completion: • Use black ink. Do NOT use pencil. • Draw one line through any changes or mistakes and re-enter the correct information above/beside. • DO NOT use correction fluid. IF YOU NEED IPRATROPIUM BROMIDE, RECORD THE FOLLOWING INFORMATION IN THIS DIARY EVERY MORNING BEFORE TAKING IT: 1. Date. Record dates in DD MMM YY format (for example: 15 JUN 04). 2. Morning Peak Flow Readings. Perform 3 peak flow measurements in the morning of each day during the study. Write down the results of your peak flow readings on a separate piece of paper before writing the highest measurement (reading) in this diary.	IF YOU NEED IPRATROPIUM BROMIDE, RECORD THE FOLLOWING INFORMATION IN THIS DIARY EVERY EVENING BEFORE TAKING IT: 3. 24 Hour Asthma Symptom Score. Circle the (one) asthma symptom score that best describes the asthma symptoms (wheeze, shortness of breath, or chest tightness) that bothered you over the past 24 hours. Do before performing the evening peak flow readings. 0 = No symptoms during the day or previous night 1 = Symptoms for one short period during the day or previous night 2 = Symptoms for two or more short periods during the day or previous night 3 = Symptoms for most of the day or previous night which did not affect my normal daily activities 4 = Symptoms for most of the day or previous night which did affect my normal daily activities 5 = Symptoms so severe that I could not go to school or perform normal daily activities 4. Daily Ipratropium Bromide Use. If you required ipratropium bromide for asthma symptoms during the past 24 hour period, record the total number of puffs administered. If none, enter zero (0). 5. Daily Albuterol Use. If you required albuterol for asthma symptoms during the past 24 hour period, record the total number of puffs administered. If none, enter zero (0). 6. Evening Peak Flow Readings. Perform 3 peak flow measurements in the evening of each day during the study. Write down the results of your peak flow readings on a separate piece of paper before writing the highest measurement (reading) in this diary. 7. Medical Problems/Medications Taken. Record all medical problems which may have occurred on that date, AND all medication(s) you took on that date to treat the problem. Do not include study-related medications.

US:ENG (USA/English)

Protocol Identifier	Subject Identifier	TREATMENT PERIOD 2 (OPEN-LABEL IPRATROPIUM BROMIDE) DIARY	Visit Description
SFA100062			Visit 4

Complete this section every morning before taking any medications.		Complete this section every evening before taking any medications.				
Date	Morning peak flow reading	Asthma symptoms score over the past 24 hours	Number of puffs of ipratropium bromide taken during the past 24 hours	Number of puffs of albuterol taken during the past 24 hours	Evening peak flow reading	Record any:
Day Month Year	(highest of 3 readings)	(circle one)			(highest of 3 readings)	• medical problems experienced • medications taken (other than study medication)
e.g., 15 JUN 04	380	0 1 2 (3) 4 5	2	2	400	headache, took 2 Tylenol
1.		0 1 2 3 4 5				
2.		0 1 2 3 4 5				
3.		0 1 2 3 4 5				
4.		0 1 2 3 4 5				
5.		0 1 2 3 4 5				
6.		0 1 2 3 4 5				
7.		0 1 2 3 4 5				
8.		0 1 2 3 4 5				
9.		0 1 2 3 4 5				
10.		0 1 2 3 4 5				
11.		0 1 2 3 4 5				
12.		0 1 2 3 4 5				

US:ENG (USA/English)



Protocol Identifier	Subject Identifier	TREATMENT PERIOD 2 (OPEN-LABEL IPRATROPIUM BROMIDE) DIARY	Visit Description
SFA100062			Visit 4

Complete this section every morning before taking any medications.		Complete this section every evening before taking any medications.					Record any: • medical problems experienced • medications taken (other than study medication)
Date Day Month Year	Morning peak flow reading (highest of 3 readings)	Asthma symptoms score over the past 24 hours (circle one)	Number of puffs of ipratropium bromide taken during the past 24 hours	Number of puffs of albuterol taken during the past 24 hours	Evening peak flow reading (highest of 3 readings)		
e.g., 15 JUN 04	380	0 1 2 (3) 4 5	2	2	400	headache, took 2 Tylenol	
13.		0 1 2 3 4 5					
14.		0 1 2 3 4 5					
15.		0 1 2 3 4 5					
16.		0 1 2 3 4 5					
17.		0 1 2 3 4 5					
18.		0 1 2 3 4 5					
19.		0 1 2 3 4 5					
20.		0 1 2 3 4 5					
21.		0 1 2 3 4 5					
22.		0 1 2 3 4 5					
23.		0 1 2 3 4 5					
24.		0 1 2 3 4 5					

US:ENG (USA/English)



Protocol Identifier	Subject Identifier	TREATMENT PERIOD 2 (OPEN-LABEL IPRATROPIUM BROMIDE) DIARY	Visit Description
SFA100062			Visit 4

Complete this section every morning before taking any medications.		Complete this section every evening before taking any medications.				
Date	Morning peak flow reading	Asthma symptoms score over the past 24 hours	Number of puffs of ipratropium bromide taken during the past 24 hours	Number of puffs of albuterol taken during the past 24 hours	Evening peak flow reading	Record any:
Day Month Year	(highest of 3 readings)	(circle one)			(highest of 3 readings)	- medical problems experienced - medications taken (other than study medication)
e.g., 15 JUN 04	380	0 1 2 (3) 4 5	2	2	400	headache, took 2 Tylenol
25.		0 1 2 3 4 5				
26.		0 1 2 3 4 5				
27.		0 1 2 3 4 5				
28.		0 1 2 3 4 5				
29.		0 1 2 3 4 5				
30.		0 1 2 3 4 5				
31.		0 1 2 3 4 5				
32.		0 1 2 3 4 5				
33.		0 1 2 3 4 5				
34.		0 1 2 3 4 5				
35.		0 1 2 3 4 5				
36.		0 1 2 3 4 5				

US:ENG (USA/English)

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Treatment Period 2 (Open-Label Ipratroprium Bromide) Diary Visit 5

Subject Identifier

SFA100062

Date of Next Clinic Visit

Day		Month		Year	

Study contact's name: _____

Clinic telephone number: _____

Reminders:

- Bring this diary, your peak flow meter, and all study medications to your next clinic visit.
- Do not take any new medications, other than the study medication provided for this study, without first contacting the study doctor.

*(For site use only; subjects **do not** complete this section.)*

I have examined all yellow copies of the diary pages in this booklet and certify by my signature that they are legible, exact copies of the original white pages. The yellow copies are now certified copies.

Signature: _____

Day		Month		Year	

Name (printed): _____

TREATMENT PERIOD 2 (OPEN-LABEL IPRATROPIUM BROMIDE) DIARY INSTRUCTIONS

Reminders: - Bring this diary, your peak flow meter, and all study medications to each clinic visit. - Do not take any new medications, other than the study medication provided for this study, without first contacting the study doctor. General rules for diary completion: - Use black ink. Do NOT use pencil. - Draw one line through any changes or mistakes and re-enter the correct information above/beside. DO NOT use correction fluid. IF YOU NEED IPRATROPIUM BROMIDE, RECORD THE FOLLOWING INFORMATION IN THIS DIARY EVERY MORNING BEFORE TAKING IT: Date. Record dates in DD MMM YY format (for example: 15 JUN 04). Morning Peak Flow Readings. Perform 3 peak flow measurements in the morning of each day during the study. Write down the results of your peak flow readings on a separate piece of paper before writing the highest measurement (reading) in this diary.	IF YOU NEED IPRATROPIUM BROMIDE, RECORD THE FOLLOWING INFORMATION IN THIS DIARY EVERY EVENING BEFORE TAKING IT: 24 Hour Asthma Symptom Score. Circle the (one) asthma symptom score that best describes the asthma symptoms (wheeze, shortness of breath, or chest tightness) that bothered you over the past 24 hours. Do before performing the evening peak flow readings. 0 = No symptoms during the day or previous night 1 = Symptoms for one short period during the day or previous night 2 = Symptoms for two or more short periods during the day or previous night 3 = Symptoms for most of the day or previous night which did not affect my normal daily activities 4 = Symptoms for most of the day or previous night which did affect my normal daily activities 5 = Symptoms so severe that I could not go to school or perform normal daily activities Daily Ipratropium Bromide Use. If you required ipratropium bromide for asthma symptoms during the past 24 hour period, record the total number of puffs administered. If none, enter zero (0). Daily Albuterol Use. If you required albuterol for asthma symptoms during the past 24 hour period, record the total number of puffs administered. If none, enter zero (0). Evening Peak Flow Readings. Perform 3 peak flow measurements in the evening of each day during the study. Write down the results of your peak flow readings on a separate piece of paper before writing the highest measurement (reading) in this diary. Medical Problems/Medications Taken. Record all medical problems which may have occurred on that date, AND all medication(s) you took on that date to treat the problem. Do not include study-related medications.

Protocol Identifier	Subject Identifier	TREATMENT PERIOD 2 (OPEN-LABEL IPRATROPIUM BROMIDE) DIARY	Visit Description
SFA100062			Visit 5

Complete this section every morning before taking any medications.		Complete this section every evening before taking any medications.					Record any: • medical problems experienced • medications taken (other than study medication)
Date Day Month Year	Morning peak flow reading (highest of 3 readings)	Asthma symptoms score over the past 24 hours (circle one)	Number of puffs of ipratropium bromide taken during the past 24 hours	Number of puffs of albuterol taken during the past 24 hours	Evening peak flow reading (highest of 3 readings)		
e.g., 15 JUN 04	380	0 1 2 3 4 5	2	2	400	headache, took 2 Tylenol	
1.		0 1 2 3 4 5					
2.		0 1 2 3 4 5					
3.		0 1 2 3 4 5					
4.		0 1 2 3 4 5					
5.		0 1 2 3 4 5					
6.		0 1 2 3 4 5					
7.		0 1 2 3 4 5					
8.		0 1 2 3 4 5					
9.		0 1 2 3 4 5					
10.		0 1 2 3 4 5					
11.		0 1 2 3 4 5					
12.		0 1 2 3 4 5					

US:ENG (USA/English)



Protocol Identifier	Subject Identifier	TREATMENT PERIOD 2 (OPEN-LABEL IPRATROPIUM BROMIDE) DIARY	Visit Description
SFA100062			Visit 5

Complete this section every morning before taking any medications.		Complete this section every evening before taking any medications.				
Date	Morning peak flow reading	Asthma symptoms score over the past 24 hours	Number of puffs of ipratropium bromide taken during the past 24 hours	Number of puffs of albuterol taken during the past 24 hours	Evening peak flow reading	Record any:
Day Month Year	(highest of 3 readings)	(circle one)			(highest of 3 readings)	• medical problems experienced • medications taken (other than study medication)
e.g., 15 JUN 04	380	0 1 2 (3) 4 5	2	2	400	headache, took 2 Tylenol
13.		0 1 2 3 4 5				
14.		0 1 2 3 4 5				
15.		0 1 2 3 4 5				
16.		0 1 2 3 4 5				
17.		0 1 2 3 4 5				
18.		0 1 2 3 4 5				
19.		0 1 2 3 4 5				
20.		0 1 2 3 4 5				
21.		0 1 2 3 4 5				
22.		0 1 2 3 4 5				
23.		0 1 2 3 4 5				
24.		0 1 2 3 4 5				

US:ENG (USA/English)



Protocol Identifier	Subject Identifier	TREATMENT PERIOD 2 (OPEN-LABEL IPRATROPIUM BROMIDE) DIARY	Visit Description
SFA100062			Visit 5

Complete this section every morning before taking any medications.		Complete this section every evening before taking any medications.				
Date	Morning peak flow reading	Asthma symptoms score over the past 24 hours	Number of puffs of ipratropium bromide taken during the past 24 hours	Number of puffs of albuterol taken during the past 24 hours	Evening peak flow reading	Record any:
Day Month Year	(highest of 3 readings)	(circle one)			(highest of 3 readings)	• medical problems experienced • medications taken (other than study medication)
e.g., 15 JUN 04	380	0 1 2 (3) 4 5	2	2	400	headache, took 2 Tylenol
25.		0 1 2 3 4 5				
26.		0 1 2 3 4 5				
27.		0 1 2 3 4 5				
28.		0 1 2 3 4 5				
29.		0 1 2 3 4 5				
30.		0 1 2 3 4 5				
31.		0 1 2 3 4 5				
32.		0 1 2 3 4 5				
33.		0 1 2 3 4 5				
34.		0 1 2 3 4 5				
35.		0 1 2 3 4 5				
36.		0 1 2 3 4 5				

US:ENG (USA/English)





Treatment Period 3 (Double-Blind) Diary Visit 6

Subject Identifier

SFA100062

Date of Next Clinic Visit

Day		Month		Year	

Study contact's name: _____

Clinic telephone number: _____

Reminders:

- Bring this diary, your peak flow meter, and all study medications to your next clinic visit.
- Do not take any new medications, other than the study medication provided for this study, without first contacting the study doctor.

*(For site use only; subjects **do not** complete this section.)*

I have examined all yellow copies of the diary pages in this booklet and certify by my signature that they are legible, exact copies of the original white pages. The yellow copies are now certified copies.

Signature: _____

Day		Month		Year	

Name (printed): _____

TREATMENT PERIOD 3 (DOUBLE-BLIND) DIARY INSTRUCTIONS

Reminders:

- Bring this diary, your peak flow meter, and all study medications to each clinic visit.
- Do not take any new medications, other than the study medication provided for this study, without first contacting the study doctor.

General rules for diary completion:

- Use black ink. Do **NOT** use pencil.
- Draw one line through any changes or mistakes and re-enter the correct information above/beside.
- **DO NOT** use correction fluid.

BEFORE USING DOUBLE-BLIND STUDY MEDICATION OR SUPPLEMENTAL ALBUTEROL OR IPRATROPIUM BROMIDE, RECORD THE FOLLOWING INFORMATION IN THIS DIARY EVERY MORNING BEFORE TAKING IT:

1. **Date.** Record dates in DD MMM YY format (for example: 15 JUN 04).
2. **Morning Peak Flow Readings.** Perform **3** peak flow measurements in the morning of each day during the study. Write down the results of your peak flow readings on a separate piece of paper before writing the highest measurement (reading) in this diary.

BEFORE USING DOUBLE-BLIND STUDY MEDICATION, OR SUPPLEMENTAL ALBUTEROL OR IPRATROPIUM BROMIDE, RECORD THE FOLLOWING INFORMATION IN THIS DIARY EVERY EVENING BEFORE TAKING IT:

3. **24 Hour Asthma Symptom Score.** Circle the (one) asthma symptom score that best describes the asthma symptoms (wheeze, shortness of breath, or chest tightness) that bothered you over the past 24 hours. Do **before** performing the evening peak flow readings.
 0 = No symptoms during the day or previous night
 1 = Symptoms for one short period during the day or previous night
 2 = Symptoms for two or more short periods during the day or previous night
 3 = Symptoms for most of the day or previous night which did not affect my normal daily activities
 4 = Symptoms for most of the day or previous night which did affect my normal daily activities
 5 = Symptoms so severe that I could not go to school or perform normal daily activities
4. **Daily Ipratropium Bromide Use.** If you required ipratropium bromide for asthma symptoms during the past 24 hour period, record the total number of puffs administered. **If none, enter zero (0).**
5. **Daily Albuterol Use.** If you required albuterol for asthma symptoms during the past 24 hour period, record the total number of puffs administered. **If none, enter zero (0).**
6. **Evening Peak Flow Readings.** Perform **3** peak flow measurements in the evening of each day during the study. Write down the results of your peak flow readings on a separate piece of paper before writing the highest measurement (reading) in this diary.
7. **Medical Problems/Medications Taken.** Record all medical problems which may have occurred on that date, AND all medication(s) you took on that date to treat the problem. **Do not include** study-related medications.

Protocol Identifier	Subject Identifier	TREATMENT PERIOD 3 (DOUBLE-BLIND) DIARY	Visit Description
SFA100062			Visit 6

Complete this section every morning before taking any medications.		Complete this section every evening before taking any medications.					Record any: • medical problems experienced • medications taken (other than study medication)
Date Day Month Year	Morning peak flow reading (highest of 3 readings)	Asthma symptoms score over the past 24 hours (circle one)	Number of puffs of ipratropium bromide taken during the past 24 hours	Number of puffs of albuterol taken during the past 24 hours	Evening peak flow reading (highest of 3 readings)		
e.g., 15 JUN 04	380	0 1 2 (3) 4 5	2	2	400	headache, took 2 Tylenol	
1.		0 1 2 3 4 5					
2.		0 1 2 3 4 5					
3.		0 1 2 3 4 5					
4.		0 1 2 3 4 5					
5.		0 1 2 3 4 5					
6.		0 1 2 3 4 5					
7.		0 1 2 3 4 5					
8.		0 1 2 3 4 5					
9.		0 1 2 3 4 5					
10.		0 1 2 3 4 5					
11.		0 1 2 3 4 5					
12.		0 1 2 3 4 5					

US:ENG (USA/English)



Protocol Identifier	Subject Identifier	TREATMENT PERIOD 3 (DOUBLE-BLIND) DIARY	Visit Description
SFA100062			Visit 6

Complete this section every morning before taking any medications.		Complete this section every evening before taking any medications.				
Date	Morning peak flow reading	Asthma symptoms score over the past 24 hours	Number of puffs of ipratropium bromide taken during the past 24 hours	Number of puffs of albuterol taken during the past 24 hours	Evening peak flow reading	Record any:
Day Month Year	(highest of 3 readings)	(circle one)			(highest of 3 readings)	• medical problems experienced • medications taken (other than study medication)
e.g., 15 JUN 04	380	0 1 2 (3) 4 5	2	2	400	headache, took 2 Tylenol
13.		0 1 2 3 4 5				
14.		0 1 2 3 4 5				
15.		0 1 2 3 4 5				
16.		0 1 2 3 4 5				
17.		0 1 2 3 4 5				
18.		0 1 2 3 4 5				
19.		0 1 2 3 4 5				
20.		0 1 2 3 4 5				
21.		0 1 2 3 4 5				
22.		0 1 2 3 4 5				
23.		0 1 2 3 4 5				
24.		0 1 2 3 4 5				

US:ENG (USA/English)



Protocol Identifier	Subject Identifier	TREATMENT PERIOD 3 (DOUBLE-BLIND) DIARY	Visit Description
SFA100062			Visit 6

Complete this section every morning before taking any medications.		Complete this section every evening before taking any medications.					Record any: • medical problems experienced • medications taken (other than study medication)
Date Day Month Year	Morning peak flow reading (highest of 3 readings)	Asthma symptoms score over the past 24 hours (circle one)	Number of puffs of ipratropium bromide taken during the past 24 hours	Number of puffs of albuterol taken during the past 24 hours	Evening peak flow reading (highest of 3 readings)		
e.g., 15 JUN 04	380	0 1 2 (3) 4 5	2	2	400	headache, took 2 Tylenol	
25.		0 1 2 3 4 5					
26.		0 1 2 3 4 5					
27.		0 1 2 3 4 5					
28.		0 1 2 3 4 5					
29.		0 1 2 3 4 5					
30.		0 1 2 3 4 5					
31.		0 1 2 3 4 5					
32.		0 1 2 3 4 5					
33.		0 1 2 3 4 5					
34.		0 1 2 3 4 5					
35.		0 1 2 3 4 5					
36.		0 1 2 3 4 5					

US:ENG (USA/English)

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Treatment Period 3 (Double-Blind) Diary Visit 7

Subject Identifier

SFA100062

Date of Next Clinic Visit

Day		Month		Year	

Study contact's name: _____

Clinic telephone number: _____

Reminders:

- Bring this diary, your peak flow meter, and all study medications to your next clinic visit.
- Do not take any new medications, other than the study medication provided for this study, without first contacting the study doctor.

*(For site use only; subjects **do not** complete this section.)*

I have examined all yellow copies of the diary pages in this booklet and certify by my signature that they are legible, exact copies of the original white pages. The yellow copies are now certified copies.

Signature: _____

Day		Month		Year	

Name (printed): _____

TREATMENT PERIOD 3 (DOUBLE-BLIND) DIARY INSTRUCTIONS

Reminders:

- Bring this diary, your peak flow meter, and all study medications to each clinic visit.
- Do not take any new medications, other than the study medication provided for this study, without first contacting the study doctor.

General rules for diary completion:

- Use black ink. Do **NOT** use pencil.
- Draw one line through any changes or mistakes and re-enter the correct information above/beside.
- **DO NOT** use correction fluid.

BEFORE USING DOUBLE-BLIND STUDY MEDICATION OR SUPPLEMENTAL ALBUTEROL OR IPRATROPIUM BROMIDE, RECORD THE FOLLOWING INFORMATION IN THIS DIARY EVERY MORNING BEFORE TAKING IT:

1. **Date.** Record dates in DD MMM YY format (for example: 15 JUN 04).
2. **Morning Peak Flow Readings.** Perform **3** peak flow measurements in the morning of each day during the study. Write down the results of your peak flow readings on a separate piece of paper before writing the highest measurement (reading) in this diary.

BEFORE USING DOUBLE-BLIND STUDY MEDICATION, OR SUPPLEMENTAL ALBUTEROL OR IPRATROPIUM BROMIDE, RECORD THE FOLLOWING INFORMATION IN THIS DIARY EVERY EVENING BEFORE TAKING IT:

3. **24 Hour Asthma Symptom Score.** Circle the (one) asthma symptom score that best describes the asthma symptoms (wheeze, shortness of breath, or chest tightness) that bothered you over the past 24 hours. Do **before** performing the evening peak flow readings.
0 = No symptoms during the day or previous night
1 = Symptoms for one short period during the day or previous night
2 = Symptoms for two or more short periods during the day or previous night
3 = Symptoms for most of the day or previous night which did not affect my normal daily activities
4 = Symptoms for most of the day or previous night which did affect my normal daily activities
5 = Symptoms so severe that I could not go to school or perform normal daily activities
4. **Daily Ipratropium Bromide Use.** If you required ipratropium bromide for asthma symptoms during the past 24 hour period, record the total number of puffs administered. **If none, enter zero (0).**
5. **Daily Albuterol Use.** If you required albuterol for asthma symptoms during the past 24 hour period, record the total number of puffs administered. **If none, enter zero (0).**
6. **Evening Peak Flow Readings.** Perform **3** peak flow measurements in the evening of each day during the study. Write down the results of your peak flow readings on a separate piece of paper before writing the highest measurement (reading) in this diary.
7. **Medical Problems/Medications Taken.** Record all medical problems which may have occurred on that date, AND all medication(s) you took on that date to treat the problem. **Do not include** study-related medications.

Protocol Identifier	Subject Identifier	TREATMENT PERIOD 3 (DOUBLE-BLIND) DIARY	Visit Description
SFA100062			Visit 7

Complete this section every morning before taking any medications.		Complete this section every evening before taking any medications.					Record any: • medical problems experienced • medications taken (other than study medication)
Date Day Month Year	Morning peak flow reading (highest of 3 readings)	Asthma symptoms score over the past 24 hours (circle one)	Number of puffs of ipratropium bromide taken during the past 24 hours	Number of puffs of albuterol taken during the past 24 hours	Evening peak flow reading (highest of 3 readings)		
e.g., 15 JUN 04	380	0 1 2 (3) 4 5	2	2	400	headache, took 2 Tylenol	
1.		0 1 2 3 4 5					
2.		0 1 2 3 4 5					
3.		0 1 2 3 4 5					
4.		0 1 2 3 4 5					
5.		0 1 2 3 4 5					
6.		0 1 2 3 4 5					
7.		0 1 2 3 4 5					
8.		0 1 2 3 4 5					
9.		0 1 2 3 4 5					
10.		0 1 2 3 4 5					
11.		0 1 2 3 4 5					
12.		0 1 2 3 4 5					

US:ENG (USA/English)

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Protocol Identifier	Subject Identifier	TREATMENT PERIOD 3 (DOUBLE-BLIND) DIARY	Visit Description
SFA100062			Visit 7

Complete this section every morning before taking any medications.		Complete this section every evening before taking any medications.					Record any: • medical problems experienced • medications taken (other than study medication)
Date Day Month Year	Morning peak flow reading (highest of 3 readings)	Asthma symptoms score over the past 24 hours (circle one)	Number of puffs of ipratropium bromide taken during the past 24 hours	Number of puffs of albuterol taken during the past 24 hours	Evening peak flow reading (highest of 3 readings)		
e.g., 15 JUN 04	380	0 1 2 (3) 4 5	2	2	400	headache, took 2 Tylenol	
13.		0 1 2 3 4 5					
14.		0 1 2 3 4 5					
15.		0 1 2 3 4 5					
16.		0 1 2 3 4 5					
17.		0 1 2 3 4 5					
18.		0 1 2 3 4 5					
19.		0 1 2 3 4 5					
20.		0 1 2 3 4 5					
21.		0 1 2 3 4 5					
22.		0 1 2 3 4 5					
23.		0 1 2 3 4 5					
24.		0 1 2 3 4 5					

US:ENG (USA/English)

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Protocol Identifier	Subject Identifier	TREATMENT PERIOD 3 (DOUBLE-BLIND) DIARY	Visit Description
SFA100062			Visit 7

Complete this section every morning before taking any medications.		Complete this section every evening before taking any medications.					Record any: • medical problems experienced • medications taken (other than study medication)
Date Day Month Year	Morning peak flow reading (highest of 3 readings)	Asthma symptoms score over the past 24 hours (circle one)	Number of puffs of ipratropium bromide taken during the past 24 hours	Number of puffs of albuterol taken during the past 24 hours	Evening peak flow reading (highest of 3 readings)		
e.g., 15 JUN 04	380	0 1 2 (3) 4 5	2	2	400	headache, took 2 Tylenol	
25.		0 1 2 3 4 5					
26.		0 1 2 3 4 5					
27.		0 1 2 3 4 5					
28.		0 1 2 3 4 5					
29.		0 1 2 3 4 5					
30.		0 1 2 3 4 5					
31.		0 1 2 3 4 5					
32.		0 1 2 3 4 5					
33.		0 1 2 3 4 5					
34.		0 1 2 3 4 5					
35.		0 1 2 3 4 5					
36.		0 1 2 3 4 5					

US:ENG (USA/English)

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Treatment Period 3 (Double-Blind) Diary Visit 8

Subject Identifier

SFA100062

Date of Next Clinic Visit

Day		Month		Year	

Study contact's name: _____

Clinic telephone number: _____

Reminders:

- Bring this diary, your peak flow meter, and all study medications to your next clinic visit.
- Do not take any new medications, other than the study medication provided for this study, without first contacting the study doctor.

*(For site use only; subjects **do not** complete this section.)*

I have examined all yellow copies of the diary pages in this booklet and certify by my signature that they are legible, exact copies of the original white pages. The yellow copies are now certified copies.

Signature: _____

Day		Month		Year	

Name (printed): _____

TREATMENT PERIOD 3 (DOUBLE-BLIND) DIARY INSTRUCTIONS

Reminders:

- Bring this diary, your peak flow meter, and all study medications to each clinic visit.
- Do not take any new medications, other than the study medication provided for this study, without first contacting the study doctor.

General rules for diary completion:

- Use black ink. Do **NOT** use pencil.
- Draw one line through any changes or mistakes and re-enter the correct information above/beside.
- **DO NOT** use correction fluid.

BEFORE USING DOUBLE-BLIND STUDY MEDICATION OR SUPPLEMENTAL ALBUTEROL OR IPRATROPIUM BROMIDE, RECORD THE FOLLOWING INFORMATION IN THIS DIARY EVERY MORNING BEFORE TAKING IT:

1. **Date.** Record dates in DD MMM YY format (for example: 15 JUN 04).
2. **Morning Peak Flow Readings.** Perform **3** peak flow measurements in the morning of each day during the study. Write down the results of your peak flow readings on a separate piece of paper before writing the highest measurement (reading) in this diary.

BEFORE USING DOUBLE-BLIND STUDY MEDICATION, OR SUPPLEMENTAL ALBUTEROL OR IPRATROPIUM BROMIDE, RECORD THE FOLLOWING INFORMATION IN THIS DIARY EVERY EVENING BEFORE TAKING IT:

3. **24 Hour Asthma Symptom Score.** Circle the (one) asthma symptom score that best describes the asthma symptoms (wheeze, shortness of breath, or chest tightness) that bothered you over the past 24 hours. Do **before** performing the evening peak flow readings.
0 = No symptoms during the day or previous night
1 = Symptoms for one short period during the day or previous night
2 = Symptoms for two or more short periods during the day or previous night
3 = Symptoms for most of the day or previous night which did not affect my normal daily activities
4 = Symptoms for most of the day or previous night which did affect my normal daily activities
5 = Symptoms so severe that I could not go to school or perform normal daily activities
4. **Daily Ipratropium Bromide Use.** If you required ipratropium bromide for asthma symptoms during the past 24 hour period, record the total number of puffs administered. **If none, enter zero (0).**
5. **Daily Albuterol Use.** If you required albuterol for asthma symptoms during the past 24 hour period, record the total number of puffs administered. **If none, enter zero (0).**
6. **Evening Peak Flow Readings.** Perform **3** peak flow measurements in the evening of each day during the study. Write down the results of your peak flow readings on a separate piece of paper before writing the highest measurement (reading) in this diary.
7. **Medical Problems/Medications Taken.** Record all medical problems which may have occurred on that date, AND all medication(s) you took on that date to treat the problem. **Do not include** study-related medications.

Protocol Identifier	Subject Identifier	TREATMENT PERIOD 3 (DOUBLE-BLIND) DIARY	Visit Description
SFA100062			Visit 8

Complete this section every morning before taking any medications.		Complete this section every evening before taking any medications.				
Date	Morning peak flow reading	Asthma symptoms score over the past 24 hours	Number of puffs of ipratropium bromide taken during the past 24 hours	Number of puffs of albuterol taken during the past 24 hours	Evening peak flow reading	Record any:
Day Month Year	(highest of 3 readings)	(circle one)			(highest of 3 readings)	• medical problems experienced • medications taken (other than study medication)
e.g., 15 JUN 04	380	0 1 2 (3) 4 5	2	2	400	headache, took 2 Tylenol
1.		0 1 2 3 4 5				
2.		0 1 2 3 4 5				
3.		0 1 2 3 4 5				
4.		0 1 2 3 4 5				
5.		0 1 2 3 4 5				
6.		0 1 2 3 4 5				
7.		0 1 2 3 4 5				
8.		0 1 2 3 4 5				
9.		0 1 2 3 4 5				
10.		0 1 2 3 4 5				
11.		0 1 2 3 4 5				
12.		0 1 2 3 4 5				

US:ENG (USA/English)

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Protocol Identifier	Subject Identifier	TREATMENT PERIOD 3 (DOUBLE-BLIND) DIARY	Visit Description
SFA100062			Visit 8

Complete this section every morning before taking any medications.		Complete this section every evening before taking any medications.					Record any: • medical problems experienced • medications taken (other than study medication)
Date Day Month Year	Morning peak flow reading (highest of 3 readings)	Asthma symptoms score over the past 24 hours (circle one)	Number of puffs of ipratropium bromide taken during the past 24 hours	Number of puffs of albuterol taken during the past 24 hours	Evening peak flow reading (highest of 3 readings)		
e.g., 15 JUN 04	380	0 1 2 (3) 4 5	2	2	400	headache, took 2 Tylenol	
13.		0 1 2 3 4 5					
14.		0 1 2 3 4 5					
15.		0 1 2 3 4 5					
16.		0 1 2 3 4 5					
17.		0 1 2 3 4 5					
18.		0 1 2 3 4 5					
19.		0 1 2 3 4 5					
20.		0 1 2 3 4 5					
21.		0 1 2 3 4 5					
22.		0 1 2 3 4 5					
23.		0 1 2 3 4 5					
24.		0 1 2 3 4 5					

US:ENG (USA/English)

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Protocol Identifier	Subject Identifier	TREATMENT PERIOD 3 (DOUBLE-BLIND) DIARY	Visit Description
SFA100062			Visit 8

Complete this section every morning before taking any medications.		Complete this section every evening before taking any medications.				
Date	Morning peak flow reading	Asthma symptoms score over the past 24 hours	Number of puffs of ipratropium bromide taken during the past 24 hours	Number of puffs of albuterol taken during the past 24 hours	Evening peak flow reading	Record any:
Day Month Year	(highest of 3 readings)	(circle one)			(highest of 3 readings)	• medical problems experienced • medications taken (other than study medication)
e.g., 15 JUN 04	380	0 1 2 (3) 4 5	2	2	400	headache, took 2 Tylenol
25.		0 1 2 3 4 5				
26.		0 1 2 3 4 5				
27.		0 1 2 3 4 5				
28.		0 1 2 3 4 5				
29.		0 1 2 3 4 5				
30.		0 1 2 3 4 5				
31.		0 1 2 3 4 5				
32.		0 1 2 3 4 5				
33.		0 1 2 3 4 5				
34.		0 1 2 3 4 5				
35.		0 1 2 3 4 5				
36.		0 1 2 3 4 5				

US:ENG (USA/English)

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Final - 26 MAY 04



Treatment Period 3 (Double-Blind) Diary Visit 9

Subject Identifier

SFA100062

Date of Next Clinic Visit

Day		Month		Year	

Study contact's name: _____

Clinic telephone number: _____

Reminders:

- Bring this diary, your peak flow meter, and all study medications to your next clinic visit.
- Do not take any new medications, other than the study medication provided for this study, without first contacting the study doctor.

*(For site use only; subjects **do not** complete this section.)*

I have examined all yellow copies of the diary pages in this booklet and certify by my signature that they are legible, exact copies of the original white pages. The yellow copies are now certified copies.

Signature: _____

Day		Month		Year	

Name (printed): _____

US:ENG (USA/English)

TREATMENT PERIOD 3 (DOUBLE-BLIND) DIARY INSTRUCTIONS

Reminders:

- Bring this diary, your peak flow meter, and all study medications to each clinic visit.
- Do not take any new medications, other than the study medication provided for this study, without first contacting the study doctor.

General rules for diary completion:

- Use black ink. Do **NOT** use pencil.
- Draw one line through any changes or mistakes and re-enter the correct information above/beside.
- **DO NOT** use correction fluid.

BEFORE USING DOUBLE-BLIND STUDY MEDICATION OR SUPPLEMENTAL ALBUTEROL OR IPRATROPIUM BROMIDE, RECORD THE FOLLOWING INFORMATION IN THIS DIARY EVERY MORNING BEFORE TAKING IT:

1. **Date.** Record dates in DD MMM YY format (for example: 15 JUN 04).
2. **Morning Peak Flow Readings.** Perform **3** peak flow measurements in the morning of each day during the study. Write down the results of your peak flow readings on a separate piece of paper before writing the highest measurement (reading) in this diary.

BEFORE USING DOUBLE-BLIND STUDY MEDICATION, OR SUPPLEMENTAL ALBUTEROL OR IPRATROPIUM BROMIDE, RECORD THE FOLLOWING INFORMATION IN THIS DIARY EVERY EVENING BEFORE TAKING IT:

3. **24 Hour Asthma Symptom Score.** Circle the (one) asthma symptom score that best describes the asthma symptoms (wheeze, shortness of breath, or chest tightness) that bothered you over the past 24 hours. Do **before** performing the evening peak flow readings.
 0 = No symptoms during the day or previous night
 1 = Symptoms for one short period during the day or previous night
 2 = Symptoms for two or more short periods during the day or previous night
 3 = Symptoms for most of the day or previous night which did not affect my normal daily activities
 4 = Symptoms for most of the day or previous night which did affect my normal daily activities
 5 = Symptoms so severe that I could not go to school or perform normal daily activities
4. **Daily Ipratropium Bromide Use.** If you required ipratropium bromide for asthma symptoms during the past 24 hour period, record the total number of puffs administered. **If none, enter zero (0).**
5. **Daily Albuterol Use.** If you required albuterol for asthma symptoms during the past 24 hour period, record the total number of puffs administered. **If none, enter zero (0).**
6. **Evening Peak Flow Readings.** Perform **3** peak flow measurements in the evening of each day during the study. Write down the results of your peak flow readings on a separate piece of paper before writing the highest measurement (reading) in this diary.
7. **Medical Problems/Medications Taken.** Record all medical problems which may have occurred on that date, AND all medication(s) you took on that date to treat the problem. **Do not include** study-related medications.

Protocol Identifier	Subject Identifier	TREATMENT PERIOD 3 (DOUBLE-BLIND) DIARY	Visit Description
SFA100062			Visit 9

Complete this section every morning before taking any medications.		Complete this section every evening before taking any medications.					Record any: • medical problems experienced • medications taken (other than study medication)
Date Day Month Year	Morning peak flow reading (highest of 3 readings)	Asthma symptoms score over the past 24 hours (circle one)	Number of puffs of ipratropium bromide taken during the past 24 hours	Number of puffs of albuterol taken during the past 24 hours	Evening peak flow reading (highest of 3 readings)		
e.g., 15 JUN 04	380	0 1 2 (3) 4 5	2	2	400	headache, took 2 Tylenol	
1.		0 1 2 3 4 5					
2.		0 1 2 3 4 5					
3.		0 1 2 3 4 5					
4.		0 1 2 3 4 5					
5.		0 1 2 3 4 5					
6.		0 1 2 3 4 5					
7.		0 1 2 3 4 5					
8.		0 1 2 3 4 5					
9.		0 1 2 3 4 5					
10.		0 1 2 3 4 5					
11.		0 1 2 3 4 5					
12.		0 1 2 3 4 5					

US:ENG (USA/English)

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Protocol Identifier	Subject Identifier	TREATMENT PERIOD 3 (DOUBLE-BLIND) DIARY	Visit Description
SFA100062			Visit 9

Complete this section every morning before taking any medications.		Complete this section every evening before taking any medications.				
Date	Morning peak flow reading	Asthma symptoms score over the past 24 hours	Number of puffs of ipratropium bromide taken during the past 24 hours	Number of puffs of albuterol taken during the past 24 hours	Evening peak flow reading	Record any:
Day Month Year	(highest of 3 readings)	(circle one)			(highest of 3 readings)	• medical problems experienced • medications taken (other than study medication)
e.g., 15 JUN 04	380	0 1 2 (3) 4 5	2	2	400	headache, took 2 Tylenol
13.		0 1 2 3 4 5				
14.		0 1 2 3 4 5				
15.		0 1 2 3 4 5				
16.		0 1 2 3 4 5				
17.		0 1 2 3 4 5				
18.		0 1 2 3 4 5				
19.		0 1 2 3 4 5				
20.		0 1 2 3 4 5				
21.		0 1 2 3 4 5				
22.		0 1 2 3 4 5				
23.		0 1 2 3 4 5				
24.		0 1 2 3 4 5				

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Protocol Identifier	Subject Identifier	TREATMENT PERIOD 3 (DOUBLE-BLIND) DIARY	Visit Description
SFA100062			Visit 9

Complete this section every morning before taking any medications.		Complete this section every evening before taking any medications.					Record any: • medical problems experienced • medications taken (other than study medication)
Date Day Month Year	Morning peak flow reading (highest of 3 readings)	Asthma symptoms score over the past 24 hours (circle one)	Number of puffs of ipratropium bromide taken during the past 24 hours	Number of puffs of albuterol taken during the past 24 hours	Evening peak flow reading (highest of 3 readings)		
e.g., 15 JUN 04	380	0 1 2 3 4 5	2	2	400	headache, took 2 Tylenol	
25.		0 1 2 3 4 5					
26.		0 1 2 3 4 5					
27.		0 1 2 3 4 5					
28.		0 1 2 3 4 5					
29.		0 1 2 3 4 5					
30.		0 1 2 3 4 5					
31.		0 1 2 3 4 5					
32.		0 1 2 3 4 5					
33.		0 1 2 3 4 5					
34.		0 1 2 3 4 5					
35.		0 1 2 3 4 5					
36.		0 1 2 3 4 5					

US:ENG (USA/English)

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Wash-Out Period Diary (Open-Label Ipratroprium Bromide) Visit 10

Subject Identifier

SFA100062

Date of Next Clinic Visit

Day		Month		Year	

Study contact's name: _____

Clinic telephone number: _____

Reminders:

- Bring this diary, your peak flow meter, and all study medications to your next clinic visit.
- Do not take any new medications, other than the study medication provided for this study, without first contacting the study doctor.

*(For site use only; subjects **do not** complete this section.)*

I have examined all yellow copies of the diary pages in this booklet and certify by my signature that they are legible, exact copies of the original white pages. The yellow copies are now certified copies.

Signature: _____

Day		Month		Year	

Name (printed): _____

US:ENG (USA/English)

TREATMENT PERIOD 2 (OPEN-LABEL IPRATROPIUM BROMIDE) DIARY INSTRUCTIONS

Reminders:

- Bring this diary, your peak flow meter, and all study medications to each clinic visit.
- Do not take any new medications, other than the study medication provided for this study, without first contacting the study doctor.

General rules for diary completion:

- Use black ink. Do **NOT** use pencil.
- Draw one line through any changes or mistakes and re-enter the correct information above/beside.
- **DO NOT** use correction fluid.

IF YOU NEED IPRATROPIUM BROMIDE, RECORD THE FOLLOWING INFORMATION IN THIS DIARY EVERY MORNING BEFORE TAKING IT:

1. **Date.** Record dates in DD MMM YY format (for example: 15 JUN 04).
2. **Morning Peak Flow Readings.** Perform **3** peak flow measurements in the morning of each day during the study. Write down the results of your peak flow readings on a separate piece of paper before writing the highest measurement (reading) in this diary.

IF YOU NEED IPRATROPIUM BROMIDE, RECORD THE FOLLOWING INFORMATION IN THIS DIARY EVERY EVENING BEFORE TAKING IT:

3. **24 Hour Asthma Symptom Score.** Circle the (one) asthma symptom score that best describes the asthma symptoms (wheeze, shortness of breath, or chest tightness) that bothered you over the past 24 hours. Do **before** performing the evening peak flow readings.
0 = No symptoms during the day or previous night
1 = Symptoms for one short period during the day or previous night
2 = Symptoms for two or more short periods during the day or previous night
3 = Symptoms for most of the day or previous night which did not affect my normal daily activities
4 = Symptoms for most of the day or previous night which did affect my normal daily activities
5 = Symptoms so severe that I could not go to school or perform normal daily activities
4. **Daily Ipratropium Bromide Use.** If you required ipratropium bromide for asthma symptoms during the past 24 hour period, record the total number of puffs administered. **If none, enter zero (0).**
5. **Daily Albuterol Use.** If you required albuterol for asthma symptoms during the past 24 hour period, record the total number of puffs administered. **If none, enter zero (0).**
6. **Evening Peak Flow Readings.** Perform **3** peak flow measurements in the evening of each day during the study. Write down the results of your peak flow readings on a separate piece of paper before writing the highest measurement (reading) in this diary.
7. **Medical Problems/Medications Taken.** Record all medical problems which may have occurred on that date, AND all medication(s) you took on that date to treat the problem. **Do not include** study-related medications.

Protocol Identifier	Subject Identifier	WASH-OUT PERIOD (OPEN-LABEL IPRATROPIUM BROMIDE) DIARY	Visit Description
SFA100062			Visit 10

Complete this section every morning before taking any medications.		Complete this section every evening before taking any medications.					Record any: • medical problems experienced • medications taken (other than study medication)
Date Day Month Year	Morning peak flow reading (highest of 3 readings)	Asthma symptoms score over the past 24 hours (circle one)	Number of puffs of ipratropium bromide taken during the past 24 hours	Number of puffs of albuterol taken during the past 24 hours	Evening peak flow reading (highest of 3 readings)		
e.g., 15 JUN 04	380	0 1 2 (3) 4 5	2	2	400	headache, took 2 Tylenol	
1.		0 1 2 3 4 5					
2.		0 1 2 3 4 5					
3.		0 1 2 3 4 5					
4.		0 1 2 3 4 5					
5.		0 1 2 3 4 5					
6.		0 1 2 3 4 5					
7.		0 1 2 3 4 5					
8.		0 1 2 3 4 5					
9.		0 1 2 3 4 5					
10.		0 1 2 3 4 5					
11.		0 1 2 3 4 5					
12.		0 1 2 3 4 5					

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Protocol Identifier	Subject Identifier	WASH-OUT PERIOD (OPEN-LABEL IPRATROPIUM BROMIDE) DIARY	Visit Description
SFA100062			Visit 10

Complete this section every morning before taking any medications.		Complete this section every evening before taking any medications.					Record any: • medical problems experienced • medications taken (other than study medication)
Date Day Month Year	Morning peak flow reading (highest of 3 readings)	Asthma symptoms score over the past 24 hours (circle one)	Number of puffs of ipratropium bromide taken during the past 24 hours	Number of puffs of albuterol taken during the past 24 hours	Evening peak flow reading (highest of 3 readings)		
e.g., 15 JUN 04	380	0 1 2 (3) 4 5	2	2	400	headache, took 2 Tylenol	
13.		0 1 2 3 4 5					
14.		0 1 2 3 4 5					
15.		0 1 2 3 4 5					
16.		0 1 2 3 4 5					
17.		0 1 2 3 4 5					
18.		0 1 2 3 4 5					
19.		0 1 2 3 4 5					
20.		0 1 2 3 4 5					
21.		0 1 2 3 4 5					
22.		0 1 2 3 4 5					
23.		0 1 2 3 4 5					
24.		0 1 2 3 4 5					

US:ENG (USA/English)

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Protocol Identifier	Subject Identifier	WASH-OUT PERIOD (OPEN-LABEL IPRATROPIUM BROMIDE) DIARY	Visit Description
SFA100062			Visit 10

Complete this section every morning before taking any medications.		Complete this section every evening before taking any medications.					Record any: • medical problems experienced • medications taken (other than study medication)
Date Day Month Year	Morning peak flow reading (highest of 3 readings)	Asthma symptoms score over the past 24 hours (circle one)	Number of puffs of ipratropium bromide taken during the past 24 hours	Number of puffs of albuterol taken during the past 24 hours	Evening peak flow reading (highest of 3 readings)		
e.g., 15 JUN 04	380	0 1 2 (3) 4 5	2	2	400	headache, took 2 Tylenol	
25.		0 1 2 3 4 5					
26.		0 1 2 3 4 5					
27.		0 1 2 3 4 5					
28.		0 1 2 3 4 5					
29.		0 1 2 3 4 5					
30.		0 1 2 3 4 5					
31.		0 1 2 3 4 5					
32.		0 1 2 3 4 5					
33.		0 1 2 3 4 5					
34.		0 1 2 3 4 5					
35.		0 1 2 3 4 5					
36.		0 1 2 3 4 5					

US:ENG (USA/English)

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LIST OF INVESTIGATORS AND IECS/IRBS FOR SFA100062 (RM2007/00065/00)

Investigator	Investigator / Center No.	Hospital/ Institution and Address	IEC/IRB Committee Chair and Name of Committee
██████ Dr. ██████	██████	██████ ████████ ██████ ████████ ██████ ████████ Kenya	██████ ██████ Chair ██████ ██████
██████ Dr. ██████	██████	██████ ████████ ██████ ████████ ██████ ████████ Kenya	██████ ██████ Chair ██████ ██████
██████ ██████ M.D.	██████	██████ ████████ ██████ ████████ Peru	Chairperson's name not provided ██████ ██████
██████ ██████ M.D.	██████	██████ ████████ ██████ ████████ Peru	Chairperson's name not provided ██████ ██████
██████ ██████ M.D.	██████	██████ ████████ ██████ ████████ ██████ ████████ USA	██████ ██████ Acting Chair ██████ ██████
██████ ██████ M.D. (replaced M.D.)	██████	██████ ████████ ██████ ████████ ██████ ████████ USA	██████ ██████ Acting Chair ██████ ██████

Investigator	Investigator / Center No.	Hospital/ Institution and Address	IEC/IRB Committee Chair and Name of Committee
[REDACTED] M.D.	[REDACTED]	[REDACTED]	[REDACTED] Acting Chair
[REDACTED] M.D.	[REDACTED]	[REDACTED]	[REDACTED] Acting Chair
[REDACTED] M.D.	[REDACTED]	[REDACTED] USA	[REDACTED] Acting Chair
[REDACTED] M.D.	[REDACTED]	[REDACTED] USA	[REDACTED] Acting Chair
[REDACTED] M.D.	[REDACTED]	[REDACTED] USA	[REDACTED] Acting Chair
[REDACTED] M.D., Ph.D.	[REDACTED]	[REDACTED] USA	[REDACTED] Acting Chair
[REDACTED] M.D.	[REDACTED]	[REDACTED] USA	[REDACTED] Acting Chair
[REDACTED] M.D.	[REDACTED]	[REDACTED] USA	[REDACTED] Acting Chair
[REDACTED] D.O.	[REDACTED]	[REDACTED] D.O. USA	[REDACTED] Acting Chair

Investigator	Investigator / Center No.	Hospital/ Institution and Address	IEC/IRB Committee Chair and Name of Committee
██████ M.D.	██████	██████ M.D. ██████ ██████ USA	██████ Acting Chair
██████ M.D.	██████	██████ ██████ USA	██████ Acting Chair
██████ M.D.	██████	██████ USA	██████ Acting Chair
██████ M.D. (replaced M.D.)	██████	██████ USA	██████ Chairs
██████ M.D. (replaced M.D. as PI)	██████	██████ USA	██████ Acting Chair
██████ M.D.	██████	██████ USA	██████ Acting Chair
██████ M.D.	██████	██████ USA	██████ Acting Chair
██████ M.D.	██████	██████ USA	██████ Acting Chair
		██████ USA	

Investigator	Investigator / Center No.	Hospital/ Institution and Address	IEC/IRB Committee Chair and Name of Committee
[REDACTED] M.D.	[REDACTED]	[REDACTED] USA	[REDACTED] Acting Chair
[REDACTED] M.D.	[REDACTED]	[REDACTED] USA	[REDACTED] Acting Chair
[REDACTED] M.D.	[REDACTED]	[REDACTED] USA	[REDACTED] Acting Chair
[REDACTED] M.D., (replaced [REDACTED] M.D., Ph.D.)	[REDACTED]	[REDACTED] USA	[REDACTED] Chairs
[REDACTED] M.D.	[REDACTED]	[REDACTED] USA	[REDACTED] Acting Chair
[REDACTED] M.D.	[REDACTED]	[REDACTED] USA	[REDACTED] Acting Chair
[REDACTED] M.D.	[REDACTED]	[REDACTED] USA	[REDACTED] Acting Chair
[REDACTED] M.D.	[REDACTED]	[REDACTED] USA	[REDACTED] Acting Chair
[REDACTED] M.D.	[REDACTED]	[REDACTED] USA	[REDACTED] Acting Chair

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Investigator	Investigator / Center No.	Hospital/ Institution and Address	IEC/IRB Committee Chair and Name of Committee
[REDACTED] M.D.	[REDACTED]	[REDACTED] USA	[REDACTED] Acting Chair
[REDACTED] M.D.	[REDACTED]	[REDACTED] USA	[REDACTED] Chairs
[REDACTED] M.D.	[REDACTED]	[REDACTED] USA	[REDACTED] Acting Chair
[REDACTED] M.D.	[REDACTED]	[REDACTED] USA	[REDACTED] Chairs
[REDACTED] M.D.	[REDACTED]	[REDACTED] USA	[REDACTED] Acting Chair
[REDACTED] M.D.	[REDACTED]	[REDACTED] USA	[REDACTED] Acting Chair
[REDACTED] M.D.	[REDACTED]	[REDACTED] USA	[REDACTED] Acting Chair
[REDACTED] M.D.	[REDACTED]	[REDACTED] USA	[REDACTED] Acting Chair

Investigator	Investigator / Center No.	Hospital/ Institution and Address	IEC/IRB Committee Chair and Name of Committee
██████ M.D.	██████	████████████████████	██████ Acting Chair
██████ M.D.	██████	████████████████████ USA	██████ Acting Chair
██████ M.D.	██████	████████████████████ USA	██████ Chair
██████ M.D.	██████	████████████████████ USA	██████ Acting Chair
██████ D.O.	██████	████████████████████ USA	██████ Acting Chair
██████ M.D.	██████	████████████████████ USA	██████ Acting Chair
██████ M.D.	██████	████████████████████ USA	██████ Acting Chair
██████ M.D.	██████	████████████████████ USA	██████ Acting Chair
██████ M.D.	██████	████████████████████ USA	██████ Acting Chair
██████ M.D.	██████	████████████████████ USA	██████ Acting Chair

Investigator	Investigator / Center No.	Hospital/ Institution and Address	IEC/IRB Committee Chair and Name of Committee
[REDACTED] M.D.	[REDACTED]	[REDACTED] USA	[REDACTED] Acting Chair
[REDACTED] M.D.	[REDACTED]	[REDACTED] USA	[REDACTED] Acting Chair
[REDACTED] M.D.	[REDACTED]	[REDACTED] USA	[REDACTED] Acting Chair
[REDACTED] M.D.	[REDACTED]	[REDACTED] USA	[REDACTED] Acting Chair
[REDACTED] M.D.	[REDACTED]	[REDACTED] USA	[REDACTED] Chair
[REDACTED] M.D.	[REDACTED]	[REDACTED] USA	[REDACTED] Acting Chair
[REDACTED] M.D., Ph.D. (replaced M.D.)	[REDACTED]	[REDACTED] USA	[REDACTED] Acting Chair
[REDACTED] M.D.	[REDACTED]	[REDACTED] USA	[REDACTED] Acting Chair

Investigator	Investigator / Center No.	Hospital/ Institution and Address	IEC/IRB Committee Chair and Name of Committee
[REDACTED] M.D.	[REDACTED]	[REDACTED] [REDACTED], USA [REDACTED]	[REDACTED] Chair [REDACTED]
[REDACTED] M.D.	[REDACTED]	[REDACTED] [REDACTED], USA [REDACTED]	[REDACTED] Acting Chair [REDACTED]
[REDACTED] M.D.	[REDACTED]	[REDACTED] [REDACTED], USA [REDACTED]	[REDACTED] Acting Chair [REDACTED]

Footnote:

These investigators received IRB approval but screened no subjects:

██████ M.D., ██████ M.D., ██████ M.D., ██████ M.D., ██████ M.D., ██████ M.D.

This section contained Principal Investigator's Curriculum Vitae and has been excluded to protect Principal Investigator privacy.

CONFIDENTIAL

Written Informed Consent Form**Study Identification: SFA100062**

Study Title: A Randomized, Parallel Group, Double-Blind, Comparative Trial Assessing Lung Function and Other Measures of Asthma Control in Adults and Adolescents, at least 12 Years of Age, with Persistent Asthma, Who Have Either a B16-Arg/Arg, a B16-Gly/Gly or a B-16 Arg/Gly Genotype and are Treated With Fluticasone Propionate/Salmeterol DISKUS Combination Product 100/50mcg or Salmeterol DISKUS 50 mcg BID

SPONSOR: GlaxoSmithKline
Five Moore Drive
PO Box 13398
Research Triangle Park, NC 27709

INVESTIGATOR:

_____ (Name)			
_____ (Address 1)		_____ (Address 2, etc.)	
_____ (City)		_____ (City)	
_____ (State)	_____ (Zip)	_____ (State)	_____ (Zip)
_____ (Phone)			

Subject Identification: Insert subject ID here

This subject information and consent form is for use in a research study which may involve both subjects who do and do not have the legal capacity to consent to their participation. Accordingly, when the subject cannot legally consent to participate, the pronouns “you” and “your” should be read as referring to the subject rather than the parent or guardian who is signing the form to give consent for the subject. When a subject is too young to consent, his/her parent or legal guardian must be willing to sign the consent form before the child can take part in the study. The information in this consent form will help you decide if you would like to take part in this study.

CONFIDENTIAL

General Information

You have been asked to take part in a clinical research study to test if your gene make-up affects the way you respond to a medicine for asthma. The study will be done on teenagers and adults. The study doctor is paid to do this research study by GlaxoSmithKline. This form gives you detailed information about this study that was previously explained to you. This form may have words or information that you do not understand. Please ask the study doctor or study nurse to explain any words or information that you do not understand.

Background and Purpose of This Study

The purpose of this form is to explain this study. This clinical research study is being done to see if your gene make-up affects the way you respond to treatment with ADVAIR DISKUS[®] (fluticasone propionate/salmeterol inhalation powder) 100/50mcg or SEREVENT[®] DISKUS[®] (salmeterol xinafoate inhalation powder) 50mcg, the medicines being given in this study for asthma.

In order to see if your gene make-up affects the way you respond to treatment, we will need blood samples to perform gene tests. Your genes, pieces of genes, or genetic material may have an effect on how your body responds to or handles a medicine.

The medicines being given in this study are approved for the treatment of asthma in the United States by the Food and Drug Administration (FDA). ADVAIR DISKUS 100/50mcg has been approved by the FDA to treat asthma in people, 4 years of age and older. One of the medicines in ADVAIR, which is one of the medicines being studied, is fluticasone propionate, an inhaled corticosteroid (a medicine that reduces inflammation in the airways of the lungs). The other medicine in ADVAIR is salmeterol (SEREVENT, a medicine that gradually opens up narrowed airways of the lungs), it has been approved by the FDA to treat asthma in people, 12 years of age and older. Advair is inhaled as a powder from a device called the DISKUS Inhaler. In this study ADVAIR (dose strength 100/50mcg) taken twice a day will be compared with SEREVENT (dose strength 50mcg) alone taken twice a day. Since both of these medicines will be taken in a way approved by the FDA, neither medicine is considered an experimental medicine.

Description of Study

Information and tests conducted at Visit 1 may show that you are not able to be in this study. After the first visit, there will be up to a 4-week waiting period during which we will decide if you are able to be in the study based on the results of your screening tests. During this time you can remain on your present short-acting bronchodilator as needed for relief of your asthma symptoms.

You will be told whether or not you can be in the study. If it is decided that you are able to be in the study, you will be contacted and Visit 2 will be scheduled. At Visit 2, you will be given an inhaler, albuterol,, to be used as needed to relieve asthma symptoms. This medicine also opens up narrowed airways of the lungs. This will be your asthma

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medicine for the next 4 weeks. You will also be given a peak flow meter and daily diary cards and told how to use them.

At Visit 3 you will be given more albuterol to use as your asthma medicine for the next 4 weeks.

At Visit 4 you will be given a different inhaler, Atrovent (ipratropium bromide) Inhalation Aerosol, to be used as needed to relieve asthma symptoms. This will be your asthma medicine for the next 4 weeks. You will also receive more albuterol for use as needed in case the Atrovent does not completely control your asthma symptoms.

At Visit 5 you will be given more Atrovent to use as your asthma medicine for the next 4 weeks. You will also be given more albuterol for use as needed in case the Atrovent does not completely control your asthma symptoms.

If you continue to qualify for this study, at Visit 6 you will be put into one of two possible study treatments by chance. The treatments are selected by a computer that has no information about you or anyone else in the study. People in the two groups will have a different treatment and their responses will be compared. There is a 50% chance you will be entered into one of the following treatment groups:

- ADVAIR **DISKUS** 100/50mcg twice daily
- Serevent **DISKUS** 50mcg twice daily

Because this is a “blinded” study, you will not know which treatment you will receive. It could be either of the two treatments described above, but your study doctor can find out what treatment you are on at any time in case it becomes necessary to know this for your safety.

You should be aware that there are no known cures for your asthma so your asthma might worsen during the study no matter which treatment you receive.

At Visit 6, you will also be given Atrovent to be used as needed to relieve acute asthma symptoms while on your study medicine. You will also receive albuterol for use as needed in case the Atrovent does not completely control your asthma symptoms.

Study Procedures/Study Visits

To be in this study, you must be at least 12 years of age and have asthma. The study doctor will determine if you can participate.

During the study, you should only use medicines that your study doctor has approved. The study doctor and study staff will talk to you about what medicines you can continue to use while in the study. You will be required to stop using certain asthma and allergy medicines for certain time periods before all the screening tests and procedures can be completed. This is called a “washout” period during which the effects of these medicines on your body are expected to decrease. The study doctor and study staff will explain this to you. If you are currently taking any medicines for treatment of asthma that must be

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stopped, you will return to the study center to complete the screening procedures following the required washout period.

In order to decide if you can take part in the study and to check your general health and asthma during the study, the following routine tests and procedures will be done at certain times during the study:

Informed Consent

You will be asked to read this form and to ask any questions you may have about it or about the study. We will not start any part of the study until your questions are answered and until you are ready and able to begin. If you want to be in the study we will ask you to sign this form.

Medical History

You will be asked to describe your past and current medical conditions (Visit 1) and to list any medicines you are currently taking (All Visits). You will also be asked if you are allergic to any drugs, soybeans or peanuts.

Vital Signs

How often your heart beats (pulse) and your blood pressure will be taken at Visits 1 and 10. Vital signs will also be taken before, during and after the maximum albuterol dose response (MADR) test.

Physical Examination

Your study doctor will give you a physical examination and check-up (Visits 1 and 10).

Blood Draw

During Visit 1, a medically trained person will take two small tubes of blood (about 2 tablespoons total) from a vein in your arm. One of the tubes of blood will be tested to determine a portion of your gene make-up that is being looked at for this study. The results from the first tube of blood will give gene make-up information and helps decide if you can be in the study. After the testing is complete the blood sample will be destroyed. If there is a problem processing your sample, we may ask you to give another sample. The other tube of blood will be stored in case there is a need to conduct further tests; it may be stored for up to 15 years. If you decide to withdraw from the study, you will be asked if you want your other tube of blood destroyed or if it can be kept.

Pregnancy Testing for All Females (of childbearing potential)

All females able to have a baby will be required to provide a urine sample for pregnancy testing at Visits 2, 4, 6, 8, 10 and 11.

Lung Function Testing (Breathing test)

This test measures your lung function (the amount of air you have in your lungs and how forcefully you can blow the air out). You will be asked to place a small tube between your lips. This tube is connected to a machine. You will be asked to take a deep breath and blow into the tube as hard, fast, and long as you can until you feel that

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you must take another breath. You will be asked to do this as many as five times at all visits.

Reversibility Test

At Visit 1, you will be given a reversibility test. The reversibility test measures your breathing before and after you have been given albuterol (a medicine to open up your air passages) to determine if your breathing improves after using albuterol. If you do not meet the reversibility requirements at Visit 1, then you can reschedule a visit to take this test again. This second test must be done within 2-7 days after the first reversibility test.

Methacholine Challenge Testing

If you do not pass the reversibility test after two tries, then you may take another test, called a methacholine challenge test, to see if you can be in the study. You do not have to take this test. This test shows how sensitive your airways or bronchial tubes are. It would be done, not to make you better but to see if you can be in the study. You will perform special breathing tests before and after breathing in different amounts of methacholine, a medicine that can cause narrowing of your airways and can make you feel like your asthma is getting worse or like you are having an asthma attack, which can be scary. If you have this test, you will be required to wear a nose-clip while doing these tests. After the test, you may be given albuterol if needed for asthma symptoms. Your study doctor will decide if you need any other treatment.

Maximum Albuterol Dose Response (MADR) Testing

Maximum albuterol dose response (MADR) testing will be performed at Visits 4, 6, and 10. To do the MADR test, you will take the breathing test and will then be given four puffs of albuterol. Fifteen minutes after taking the albuterol, you will take the breathing test again, and then two more puffs of albuterol. After fifteen minutes, you will take the breathing test once more. If the change in your breathing is 5% or less, the test will be stopped; if the change in your breathing is more than 5%, then you will take two more puffs of albuterol, and you will take the breathing test again. The albuterol may make you feel jittery and make your heart race.

Your vital signs (pulse and blood pressure) will also be monitored while performing MADR testing.

Peak Expiratory Flow (PEF)

This test measures how fast you can blow air from your lungs. Your study coordinator will teach you how to use the peak flow meter. You will be told to measure peak flow twice daily:

- **before** the morning dose of study medicine
- **before** the evening dose of study medicine.

You will have to write the best of three tries on the diary card two times a day.

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Diary Cards

Every day you will write this information on a study diary card:

- Your best morning and evening peak flow (this will be explained by your study coordinator)
- The number of puffs of albuterol and Atrovent (ipratropium bromide) you used during the day,
- Any medicines you have taken other than study medicine.
- Any medical problems you might have had.
- You will be told by your study coordinator to write down a 24-hour asthma symptom score before doing the evening peak flow measurement and taking the evening dose of study medicine. You must bring your completed diary card with you to each visit (Visits 2-11).

Study Medicine

You must bring your used and unused study medicine with you to each visit.

Subject Responsibilities

As a subject in this study, you must:

- Keep all study visit appointments.
- Take all medicines as told by the study staff.
- Tell the study doctor before taking any other medicines besides study medicines.
- Complete daily diary cards.
- Tell the study doctor if your asthma gets worse or if your PEF falls below the AM PEF stability limit for 2 or more consecutive days. This will be explained by the study coordinator or study doctor.
- Tell the study doctor if you have any other health problems.
- Return all used and unused study medicine, Atrovent (ipratropium bromide), and albuterol at each visit.
- Follow instructions given to you by the study staff.
- Do peak flow measurements each morning and evening as instructed by study staff.

Expected Length of Study and Number of Subjects

About 540 male and female subjects who are at least 12 years old will take part in this study in at least 60-80 different clinics over the United States and other countries. You may be in this study up to 38 weeks (about 9 months) and will need to visit with your study doctor about 11 times. You will be scheduled to visit with your study doctor every four weeks during the study. Each visit will last 1 to 2 hours. All visits will be scheduled between 6 a.m. and 11 a.m.

For Females Only:

All females except those who are pregnant, nursing or planning to get pregnant during the time of the study may be in this study. There are no requirements that a woman who is

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able to get pregnant use a birth control method during study participation. If you have questions about methods of birth control, you should speak with your doctor.

All females able to have a baby will take a urine pregnancy test at Visits 2, 4, 6, 8, 10 and 11. This test must be negative at Visits 2, 4 and Visit 6 to allow you to be in the study. Any female subject who becomes pregnant during the study will be immediately dropped from the study. GlaxoSmithKline will be told within 24 hours of the study doctor's learning about the pregnancy.

Risks and Discomforts

Your asthma may not get better or may get worse while being in this study. Uncontrolled asthma may be life-threatening. If you feel that your asthma is getting worse, use your rescue medicine (as discussed with your study doctor) then call _____ at _____ immediately.

You may have shortness of breath, coughing, light-headedness or fainting, and chest tightness while doing the pulmonary function tests. If any of these things should happen to you, you will receive medical treatment.

If you take part in the methacholine challenge test, you will experience symptoms of asthma, which are usually mild, last only a few minutes, and disappear after taking albuterol. These symptoms include shortness of breath, chest tightness, cough, wheezing, and light-headedness. There is a very small chance of severe narrowing of your airways, which could cause severe shortness of breath. If this occurs, you will be treated immediately.

Taking the study medicine may involve unknown risks to an embryo, fetus (unborn baby) or nursing infant. Therefore, if you are pregnant, planning to become pregnant or breast feeding, you cannot be in this study. If you become pregnant during the study you should let the study doctor know immediately. The study medicine will be stopped and you will not be allowed in the study.

During the first 16 weeks of the study you will not be receiving regular doses of active medicine to treat your asthma and symptoms may get worse, stay the same, or get better. Even though the rescue medicine may make you feel better, there is a chance that your asthma may get worse. If you feel that your asthma is getting worse, use the rescue medicine given to you. If your asthma does not get better after using the rescue medicine, call the study doctor at the phone number listed on page 1 of this form or go immediately to the emergency room for medical attention, or call 911, depending on how bad your symptoms are.

Risks Associated with Study Medicines

Only the person for whom it has been prescribed should take the study medicine, and it must be kept out of the reach of children and persons not able to read or understand.

The following are the most common side effects of these medicines, but there are other effects that do not happen as often that are not listed.

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Albuterol sulfate Inhalation Aerosol

Albuterol is available by prescription and has been associated with:

Nervousness	Headache
Dizziness	Weakness
Nausea	Vomiting
Fast pulse rate	Awareness of heart beating
Angina-type chest pain	Flushing of skin
Tremor (shakiness of hands)	Sweating

Atrovent (ipratropium bromide) Inhalation Aerosol

Atrovent (ipratropium bromide) Inhalation Aerosol has been used in a number of asthma clinical trials, as a primary rescue therapy. While Atrovent acts like albuterol, it works slower. Although Atrovent is not approved by the FDA as a primary rescue therapy for asthma, severe side effects from using this medicine are very rare. This study includes albuterol as a second rescue medicine.

Note: Atrovent is not to be taken if you are allergic to soybeans or peanuts. Please notify your study doctor if you have these allergies.

Atrovent (ipratropium bromide) Inhalation Aerosol is available by prescription and has been associated with:

Awareness of heart beating	Blurred vision
Nervousness	Dry mouth
Headache	Cough
Dizziness	Worsening of symptoms
Rash	Urinary difficulty
Nausea	Fatigue (tiredness)
Vomiting	Insomnia (difficulty sleeping)
Gastrointestinal distress/discomfort	Hoarseness
Tremor (shakiness of hands)	

ADVAIR DISKUS® (fluticasone propionate/salmeterol inhalation powder) 100/50

Some people have reported the following when taking fluticasone propionate/salmeterol combination (Advair®):

Hoarseness	Dry throat/ Dry mouth
Irritated throat	Lightheadedness
Headache	Flushing of the skin
Awareness of heart beating	Anxiety
Feeling edgy or nervous	Increased pulse
Cough	Tremor or shakiness of the hands
Wheezing/breathing difficulty	
Mouth irritation or infection (increased risk of fungal infection in the mouth and throat)	

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**SEREVENT® DISKUS® (salmeterol xinafoate inhalation powder)
50mcg**

You may experience some of the following with SEREVENT® DISKUS®:

Headaches	Cough
Tremor (shakiness of the hands)	Anxiety
Palpitations (awareness of the heart beating)	Joint pain
Feeling of nervousness	Throat irritation
Hypersensitivity reaction (rash, swelling)	Hives
Bronchospasm (wheezing or trouble breathing)	Increased or irregular heart rate

Other side effects that have been reported and may be medicine-related include:

Stomach upset	Muscle cramps
Nausea	Abdominal pain
Vomiting	

Changes in blood glucose (blood sugar), potassium (blood mineral) or blood pressure

Data from a large placebo-controlled US study that compared the safety of salmeterol (SEREVENT Inhalation Aerosol) or placebo added to usual asthma therapy showed a small but significant increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,174 patients treated for 28 weeks) versus those on placebo (4 out of 13,179). Subgroup analyses suggest the risk may be greater in African American patients compared to Caucasians. This study was stopped early because of the findings in African Americans and difficulties in enrollment. This study was not designed to show whether the use of an inhaled steroid like Flovent (fluticasone propionate), the other component of Advair, protects from the risk. Therefore, it is not known whether the findings of this study apply to Advair.

Risks Associated with Gene tests

The physical risks of giving this blood sample are the same as those for any blood sample taken from a vein. You may feel faint, feel mild pain, bruising, irritation or redness at the site of puncture. In rare cases, you may develop an infection.

There is a risk of discrimination against persons who have certain medical conditions and it is unknown what other conditions this gene information will be associated with in the future. There is a chance that this could affect your ability to get or keep health insurance, life insurance or a job. GSK has taken reasonable steps to keep your research information private but under certain circumstances the information may have to be released by law or you might tell people about it.

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Unforeseen Risks

There may be other risks from being in this study that are unknown, including allergic reaction, which if not treated quickly, could become life-threatening.

Alternative (Other) Treatments

Some other medicines (taken by mouth or breathed in) are available for the treatment of asthma. These include medicines which help to open the air passages in the lungs (beta-agonists, e.g. albuterol, Serevent, Advair, Alupent®, and theophylline), and medicines which reduce the inflammation in the airways of the lungs (inhaled corticosteroids, e.g. QVAR®, Flovent®, Pulmicort® or leukotriene antagonists, e.g. Accolate® or Singulair®). If you decide not to be in this study, your study doctor will try to control your asthma with one or more of these medicines and will discuss the most common side effects of these medicines with you.

Possible Benefits

A possible benefit of this study is an improvement of your asthma. However, this benefit cannot be guaranteed. Although this study may not be of direct benefit to you, you may receive helpful information about asthma and its treatment from being in this study.

Compensation for Study-Related Injury

If, as a result of being in the study, you are hurt by the study medicine or study-related procedures done according to the study protocol, GSK will pay for reasonable and necessary medical expenses to treat the injury that are not covered by your medical insurance. GSK is not offering to pay you for any other expenses (such as, lost wages or payments for emotional distress), but you will not lose any of your legal rights as a research subject by signing this consent form.

Cost

There will be no cost to you for the study medicines or clinic visits. All expenses directly related to procedures or treatment required by the study will be provided at no cost to you.

Payment for Participation

In addition you will receive payment based upon your participation. If you qualify for the study after Visit 1 and successfully finish the study, you will be given \$_____. If you withdraw before finishing the study or if the study is stopped through no fault of yours, you will receive a partial payment based upon your participation in the study, \$_____ per visit.

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Voluntary Participation/Withdrawal

Your participation in this study is voluntary. If you do decide to take part, you will be given this information to keep and be asked to sign this consent form. You may decline to take part in this study, or once in the study you may decide to stop being in the study at any time. You must tell your study doctor if you decide to do this. Your decision not to take part in the study or to stop being in the study will not affect your current or future medical care, or any benefits to which you may otherwise be entitled.

If you decide to stop being in the study because of the gene research, then your second tube of blood will be destroyed.

If you decide to stop being in the study for any other reason, then you will be asked if you would like your second tube of blood to be destroyed or if the sample can be kept for research. This sample may be stored for up to 15 years.

Termination of Subject Study Participation

If your asthma gets worse and you need to go to the hospital, or need more asthma medicine, you will not be allowed to continue in the study. In this case, you will be asked to complete the Subject Discontinuation procedures, your study medicine will be collected, and your study doctor will recommend appropriate treatment for your asthma. You will be asked to return to the care of your regular doctor.

You are encouraged to contact your study doctor should you decide not to continue in the study. He/she will explain the best way for you to stop being in the study.

Although not expected, the sponsor or study doctor may stop your participation in this study at any time for one or more of the following reasons:

1. It is not in the best interest of your health to continue treatment;
2. Something serious happens to you, which may require treatment;
3. You do not follow your doctors' instructions;
4. The sponsor or FDA stops the study; or
5. You become pregnant.

Subject Confidentiality

Maintaining confidentiality is important to GlaxoSmithKline. Your personal information (for example, your gender, age, the details of your medical conditions), blood sample and other information (the data collected by GlaxoSmithKline as part of the study) will be identified by a number (i.e., coded). As part of the study, medical information about you will be collected and analyzed along with your blood sample. This medical information

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may include your asthma history, your family's asthma history, as well as other information.

Your name and address are not included in the information kept by GlaxoSmithKline - only your study doctor will keep this information. Your study doctor has been told to keep your medical information and gene information including your written informed consent form in a separate, secure file, which is **not** part of your medical records. GlaxoSmithKline will comply with internal procedures to protect personal and other information even in countries where data privacy laws are less strict than in Europe/US.

GSK will control access to its files that hold your information and results. Your name will **not** be in any articles or reports about this research.

GSK or those working with GSK (for example, other researchers) will only work with your blood samples for the use stated in this consent. GSK will require anyone who works with your blood samples to agree to hold the research information and any individual results in confidence.

Your study doctor and his or her staff may be able to see your gene research results at the end of the study. Your individual results will only be shared with you at that time through the study doctor if you ask to see the results. Your individual results will also be shared if it is a requirement of a governmental agency or other legal authority that GSK make these results available. GSK will not release individual results to anyone else (e.g., family members, primary care physicians, insurers, or employers) under any circumstance, unless required by law. Your gene study results are not for clinical diagnosis or treatment.

Medical information, blood samples and research results from you and other research participants may be studied by GSK to make medicines or tests to determine the body's response to or handling of medicine. Your information and any results will be put on a computer and stored in electronic databases. International regulations for information on computers and laws on processing personal information will be followed. Your medical information, blood samples, and results could be sent to other researchers working with GSK and to other GSK sites.

You agree that, while the study is still going on, you may not be given certain medical information about you that is related to the study. This may include, for example, information about whether you are receiving ADVAIR or SEREVENT, or any other information that is "blinded" (that is, kept secret during the study to prevent bias). While a request to see your medical information can be denied, the study doctor and staff will not automatically deny a request, but will consider whether it is medically appropriate under the circumstances to allow you to see to this information. Your agreement that you may be denied access to your study-related medical information during the study will not be used to deny you access to that information after the study is completed at all locations and study results are analysed.

By agreeing to take part in this research, you will allow your medical information and gene results to be collected and analyzed. The people who may collect and analyze this research include the study doctor, his/her staff and professionals at other locations that

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are helping your study doctor, GSK, people working with GSK on this research, ethics committees and regulatory authorities like the FDA. These persons are required to maintain the confidentiality of your information.

Disclosure of Protected Health Information

Authorization to use or disclose your medical information as described above is not time-limited (that is, will not expire). If you decide not to sign this consent, you will not be included in the study. You may withdraw this authorization at any time in writing. If you sign this consent and decide later to withdraw the authorization, you will be withdrawn from the study at that time. Information collected up to the time you withdraw your authorization will continue to be used as study data. Once information is disclosed under this authorization to someone who is not a health care provider, the information is no longer protected by the US privacy rules (called the HIPAA privacy regulations) and could be disclosed to others by the recipient.

Commercial Issues

GSK and/or others intend to claim sole ownership of any research results consistent with this consent. The results of this research may have commercial or intellectual property value. You agree that GSK can apply for patents. You will not receive any financial benefit that might result from this research study.

Emergency Contact

If you have any questions concerning your participation in this study, or if at any time you feel you have experienced a research-related injury or a reaction to the study medicine, you may contact the following person(s):

Name (Principal Investigator),

Address

Name (Co-ordinator)

Address

Telephone Number

If you have any questions about your rights as a study subject you may call (Insert IRB and address and phone number). An IRB is an independent group of people who have reviewed this research study with the welfare of the subject in mind.

Do not sign this consent form unless you have had a chance to ask questions and received satisfactory answers to all your questions.

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Study Data

Your information will be processed electronically (i.e., by a computer) or manually and analysed to determine outcome of this study. GlaxoSmithKline may use your information for other medical/health care purposes related to development of this study medicine. For this purpose only your coded information will be used.

Your information may/could be sent to regulatory authorities, to the IEC/IRB, to other doctors and/or organizations working with GlaxoSmithKline. It may also be sent to other GlaxoSmithKline sites in this country and in other countries where there may be different or lesser standards for looking after it. GlaxoSmithKline will apply the same standard in the protection of your information to the extent permitted by law.

You have the right to ask the study doctor about the data being collected on you for the study and about the purpose of this data. You have the right to ask the study doctor to allow you to see your personal information and to have any needed corrections to it made.

New Findings

Sometimes during the course of a research project, new information becomes available about the treatment/medicine that is being studied. If this happens, your study doctor will tell you about new information that may affect your willingness to stay in this study.

Subject's Statement of Consent / Parent/Guardian Permission:

I confirm that I have read the statements in this informed consent form for this study. I confirm that the study information and procedures have been explained to me by _____ on _____ during the consent process for this study. I have been told that my participation (or my child's participation) is voluntary. I know enough about the purpose, methods, risks and benefits of the research study to judge that I want to take part in it (or give permission for my child/ward to participate). I have been told that I have not given up any of my (or my child's) legal rights by agreeing to take part in this study.

I confirm that I have had the opportunity to ask questions about this study and I am satisfied with the answers and explanations that have been provided.

I have been given time and opportunity to read the information carefully, to discuss it with others and to decide whether or not to take part in this study (or to give permission for my child to take part).

I voluntarily agree to take part in this study. / I give my permission for my child/ward to take part in this study.

I have been told that I will receive a signed and dated copy of this consent form for my records.

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Subject's Signature _____ **Date:** _____

Printed name of Subject _____

***Signature of Legally Acceptable Representative** _____ **Date:** _____

***Printed name of Legally Acceptable Representative** _____

Description of LAR authority (i.e., parent/guardian, etc. _____

***Signature of Witness** _____ **Date:** _____

***Printed name of Witness** _____

Signature of Person conducting Consent _____ **Date:** _____

Printed Name of Person conducting Consent _____

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Subject's Statement of Assent (when subject is a minor)

You are being asked if you would like to participate in a research study. Being in this study is voluntary. You may decide to participate or not. Even though your parents/guardians may say it is okay, you don't have to participate if you don't want to. If you have not had a chance to speak with the study doctor or staff without your parent(s)/guardian(s) and would like to do so, please ask to speak with them alone. They will assure you may speak privately.

If you decide to enter the study, you may stop participating at any time. If you decide not to participate or to withdraw, it will not lead to any penalty or affect your regular medical care. If there is anything you do not understand about the study after reading this information, please ask your study doctor or study staff member.

I agree to participate in this study.

Subject's Signature _____ **Date:** _____

Printed name of Subject _____

Master Schedule Detail Report

StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

Treatments and Sequences defined for study

<u>Treatments</u>			
<u>Sequence</u>	<u>Code</u>	<u>Description</u>	<u>Period</u>
Fluticasone propionate/salmeterol 100/50mcg BID	FS	Fluticasone propionate/salmeterol 100/50mcg BID	1
Salmeterol xinafoate 50mcg BID	SX	Salmeterol xinafoate 50mcg BID	1

Schedule Summary

<u>Schedule No.</u>	<u>Created by</u>	<u>Lock 1</u>	<u>Lock 2</u>	<u>Blind Status</u>
1	[REDACTED]	Locked	Locked	Unblinded

Master Schedule Detail Report

StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

Schedule Details

Schedule: 1 Initial random codes

Date Generated: 20-MAY-2004

Date Unblinded: 05-APR-2007

Generated by: [REDACTED]

<u>Stratum</u>	<u>Block Size</u>	<u>Rand. No. Range</u>	<u>No. in Range</u>	<u>Seed</u>
Arg/Arg genotype, Black ethnicity	6	[REDACTED]	240	6810642
Arg/Arg genotype, Hispanic or Latino ethnicity	6		240	4604569
Arg/Arg genotype, Caucasian or Other ethnicity	6		240	2274731
Gly/Gly genotype, Black ethnicity	6		240	5552454
Gly/Gly genotype, Hispanic or Latino ethnicity	6		240	1779839
Gly/Gly genotype, Caucasian or Other ethnicity	6		240	2829576
Arg/Gly genotype, Black ethnicity	6		240	7558418
Arg/Gly genotype, Hispanic or Latino ethnicity	6		240	5908845
Arg/Gly genotype, Caucasian or Other ethnicity	6		240	5190549

Allocation Ratios for Arg/Arg genotype, Black ethnicity

<u>Treatment Sequence</u>	<u>Ratio</u>
Fluticasone propionate/salmeterol 100/50mcg BID	1
Salmeterol xinafoate 50mcg BID	1

Allocation Ratios for Arg/Arg genotype, Hispanic or Latino ethnicity

<u>Treatment Sequence</u>	<u>Ratio</u>
Fluticasone propionate/salmeterol 100/50mcg BID	1
Salmeterol xinafoate 50mcg BID	1

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StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

Allocation Ratios for Arg/Arg genotype, Caucasian or Other ethnicity

Allocation Ratios for Arg/Gly genotype, Hispanic or Latino ethnicity

<u>Treatment Sequence</u>	<u>Ratio</u>	<u>Treatment Sequence</u>	<u>Ratio</u>
Fluticasone propionate/salmeterol 100/50mcg BID	1	Fluticasone propionate/salmeterol 100/50mcg BID	1
Salmeterol xinafoate 50mcg BID	1	Salmeterol xinafoate 50mcg BID	1
Allocation Ratios for Gly/Gly genotype, Black ethnicity		Allocation Ratios for Arg/Gly genotype, Caucasian or Other ethnicity	

<u>Treatment Sequence</u>	<u>Ratio</u>	<u>Treatment Sequence</u>	<u>Ratio</u>
Fluticasone propionate/salmeterol 100/50mcg BID	1	Fluticasone propionate/salmeterol 100/50mcg BID	1
Salmeterol xinafoate 50mcg BID	1	Salmeterol xinafoate 50mcg BID	1
Allocation Ratios for Gly/Gly genotype, Hispanic or Latino ethnicity			

<u>Treatment Sequence</u>	<u>Ratio</u>
Fluticasone propionate/salmeterol 100/50mcg BID	1
Salmeterol xinafoate 50mcg BID	1
Allocation Ratios for Gly/Gly genotype, Caucasian or Other ethnicity	

<u>Treatment Sequence</u>	<u>Ratio</u>
Fluticasone propionate/salmeterol 100/50mcg BID	1
Salmeterol xinafoate 50mcg BID	1
Allocation Ratios for Arg/Gly genotype, Black ethnicity	

<u>Treatment Sequence</u>	<u>Ratio</u>
Fluticasone propionate/salmeterol 100/50mcg BID	1
Salmeterol xinafoate 50mcg BID	1

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Master Schedule Detail Report

StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

Schedule No: 1

Stratum Arg/Arg genotype, Black ethnicity

Randomisation
Number

Treatment / Sequence

Randomisation
Number

Fluticasone
propionate/salmeterol
100/50mcg BID

Salmeterol xinafoate 50mcg
BID

Fluticasone
propionate/salmeterol
100/50mcg BID

Salmeterol xinafoate 50mcg
BID

Salmeterol xinafoate 50mcg
BID

Fluticasone
propionate/salmeterol
100/50mcg BID

Salmeterol xinafoate 50mcg
BID

Salmeterol xinafoate 50mcg
BID

Salmeterol xinafoate 50mcg
BID

Fluticasone
propionate/salmeterol
100/50mcg BID

Fluticasone
propionate/salmeterol
100/50mcg BID

Fluticasone
propionate/salmeterol
100/50mcg BID

Fluticasone
propionate/salmeterol
100/50mcg BID

Fluticasone
propionate/salmeterol
100/50mcg BID

Fluticasone
propionate/salmeterol
100/50mcg BID

Fluticasone
propionate/salmeterol
100/50mcg BID

Fluticasone
propionate/salmeterol
100/50mcg BID

Salmeterol xinafoate 50mcg
BID

Salmeterol xinafoate 50mcg
BID

Salmeterol xinafoate 50mcg
BID

Fluticasone
propionate/salmeterol
100/50mcg BID

Fluticasone
propionate/salmeterol
100/50mcg BID

Fluticasone
propionate/salmeterol
100/50mcg BID

Salmeterol xinafoate 50mcg
BID

Salmeterol xinafoate 50mcg
BID

Salmeterol xinafoate 50mcg
BID

Fluticasone
propionate/salmeterol
100/50mcg BID

Fluticasone
propionate/salmeterol
100/50mcg BID

Salmeterol xinafoate 50mcg
BID

Fluticasone
propionate/salmeterol
100/50mcg BID

Salmeterol xinafoate 50mcg
BID

Fluticasone
propionate/salmeterol

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Master Schedule Detail Report

StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	100/50mcg BID		Fluticasone
	Fluticasone		propionate/salmeterol
	propionate/salmeterol		100/50mcg BID
	100/50mcg BID		Fluticasone
	Salmeterol xinafoate 50mcg		propionate/salmeterol
	BID		100/50mcg BID
	Salmeterol xinafoate 50mcg		Salmeterol xinafoate 50mcg
	BID		BID
	Salmeterol xinafoate 50mcg		Fluticasone
	BID		propionate/salmeterol
	Fluticasone		100/50mcg BID
	propionate/salmeterol		Salmeterol xinafoate 50mcg
	100/50mcg BID		BID
	Fluticasone		Salmeterol xinafoate 50mcg
	propionate/salmeterol		BID
	100/50mcg BID		Fluticasone
	Fluticasone		propionate/salmeterol
	propionate/salmeterol		100/50mcg BID
	100/50mcg BID		Fluticasone
	Salmeterol xinafoate 50mcg		propionate/salmeterol
	BID		100/50mcg BID
	Fluticasone		Salmeterol xinafoate 50mcg
	propionate/salmeterol		BID
	100/50mcg BID		Fluticasone
	Salmeterol xinafoate 50mcg		propionate/salmeterol
	BID		100/50mcg BID
	Salmeterol xinafoate 50mcg		Salmeterol xinafoate 50mcg
	BID		BID
	Salmeterol xinafoate 50mcg		Salmeterol xinafoate 50mcg
	BID		BID
	Fluticasone		Salmeterol xinafoate 50mcg
	propionate/salmeterol		BID
	100/50mcg BID		Fluticasone
	Fluticasone		propionate/salmeterol
	propionate/salmeterol		100/50mcg BID
	100/50mcg BID		Fluticasone

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Master Schedule Detail Report

StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	propionate/salmeterol 100/50mcg BID		100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID

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Master Schedule Detail Report

StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	Fluticasone propionate/salmeterol 100/50mcg BID		100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol		

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StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	Salmeterol xinafoate 50mcg BID		BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg		Fluticasone propionate/salmeterol

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StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	100/50mcg BID		Fluticasone
	Salmeterol xinafoate 50mcg BID		propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID

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StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg

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StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	BID		BID
	Fluticasone		Salmeterol xinafoate 50mcg
	propionate/salmeterol		BID
	100/50mcg BID		Fluticasone
	Fluticasone		propionate/salmeterol
	propionate/salmeterol		100/50mcg BID
	100/50mcg BID		Fluticasone
	Salmeterol xinafoate 50mcg		propionate/salmeterol
	BID		100/50mcg BID
	Salmeterol xinafoate 50mcg		Salmeterol xinafoate 50mcg
	BID		BID
	Fluticasone		Salmeterol xinafoate 50mcg
	propionate/salmeterol		BID
	100/50mcg BID		Fluticasone
	Salmeterol xinafoate 50mcg		propionate/salmeterol
	BID		100/50mcg BID
	Salmeterol xinafoate 50mcg		Salmeterol xinafoate 50mcg
	BID		BID
	Fluticasone		Salmeterol xinafoate 50mcg
	propionate/salmeterol		BID
	100/50mcg BID		Fluticasone
	Fluticasone		propionate/salmeterol
	propionate/salmeterol		100/50mcg BID
	100/50mcg BID		Fluticasone
	Fluticasone		propionate/salmeterol
	propionate/salmeterol		100/50mcg BID
	100/50mcg BID		Fluticasone
	Salmeterol xinafoate 50mcg		propionate/salmeterol
	BID		100/50mcg BID
	Fluticasone		Salmeterol xinafoate 50mcg
	propionate/salmeterol		BID
	100/50mcg BID		Salmeterol xinafoate 50mcg
	Fluticasone		BID
	propionate/salmeterol		Salmeterol xinafoate 50mcg
	100/50mcg BID		BID
	Salmeterol xinafoate 50mcg		

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StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

Randomisation **Treatment / Sequence**

Number

	Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID

Master Schedule Detail Report

StudyID: SFA100062**Description:** Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD**Schedule No:** 1**Stratum** Arg/Arg genotype, Hispanic or Latino ethnicity**Randomisation** **Treatment / Sequence**
Number**Randomisation** **Treatment / Sequence**
Number

		propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID	Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID	Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID	Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID	Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID	Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID	Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID	Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID	Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID	Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID	Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID	Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID	Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID	Salmeterol xinafoate 50mcg BID
	Fluticasone	

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Master Schedule Detail Report

StudyID: SFA100062**Description:** Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
			Fluticasone

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StudyID: SFA100062**Description:** Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	propionate/salmeterol 100/50mcg BID		100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol		Fluticasone propionate/salmeterol 100/50mcg BID

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StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	Fluticasone propionate/salmeterol 100/50mcg BID		BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg		Fluticasone propionate/salmeterol 100/50mcg BID

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Master Schedule Detail Report

StudyID: SFA100062**Description:** Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID

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Master Schedule Detail Report

StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg

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Master Schedule Detail Report

StudyID: SFA100062**Description:** Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	BID		Salmeterol xinafoate 50mcg
	Salmeterol xinafoate 50mcg		BID
	BID		Fluticasone
	Fluticasone		propionate/salmeterol
	propionate/salmeterol		100/50mcg BID
	100/50mcg BID		Salmeterol xinafoate 50mcg
	Salmeterol xinafoate 50mcg		BID
	BID		Fluticasone
	Salmeterol xinafoate 50mcg		propionate/salmeterol
	BID		100/50mcg BID
	Fluticasone		Salmeterol xinafoate 50mcg
	propionate/salmeterol		BID
	100/50mcg BID		Fluticasone
	Fluticasone		propionate/salmeterol
	propionate/salmeterol		100/50mcg BID
	100/50mcg BID		Salmeterol xinafoate 50mcg
	Salmeterol xinafoate 50mcg		BID
	BID		Salmeterol xinafoate 50mcg
	Fluticasone		BID
	propionate/salmeterol		Fluticasone
	100/50mcg BID		propionate/salmeterol
	Salmeterol xinafoate 50mcg		100/50mcg BID
	BID		Fluticasone
	Salmeterol xinafoate 50mcg		propionate/salmeterol
	BID		100/50mcg BID
	Fluticasone		Fluticasone
	propionate/salmeterol		propionate/salmeterol
	100/50mcg BID		100/50mcg BID
	Salmeterol xinafoate 50mcg		Salmeterol xinafoate 50mcg
	BID		BID
	Fluticasone		Fluticasone
	propionate/salmeterol		propionate/salmeterol
	100/50mcg BID		100/50mcg BID
	Fluticasone		Salmeterol xinafoate 50mcg
	propionate/salmeterol		BID
	100/50mcg BID		Salmeterol xinafoate 50mcg

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StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	BID		BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID

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StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

Randomisation **Treatment / Sequence**
Number

	Fluticasone
	propionate/salmeterol
	100/50mcg BID
	Salmeterol xinafoate 50mcg
	BID
	Fluticasone
	propionate/salmeterol
	100/50mcg BID
	Salmeterol xinafoate 50mcg
	BID
	Salmeterol xinafoate 50mcg
	BID
	Fluticasone
	propionate/salmeterol
	100/50mcg BID
	Fluticasone
	propionate/salmeterol
	100/50mcg BID
	Salmeterol xinafoate 50mcg
	BID
	Fluticasone
	propionate/salmeterol
	100/50mcg BID
	Salmeterol xinafoate 50mcg
	BID
	Salmeterol xinafoate 50mcg
	BID

Master Schedule Detail Report

StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

Schedule No: 1

Stratum Arg/Arg genotype, Caucasian or Other ethnicity

Randomisation

Number

Treatment / Sequence

Randomisation **Treatment / Sequence**

Number

			propionate/salmeterol 100/50mcg BID
	Fluticasone		Fluticasone
	propionate/salmeterol 100/50mcg BID		propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone
	Fluticasone		propionate/salmeterol 100/50mcg BID
	propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone		Fluticasone
	propionate/salmeterol 100/50mcg BID		propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone
	Salmeterol xinafoate 50mcg BID		propionate/salmeterol 100/50mcg BID
	Fluticasone		Salmeterol xinafoate 50mcg BID
	propionate/salmeterol 100/50mcg BID		Fluticasone
	Fluticasone		propionate/salmeterol 100/50mcg BID
	propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone		Fluticasone
	propionate/salmeterol 100/50mcg BID		propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone
	Salmeterol xinafoate 50mcg BID		propionate/salmeterol 100/50mcg BID
	Fluticasone		Salmeterol xinafoate 50mcg BID
			Salmeterol xinafoate 50mcg

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Master Schedule Detail Report

StudyID: SFA100062**Description:** Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	BID		Salmeterol xinafoate 50mcg
	Fluticasone		BID
	propionate/salmeterol		Salmeterol xinafoate 50mcg
	100/50mcg BID		BID
	Salmeterol xinafoate 50mcg		Salmeterol xinafoate 50mcg
	BID		BID
	Fluticasone		Fluticasone
	propionate/salmeterol		propionate/salmeterol
	100/50mcg BID		100/50mcg BID
	Salmeterol xinafoate 50mcg		Fluticasone
	BID		propionate/salmeterol
	Salmeterol xinafoate 50mcg		100/50mcg BID
	BID		Fluticasone
	Fluticasone		propionate/salmeterol
	propionate/salmeterol		100/50mcg BID
	100/50mcg BID		Fluticasone
	Fluticasone		propionate/salmeterol
	propionate/salmeterol		100/50mcg BID
	100/50mcg BID		Salmeterol xinafoate 50mcg
	Salmeterol xinafoate 50mcg		BID
	BID		Salmeterol xinafoate 50mcg
	Fluticasone		BID
	propionate/salmeterol		Fluticasone
	100/50mcg BID		propionate/salmeterol
	Salmeterol xinafoate 50mcg		100/50mcg BID
	BID		Salmeterol xinafoate 50mcg
	Fluticasone		BID
	propionate/salmeterol		Fluticasone
	100/50mcg BID		propionate/salmeterol
	Fluticasone		100/50mcg BID
	propionate/salmeterol		Salmeterol xinafoate 50mcg
	100/50mcg BID		BID
	Salmeterol xinafoate 50mcg		Salmeterol xinafoate 50mcg
	BID		BID
	Salmeterol xinafoate 50mcg		Fluticasone
	BID		propionate/salmeterol

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StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation</u> <u>Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation</u> <u>Number</u>	<u>Treatment / Sequence</u>
	100/50mcg BID		100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID

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StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	Salmeterol xinafoate 50mcg BID		propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone		

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StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	Fluticasone propionate/salmeterol 100/50mcg BID		100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID

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StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	Fluticasone propionate/salmeterol 100/50mcg BID		BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID

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Master Schedule Detail Report

StudyID: SFA100062**Description:** Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	100/50mcg BID		Fluticasone
	Salmeterol xinafoate 50mcg BID		propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID

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StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	BID		Fluticasone
	Fluticasone		propionate/salmeterol
	propionate/salmeterol		100/50mcg BID
	100/50mcg BID		Salmeterol xinafoate 50mcg
	Fluticasone		BID
	propionate/salmeterol		Fluticasone
	100/50mcg BID		propionate/salmeterol
	Salmeterol xinafoate 50mcg		100/50mcg BID
	BID		Salmeterol xinafoate 50mcg
	Fluticasone		BID
	propionate/salmeterol		Salmeterol xinafoate 50mcg
	100/50mcg BID		BID
	Fluticasone		Fluticasone
	propionate/salmeterol		propionate/salmeterol
	100/50mcg BID		100/50mcg BID
	Salmeterol xinafoate 50mcg		Fluticasone
	BID		propionate/salmeterol
	Salmeterol xinafoate 50mcg		100/50mcg BID
	BID		Salmeterol xinafoate 50mcg
	Salmeterol xinafoate 50mcg		BID
	BID		Fluticasone
	Fluticasone		propionate/salmeterol
	propionate/salmeterol		100/50mcg BID
	100/50mcg BID		Salmeterol xinafoate 50mcg
	Fluticasone		BID
	propionate/salmeterol		Fluticasone
	100/50mcg BID		propionate/salmeterol
	Fluticasone		100/50mcg BID
	propionate/salmeterol		Fluticasone
	100/50mcg BID		propionate/salmeterol
	Salmeterol xinafoate 50mcg		100/50mcg BID
	BID		Salmeterol xinafoate 50mcg
	Salmeterol xinafoate 50mcg		BID
	BID		Fluticasone
	Salmeterol xinafoate 50mcg		propionate/salmeterol
	BID		100/50mcg BID

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StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

Randomisation **Treatment / Sequence**

Number

	Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID

StudyID: SFA100062
Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

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StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	BID		Fluticasone
	Salmeterol xinafoate 50mcg		propionate/salmeterol
	BID		100/50mcg BID
	Fluticasone		Salmeterol xinafoate 50mcg
	propionate/salmeterol		BID
	100/50mcg BID		Fluticasone
	Fluticasone		propionate/salmeterol
	propionate/salmeterol		100/50mcg BID
	100/50mcg BID		Salmeterol xinafoate 50mcg
	Fluticasone		BID
	propionate/salmeterol		Salmeterol xinafoate 50mcg
	100/50mcg BID		BID
	Salmeterol xinafoate 50mcg		Fluticasone
	BID		propionate/salmeterol
	Salmeterol xinafoate 50mcg		100/50mcg BID
	BID		Fluticasone
	Fluticasone		propionate/salmeterol
	propionate/salmeterol		100/50mcg BID
	100/50mcg BID		Salmeterol xinafoate 50mcg
	Salmeterol xinafoate 50mcg		BID
	BID		Fluticasone
	Fluticasone		propionate/salmeterol
	propionate/salmeterol		100/50mcg BID
	100/50mcg BID		Fluticasone
	Salmeterol xinafoate 50mcg		propionate/salmeterol
	BID		100/50mcg BID
	Fluticasone		Salmeterol xinafoate 50mcg
	propionate/salmeterol		BID
	100/50mcg BID		Salmeterol xinafoate 50mcg
	Fluticasone		BID
	propionate/salmeterol		Salmeterol xinafoate 50mcg
	100/50mcg BID		BID
	Salmeterol xinafoate 50mcg		Salmeterol xinafoate 50mcg
	BID		BID
	Salmeterol xinafoate 50mcg		Fluticasone
	BID		propionate/salmeterol

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StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	100/50mcg BID		BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID

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StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID

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StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	100/50mcg BID		Fluticasone
	Fluticasone		propionate/salmeterol
	propionate/salmeterol		100/50mcg BID
	100/50mcg BID		Fluticasone
	Salmeterol xinafoate 50mcg		propionate/salmeterol
	BID		100/50mcg BID
	Salmeterol xinafoate 50mcg		Fluticasone
	BID		propionate/salmeterol
	Fluticasone		100/50mcg BID
	propionate/salmeterol		Salmeterol xinafoate 50mcg
	100/50mcg BID		BID
	Fluticasone		Salmeterol xinafoate 50mcg
	propionate/salmeterol		BID
	100/50mcg BID		Fluticasone
	Salmeterol xinafoate 50mcg		propionate/salmeterol
	BID		100/50mcg BID
	Salmeterol xinafoate 50mcg		Salmeterol xinafoate 50mcg
	BID		BID
	Fluticasone		Fluticasone
	propionate/salmeterol		propionate/salmeterol
	100/50mcg BID		100/50mcg BID
	Salmeterol xinafoate 50mcg		Fluticasone
	BID		propionate/salmeterol
	Salmeterol xinafoate 50mcg		100/50mcg BID
	BID		Salmeterol xinafoate 50mcg
	Fluticasone		BID
	propionate/salmeterol		Fluticasone
	100/50mcg BID		propionate/salmeterol
	Fluticasone		100/50mcg BID
	propionate/salmeterol		Fluticasone
	100/50mcg BID		propionate/salmeterol
	Salmeterol xinafoate 50mcg		100/50mcg BID
	BID		Salmeterol xinafoate 50mcg
	Salmeterol xinafoate 50mcg		BID
	BID		Salmeterol xinafoate 50mcg
			BID

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StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	Salmeterol xinafoate 50mcg BID		BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol

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StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID

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StudyID: SFA100062**Description:** Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	BID		Salmeterol xinafoate 50mcg
	Fluticasone		BID
	propionate/salmeterol		Fluticasone
	100/50mcg BID		propionate/salmeterol
	Fluticasone		100/50mcg BID
	propionate/salmeterol		Salmeterol xinafoate 50mcg
	100/50mcg BID		BID
	Salmeterol xinafoate 50mcg		Fluticasone
	BID		propionate/salmeterol
	Salmeterol xinafoate 50mcg		100/50mcg BID
	BID		Salmeterol xinafoate 50mcg
	Fluticasone		BID
	propionate/salmeterol		Fluticasone
	100/50mcg BID		propionate/salmeterol
	Fluticasone		100/50mcg BID
	propionate/salmeterol		Salmeterol xinafoate 50mcg
	100/50mcg BID		BID
	Salmeterol xinafoate 50mcg		Fluticasone
	BID		propionate/salmeterol
	Salmeterol xinafoate 50mcg		100/50mcg BID
	BID		Salmeterol xinafoate 50mcg
	Fluticasone		BID
	propionate/salmeterol		Salmeterol xinafoate 50mcg
	100/50mcg BID		BID
	Salmeterol xinafoate 50mcg		Fluticasone
	BID		propionate/salmeterol
	Salmeterol xinafoate 50mcg		100/50mcg BID
	BID		Fluticasone
	Salmeterol xinafoate 50mcg		propionate/salmeterol
	BID		100/50mcg BID
	Fluticasone		Fluticasone
	propionate/salmeterol		propionate/salmeterol
	100/50mcg BID		100/50mcg BID
	Fluticasone		Salmeterol xinafoate 50mcg
	propionate/salmeterol		BID
	100/50mcg BID		Fluticasone

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StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

Randomisation **Treatment / Sequence**
Number

propionate/salmeterol
100/50mcg BID

Salmeterol xinafoate 50mcg
BID

Fluticasone
propionate/salmeterol
100/50mcg BID

Salmeterol xinafoate 50mcg
BID

Fluticasone
propionate/salmeterol
100/50mcg BID

Salmeterol xinafoate 50mcg
BID

Salmeterol xinafoate 50mcg
BID

Fluticasone
propionate/salmeterol
100/50mcg BID

Salmeterol xinafoate 50mcg
BID

Fluticasone
propionate/salmeterol
100/50mcg BID

Salmeterol xinafoate 50mcg
BID

Master Schedule Detail Report

StudyID: SFA100062**Description:** Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

Schedule No:	1	Randomisation	Treatment / Sequence
Stratum	Gly/Gly genotype, Hispanic or Latino ethnicity	Number	
	tion	Treatment / Sequence	
			BID
			Fluticasone
			propionate/salmeterol
			100/50mcg BID
			Fluticasone
			propionate/salmeterol
			100/50mcg BID
			Fluticasone
			propionate/salmeterol
			100/50mcg BID
			Salmeterol xinafoate 50mcg
			BID
			Salmeterol xinafoate 50mcg
			BID
			Fluticasone
			propionate/salmeterol
			100/50mcg BID
			Fluticasone
			propionate/salmeterol
			100/50mcg BID
			Salmeterol xinafoate 50mcg
			BID
			Salmeterol xinafoate 50mcg
			BID
			Fluticasone
			propionate/salmeterol
			100/50mcg BID
			Fluticasone
			propionate/salmeterol
			100/50mcg BID
			Salmeterol xinafoate 50mcg
			BID
			Fluticasone
			propionate/salmeterol
			100/50mcg BID
			Salmeterol xinafoate 50mcg
			BID

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Master Schedule Detail Report

StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID

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Master Schedule Detail Report

StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	100/50mcg BID		Fluticasone
	Fluticasone		propionate/salmeterol
	propionate/salmeterol		100/50mcg BID
	100/50mcg BID		Salmeterol xinafoate 50mcg
	Fluticasone		BID
	propionate/salmeterol		Fluticasone
	100/50mcg BID		propionate/salmeterol
	Salmeterol xinafoate 50mcg		100/50mcg BID
	BID		Salmeterol xinafoate 50mcg
	Fluticasone		BID
	propionate/salmeterol		Fluticasone
	100/50mcg BID		propionate/salmeterol
	Salmeterol xinafoate 50mcg		100/50mcg BID
	BID		Fluticasone
	Salmeterol xinafoate 50mcg		propionate/salmeterol
	BID		100/50mcg BID
	Fluticasone		Salmeterol xinafoate 50mcg
	propionate/salmeterol		BID
	100/50mcg BID		Salmeterol xinafoate 50mcg
	Salmeterol xinafoate 50mcg		BID
	BID		Salmeterol xinafoate 50mcg
	Fluticasone		BID
	propionate/salmeterol		Fluticasone
	100/50mcg BID		propionate/salmeterol
	Salmeterol xinafoate 50mcg		100/50mcg BID
	BID		Salmeterol xinafoate 50mcg
	Fluticasone		BID
	propionate/salmeterol		Fluticasone
	100/50mcg BID		propionate/salmeterol
	Salmeterol xinafoate 50mcg		100/50mcg BID
	BID		Fluticasone
	Salmeterol xinafoate 50mcg		propionate/salmeterol
	BID		100/50mcg BID
	Fluticasone		Fluticasone
	propionate/salmeterol		propionate/salmeterol
	100/50mcg BID		100/50mcg BID

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Master Schedule Detail Report

StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation</u> <u>Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation</u> <u>Number</u>	<u>Treatment / Sequence</u>
	Salmeterol xinafoate 50mcg BID		BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID

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Master Schedule Detail Report

StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		

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StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	Fluticasone propionate/salmeterol 100/50mcg BID		BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg		Salmeterol xinafoate 50mcg

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Master Schedule Detail Report

StudyID: SFA100062**Description:** Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	BID		Salmeterol xinafoate 50mcg
	Fluticasone		BID
	propionate/salmeterol		Fluticasone
	100/50mcg BID		propionate/salmeterol
	Salmeterol xinafoate 50mcg		100/50mcg BID
	BID		Salmeterol xinafoate 50mcg
	Fluticasone		BID
	propionate/salmeterol		Fluticasone
	100/50mcg BID		propionate/salmeterol
	Fluticasone		100/50mcg BID
	propionate/salmeterol		Salmeterol xinafoate 50mcg
	100/50mcg BID		BID
	Salmeterol xinafoate 50mcg		Fluticasone
	BID		propionate/salmeterol
	Fluticasone		100/50mcg BID
	propionate/salmeterol		Fluticasone
	100/50mcg BID		propionate/salmeterol
	Salmeterol xinafoate 50mcg		100/50mcg BID
	BID		Salmeterol xinafoate 50mcg
	Salmeterol xinafoate 50mcg		BID
	BID		Salmeterol xinafoate 50mcg
	Fluticasone		BID
	propionate/salmeterol		Fluticasone
	100/50mcg BID		propionate/salmeterol
	Salmeterol xinafoate 50mcg		100/50mcg BID
	BID		Salmeterol xinafoate 50mcg
	Salmeterol xinafoate 50mcg		BID
	BID		Fluticasone
	Salmeterol xinafoate 50mcg		propionate/salmeterol
	BID		100/50mcg BID
	Fluticasone		Salmeterol xinafoate 50mcg
	propionate/salmeterol		BID
	100/50mcg BID		Salmeterol xinafoate 50mcg
	Fluticasone		BID
	propionate/salmeterol		Fluticasone
	100/50mcg BID		propionate/salmeterol

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Master Schedule Detail Report

StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	100/50mcg BID		Fluticasone
	Fluticasone		propionate/salmeterol
	propionate/salmeterol		100/50mcg BID
	100/50mcg BID		Salmeterol xinafoate 50mcg
	Fluticasone		BID
	propionate/salmeterol		Salmeterol xinafoate 50mcg
	100/50mcg BID		BID
	Salmeterol xinafoate 50mcg		Salmeterol xinafoate 50mcg
	BID		BID
	Salmeterol xinafoate 50mcg		Fluticasone
	BID		propionate/salmeterol
	Fluticasone		100/50mcg BID
	propionate/salmeterol		Fluticasone
	100/50mcg BID		propionate/salmeterol
	Salmeterol xinafoate 50mcg		100/50mcg BID
	BID		Fluticasone
	Fluticasone		propionate/salmeterol
	propionate/salmeterol		100/50mcg BID
	100/50mcg BID		Fluticasone
	Salmeterol xinafoate 50mcg		propionate/salmeterol
	BID		100/50mcg BID
	Fluticasone		Fluticasone
	propionate/salmeterol		propionate/salmeterol
	100/50mcg BID		100/50mcg BID
	Salmeterol xinafoate 50mcg		Salmeterol xinafoate 50mcg
	BID		BID
	Fluticasone		Fluticasone
	propionate/salmeterol		propionate/salmeterol
	100/50mcg BID		100/50mcg BID
	Fluticasone		Salmeterol xinafoate 50mcg
	propionate/salmeterol		BID
	100/50mcg BID		Salmeterol xinafoate 50mcg
	Salmeterol xinafoate 50mcg		BID
	BID		Salmeterol xinafoate 50mcg
	Salmeterol xinafoate 50mcg		BID
	BID		Fluticasone

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Master Schedule Detail Report

StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

Randomisation **Treatment / Sequence**
Number

propionate/salmeterol
100/50mcg BID

Salmeterol xinafoate 50mcg
BID

Salmeterol xinafoate 50mcg
BID

Fluticasone
propionate/salmeterol
100/50mcg BID

Fluticasone
propionate/salmeterol
100/50mcg BID

Fluticasone
propionate/salmeterol
100/50mcg BID

Fluticasone
propionate/salmeterol
100/50mcg BID

Fluticasone
propionate/salmeterol
100/50mcg BID

Salmeterol xinafoate 50mcg
BID

Salmeterol xinafoate 50mcg
BID

Salmeterol xinafoate 50mcg
BID

Master Schedule Detail Report

StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

Schedule No: 1

Stratum Gly/Gly genotype, Caucasian or Other ethnicity

Randomisation
Number

Treatment / Sequence

Randomisation
Number

Fluticasone
propionate/salmeterol
100/50mcg BID
Salmeterol xinafoate 50mcg
BID
Salmeterol xinafoate 50mcg
BID
Fluticasone
propionate/salmeterol
100/50mcg BID
Fluticasone
propionate/salmeterol
100/50mcg BID
Salmeterol xinafoate 50mcg
BID
Fluticasone
propionate/salmeterol
100/50mcg BID
Fluticasone
propionate/salmeterol
100/50mcg BID
Salmeterol xinafoate 50mcg
BID
Salmeterol xinafoate 50mcg
BID
Salmeterol xinafoate 50mcg
BID
Fluticasone
propionate/salmeterol
100/50mcg BID
Fluticasone
propionate/salmeterol
100/50mcg BID

Salmeterol xinafoate 50mcg
BID
Salmeterol xinafoate 50mcg
BID
Salmeterol xinafoate 50mcg
BID
Fluticasone
propionate/salmeterol
100/50mcg BID
Fluticasone
propionate/salmeterol
100/50mcg BID
Fluticasone
propionate/salmeterol
100/50mcg BID
Salmeterol xinafoate 50mcg
BID
Fluticasone
propionate/salmeterol
100/50mcg BID
Salmeterol xinafoate 50mcg
BID
Fluticasone
propionate/salmeterol
100/50mcg BID
Salmeterol xinafoate 50mcg
BID
Fluticasone
propionate/salmeterol
100/50mcg BID
Salmeterol xinafoate 50mcg

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Master Schedule Detail Report

StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	BID		Fluticasone
	Salmeterol xinafoate 50mcg		propionate/salmeterol
	BID		100/50mcg BID
	Fluticasone		Salmeterol xinafoate 50mcg
	propionate/salmeterol		BID
	100/50mcg BID		Salmeterol xinafoate 50mcg
	Salmeterol xinafoate 50mcg		BID
	BID		Salmeterol xinafoate 50mcg
	Fluticasone		BID
	propionate/salmeterol		Fluticasone
	100/50mcg BID		propionate/salmeterol
	Fluticasone		100/50mcg BID
	propionate/salmeterol		Fluticasone
	100/50mcg BID		propionate/salmeterol
	Salmeterol xinafoate 50mcg		100/50mcg BID
	BID		Fluticasone
	Fluticasone		propionate/salmeterol
	propionate/salmeterol		100/50mcg BID
	100/50mcg BID		Salmeterol xinafoate 50mcg
	Salmeterol xinafoate 50mcg		BID
	BID		Fluticasone
	Fluticasone		propionate/salmeterol
	propionate/salmeterol		100/50mcg BID
	100/50mcg BID		Salmeterol xinafoate 50mcg
	Salmeterol xinafoate 50mcg		BID
	BID		Fluticasone
	Fluticasone		propionate/salmeterol
	propionate/salmeterol		100/50mcg BID
	100/50mcg BID		Salmeterol xinafoate 50mcg
	Salmeterol xinafoate 50mcg		BID
	BID		Salmeterol xinafoate 50mcg
	Fluticasone		BID
	propionate/salmeterol		Fluticasone
	100/50mcg BID		propionate/salmeterol
	Salmeterol xinafoate 50mcg		100/50mcg BID
	BID		Salmeterol xinafoate 50mcg

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Master Schedule Detail Report

StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	BID		Fluticasone
	Fluticasone		propionate/salmeterol
	propionate/salmeterol		100/50mcg BID
	100/50mcg BID		Fluticasone
	Fluticasone		propionate/salmeterol
	propionate/salmeterol		100/50mcg BID
	100/50mcg BID		Fluticasone
	Salmeterol xinafoate 50mcg		propionate/salmeterol
	BID		100/50mcg BID
	Fluticasone		Salmeterol xinafoate 50mcg
	propionate/salmeterol		BID
	100/50mcg BID		Salmeterol xinafoate 50mcg
	Fluticasone		BID
	propionate/salmeterol		Fluticasone
	100/50mcg BID		propionate/salmeterol
	Fluticasone		100/50mcg BID
	propionate/salmeterol		Salmeterol xinafoate 50mcg
	100/50mcg BID		BID
	Salmeterol xinafoate 50mcg		Fluticasone
	BID		propionate/salmeterol
	Salmeterol xinafoate 50mcg		100/50mcg BID
	BID		Fluticasone
	Salmeterol xinafoate 50mcg		propionate/salmeterol
	BID		100/50mcg BID
	Salmeterol xinafoate 50mcg		Salmeterol xinafoate 50mcg
	BID		BID
	Fluticasone		Salmeterol xinafoate 50mcg
	propionate/salmeterol		BID
	100/50mcg BID		Fluticasone
	Fluticasone		propionate/salmeterol
	propionate/salmeterol		100/50mcg BID
	100/50mcg BID		Salmeterol xinafoate 50mcg
	Salmeterol xinafoate 50mcg		BID
	BID		Salmeterol xinafoate 50mcg
	Salmeterol xinafoate 50mcg		BID
	BID		Salmeterol xinafoate 50mcg

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Master Schedule Detail Report

StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	BID		Fluticasone
	Fluticasone		propionate/salmeterol
	propionate/salmeterol		100/50mcg BID
	100/50mcg BID		Fluticasone
	Fluticasone		propionate/salmeterol
	propionate/salmeterol		100/50mcg BID
	100/50mcg BID		Salmeterol xinafoate 50mcg
	Salmeterol xinafoate 50mcg		BID
	BID		Salmeterol xinafoate 50mcg
	Fluticasone		BID
	propionate/salmeterol		Fluticasone
	100/50mcg BID		propionate/salmeterol
	Salmeterol xinafoate 50mcg		100/50mcg BID
	BID		Salmeterol xinafoate 50mcg
	Salmeterol xinafoate 50mcg		BID
	BID		Fluticasone
	Fluticasone		propionate/salmeterol
	propionate/salmeterol		100/50mcg BID
	100/50mcg BID		Fluticasone
	Fluticasone		propionate/salmeterol
	propionate/salmeterol		100/50mcg BID
	100/50mcg BID		Salmeterol xinafoate 50mcg
	Salmeterol xinafoate 50mcg		BID
	BID		Fluticasone
	Fluticasone		propionate/salmeterol
	propionate/salmeterol		100/50mcg BID
	100/50mcg BID		Salmeterol xinafoate 50mcg
	Salmeterol xinafoate 50mcg		BID
	BID		Fluticasone
	Salmeterol xinafoate 50mcg		propionate/salmeterol
	BID		100/50mcg BID
	Salmeterol xinafoate 50mcg		Fluticasone
	BID		propionate/salmeterol
	Fluticasone		100/50mcg BID
	propionate/salmeterol		Salmeterol xinafoate 50mcg
	100/50mcg BID		BID

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StudyID: SFA100062
Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation</u>	<u>Treatment / Sequence</u>	<u>Randomisation</u>	<u>Treatment / Sequence</u>
<u>Number</u>		<u>Number</u>	
	Fluticasone propionate/salmeterol 100/50mcg BID		BID Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID

StudyID: SFA100062
Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation</u>	<u>Treatment / Sequence</u>	<u>Randomisation</u>	<u>Treatment / Sequence</u>
<u>Number</u>		<u>Number</u>	
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol

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StudyID: SFA100062**Description:** Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	100/50mcg BID		Fluticasone
	Fluticasone		propionate/salmeterol
	propionate/salmeterol		100/50mcg BID
	100/50mcg BID		Salmeterol xinafoate 50mcg
	Salmeterol xinafoate 50mcg		BID
	BID		Salmeterol xinafoate 50mcg
	Fluticasone		BID
	propionate/salmeterol		Salmeterol xinafoate 50mcg
	100/50mcg BID		BID
	Salmeterol xinafoate 50mcg		Fluticasone
	BID		propionate/salmeterol
	Salmeterol xinafoate 50mcg		100/50mcg BID
	BID		Fluticasone
	Fluticasone		propionate/salmeterol
	propionate/salmeterol		100/50mcg BID
	100/50mcg BID		Fluticasone
	Salmeterol xinafoate 50mcg		propionate/salmeterol
	BID		100/50mcg BID
	Fluticasone		Salmeterol xinafoate 50mcg
	propionate/salmeterol		BID
	100/50mcg BID		Salmeterol xinafoate 50mcg
	Fluticasone		BID
	propionate/salmeterol		Fluticasone
	100/50mcg BID		propionate/salmeterol
	Salmeterol xinafoate 50mcg		100/50mcg BID
	BID		Salmeterol xinafoate 50mcg
	Salmeterol xinafoate 50mcg		BID
	BID		Fluticasone
	Fluticasone		propionate/salmeterol
	propionate/salmeterol		100/50mcg BID
	100/50mcg BID		Salmeterol xinafoate 50mcg
	Fluticasone		BID
	propionate/salmeterol		Fluticasone
	100/50mcg BID		propionate/salmeterol
	Salmeterol xinafoate 50mcg		100/50mcg BID
	BID		Salmeterol xinafoate 50mcg

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StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	BID		Fluticasone
	Fluticasone		propionate/salmeterol
	propionate/salmeterol		100/50mcg BID
	100/50mcg BID		Salmeterol xinafoate 50mcg
	Salmeterol xinafoate 50mcg		BID
	BID		Fluticasone
	Fluticasone		propionate/salmeterol
	propionate/salmeterol		100/50mcg BID
	100/50mcg BID		Salmeterol xinafoate 50mcg
	Salmeterol xinafoate 50mcg		BID
	BID		Salmeterol xinafoate 50mcg
	Fluticasone		BID
	propionate/salmeterol		Fluticasone
	100/50mcg BID		propionate/salmeterol
	Fluticasone		100/50mcg BID
	propionate/salmeterol		Fluticasone
	100/50mcg BID		propionate/salmeterol
	Fluticasone		100/50mcg BID
	propionate/salmeterol		Fluticasone
	100/50mcg BID		propionate/salmeterol
	Salmeterol xinafoate 50mcg		100/50mcg BID
	BID		Salmeterol xinafoate 50mcg
	Salmeterol xinafoate 50mcg		BID
	BID		Fluticasone
	Salmeterol xinafoate 50mcg		propionate/salmeterol
	BID		100/50mcg BID
	Fluticasone		Salmeterol xinafoate 50mcg
	propionate/salmeterol		BID
	100/50mcg BID		Salmeterol xinafoate 50mcg
	Salmeterol xinafoate 50mcg		BID
	BID		Fluticasone
	Salmeterol xinafoate 50mcg		propionate/salmeterol
	BID		100/50mcg BID
	Fluticasone		Fluticasone
	propionate/salmeterol		propionate/salmeterol
	100/50mcg BID		100/50mcg BID

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StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

Randomisation **Treatment / Sequence**
Number

	Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID

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StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	BID		Fluticasone
	Fluticasone		propionate/salmeterol
	propionate/salmeterol		100/50mcg BID
	100/50mcg BID		Fluticasone
	Salmeterol xinafoate 50mcg		propionate/salmeterol
	BID		100/50mcg BID
	Fluticasone		Salmeterol xinafoate 50mcg
	propionate/salmeterol		BID
	100/50mcg BID		Salmeterol xinafoate 50mcg
	Salmeterol xinafoate 50mcg		BID
	BID		Salmeterol xinafoate 50mcg
	Fluticasone		BID
	propionate/salmeterol		Fluticasone
	100/50mcg BID		propionate/salmeterol
	Salmeterol xinafoate 50mcg		100/50mcg BID
	BID		Fluticasone
	Fluticasone		propionate/salmeterol
	propionate/salmeterol		100/50mcg BID
	100/50mcg BID		Fluticasone
	Salmeterol xinafoate 50mcg		propionate/salmeterol
	BID		100/50mcg BID
	Fluticasone		Fluticasone
	propionate/salmeterol		propionate/salmeterol
	100/50mcg BID		100/50mcg BID
	Fluticasone		Salmeterol xinafoate 50mcg
	propionate/salmeterol		BID
	100/50mcg BID		Salmeterol xinafoate 50mcg
	Salmeterol xinafoate 50mcg		BID
	BID		Salmeterol xinafoate 50mcg
	Salmeterol xinafoate 50mcg		BID
	BID		Salmeterol xinafoate 50mcg
	Fluticasone		BID
	propionate/salmeterol		Fluticasone
	100/50mcg BID		propionate/salmeterol
	Salmeterol xinafoate 50mcg		100/50mcg BID
	BID		Fluticasone

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StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	propionate/salmeterol 100/50mcg BID		100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol		

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StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID

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StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	100/50mcg BID		Fluticasone
	Fluticasone		propionate/salmeterol
	propionate/salmeterol		100/50mcg BID
	100/50mcg BID		Fluticasone
	Salmeterol xinafoate 50mcg		propionate/salmeterol
	BID		100/50mcg BID
	Salmeterol xinafoate 50mcg		Salmeterol xinafoate 50mcg
	BID		BID
	Fluticasone		Salmeterol xinafoate 50mcg
	propionate/salmeterol		BID
	100/50mcg BID		Salmeterol xinafoate 50mcg
	Salmeterol xinafoate 50mcg		BID
	BID		Salmeterol xinafoate 50mcg
	Fluticasone		BID
	propionate/salmeterol		Fluticasone
	100/50mcg BID		propionate/salmeterol
	Salmeterol xinafoate 50mcg		100/50mcg BID
	BID		Fluticasone
	Fluticasone		propionate/salmeterol
	propionate/salmeterol		100/50mcg BID
	100/50mcg BID		Fluticasone
	Fluticasone		propionate/salmeterol
	propionate/salmeterol		100/50mcg BID
	100/50mcg BID		Salmeterol xinafoate 50mcg
	Salmeterol xinafoate 50mcg		BID
	BID		Salmeterol xinafoate 50mcg
	Fluticasone		BID
	propionate/salmeterol		Fluticasone
	100/50mcg BID		propionate/salmeterol
	Salmeterol xinafoate 50mcg		100/50mcg BID
	BID		Fluticasone
	Salmeterol xinafoate 50mcg		propionate/salmeterol
	BID		100/50mcg BID
	Fluticasone		Salmeterol xinafoate 50mcg
	propionate/salmeterol		BID
	100/50mcg BID		Salmeterol xinafoate 50mcg

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StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	BID		100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID

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StudyID: SFA100062**Description:** Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	Salmeterol xinafoate 50mcg BID		BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID

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StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID

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StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation</u>	<u>Treatment / Sequence</u>
<u>Number</u>	

	Salmeterol xinafoate 50mcg BID

	Salmeterol xinafoate 50mcg BID

	Fluticasone propionate/salmeterol 100/50mcg BID

	Fluticasone propionate/salmeterol 100/50mcg BID

	Fluticasone propionate/salmeterol 100/50mcg BID

	Salmeterol xinafoate 50mcg BID

	Fluticasone propionate/salmeterol 100/50mcg BID

	Salmeterol xinafoate 50mcg BID

	Fluticasone propionate/salmeterol 100/50mcg BID

	Salmeterol xinafoate 50mcg BID

	Fluticasone propionate/salmeterol 100/50mcg BID

Master Schedule Detail Report

StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

Schedule No: 1

Stratum Arg/Gly genotype, Hispanic or Latino ethnicity

Randomisation
Number

Treatment / Sequence

Randomisation
Number

Fluticasone
propionate/salmeterol
100/50mcg BID

Fluticasone
propionate/salmeterol
100/50mcg BID

Salmeterol xinafoate 50mcg
BID

Salmeterol xinafoate 50mcg
BID

Salmeterol xinafoate 50mcg
BID

Fluticasone
propionate/salmeterol
100/50mcg BID

Salmeterol xinafoate 50mcg
BID

Salmeterol xinafoate 50mcg
BID

Fluticasone
propionate/salmeterol
100/50mcg BID

Salmeterol xinafoate 50mcg
BID

Fluticasone
propionate/salmeterol
100/50mcg BID

Fluticasone
propionate/salmeterol
100/50mcg BID

Fluticasone
propionate/salmeterol
100/50mcg BID

Salmeterol xinafoate 50mcg
BID

Fluticasone
propionate/salmeterol
100/50mcg BID

Salmeterol xinafoate 50mcg
BID

Fluticasone
propionate/salmeterol
100/50mcg BID

Salmeterol xinafoate 50mcg
BID

Salmeterol xinafoate 50mcg
BID

Fluticasone
propionate/salmeterol
100/50mcg BID

Fluticasone
propionate/salmeterol
100/50mcg BID

Salmeterol xinafoate 50mcg
BID

Fluticasone
propionate/salmeterol
100/50mcg BID

Fluticasone
propionate/salmeterol
100/50mcg BID

Fluticasone
propionate/salmeterol
100/50mcg BID

Salmeterol xinafoate 50mcg
BID

Salmeterol xinafoate 50mcg

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Master Schedule Detail Report

StudyID: SFA100062**Description:** Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	BID		Fluticasone
	Fluticasone		propionate/salmeterol
	propionate/salmeterol		100/50mcg BID
	100/50mcg BID		Salmeterol xinafoate 50mcg
	Salmeterol xinafoate 50mcg		BID
	BID		Fluticasone
	Salmeterol xinafoate 50mcg		propionate/salmeterol
	BID		100/50mcg BID
	Salmeterol xinafoate 50mcg		Salmeterol xinafoate 50mcg
	BID		BID
	Salmeterol xinafoate 50mcg		Fluticasone
	BID		propionate/salmeterol
	Fluticasone		100/50mcg BID
	propionate/salmeterol		Salmeterol xinafoate 50mcg
	100/50mcg BID		BID
	Fluticasone		Fluticasone
	propionate/salmeterol		propionate/salmeterol
	100/50mcg BID		100/50mcg BID
	Fluticasone		Salmeterol xinafoate 50mcg
	propionate/salmeterol		BID
	100/50mcg BID		Salmeterol xinafoate 50mcg
	Fluticasone		BID
	propionate/salmeterol		Salmeterol xinafoate 50mcg
	100/50mcg BID		BID
	Salmeterol xinafoate 50mcg		Fluticasone
	BID		propionate/salmeterol
	Salmeterol xinafoate 50mcg		100/50mcg BID
	BID		Fluticasone
	Fluticasone		propionate/salmeterol
	propionate/salmeterol		100/50mcg BID
	100/50mcg BID		Fluticasone
	Fluticasone		propionate/salmeterol
	propionate/salmeterol		100/50mcg BID
	100/50mcg BID		Salmeterol xinafoate 50mcg
	Salmeterol xinafoate 50mcg		BID
	BID		Salmeterol xinafoate 50mcg

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Master Schedule Detail Report

StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	BID		Fluticasone
	Fluticasone		propionate/salmeterol
	propionate/salmeterol		100/50mcg BID
	100/50mcg BID		Salmeterol xinafoate 50mcg
	Salmeterol xinafoate 50mcg		BID
	BID		Fluticasone
	Fluticasone		propionate/salmeterol
	propionate/salmeterol		100/50mcg BID
	100/50mcg BID		Salmeterol xinafoate 50mcg
	Salmeterol xinafoate 50mcg		BID
	BID		Salmeterol xinafoate 50mcg
	Fluticasone		BID
	propionate/salmeterol		Fluticasone
	100/50mcg BID		propionate/salmeterol
	Fluticasone		100/50mcg BID
	propionate/salmeterol		Fluticasone
	100/50mcg BID		propionate/salmeterol
	Salmeterol xinafoate 50mcg		100/50mcg BID
	BID		Fluticasone
	Fluticasone		propionate/salmeterol
	propionate/salmeterol		100/50mcg BID
	100/50mcg BID		Salmeterol xinafoate 50mcg
	Salmeterol xinafoate 50mcg		BID
	BID		Fluticasone
	Salmeterol xinafoate 50mcg		propionate/salmeterol
	BID		100/50mcg BID
	Fluticasone		Fluticasone
	propionate/salmeterol		propionate/salmeterol
	100/50mcg BID		100/50mcg BID
	Salmeterol xinafoate 50mcg		Salmeterol xinafoate 50mcg
	BID		BID
	Salmeterol xinafoate 50mcg		Salmeterol xinafoate 50mcg
	BID		BID
	Fluticasone		Fluticasone
	propionate/salmeterol		propionate/salmeterol
	100/50mcg BID		100/50mcg BID

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StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	Salmeterol xinafoate 50mcg BID		100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol		Salmeterol xinafoate 50mcg BID

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Master Schedule Detail Report

StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
			Fluticasone propionate/salmeterol

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StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	100/50mcg BID		Fluticasone
	Salmeterol xinafoate 50mcg BID		propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID

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StudyID: SFA100062**Description:** Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	BID		BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg		Fluticasone propionate/salmeterol

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StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	100/50mcg BID		Fluticasone
	Salmeterol xinafoate 50mcg BID		propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
			Salmeterol xinafoate 50mcg

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StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

Randomisation **Treatment / Sequence**
Number

BID
Salmeterol xinafoate 50mcg
BID
Fluticasone
propionate/salmeterol
100/50mcg BID
Salmeterol xinafoate 50mcg
BID
Fluticasone
propionate/salmeterol
100/50mcg BID
Fluticasone
propionate/salmeterol
100/50mcg BID
Fluticasone
propionate/salmeterol
100/50mcg BID
Salmeterol xinafoate 50mcg
BID
Salmeterol xinafoate 50mcg
BID
Fluticasone
propionate/salmeterol
100/50mcg BID
Salmeterol xinafoate 50mcg
BID
Fluticasone
propionate/salmeterol
100/50mcg BID

StudyID: SFA100062
Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

Schedule No: 1	Stratum	Arg/Gly genotype, Caucasian or Other ethnicity	Randomisation Number	Treatment / Sequence
				Salmeterol xinafoate 50mcg BID
		Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
		Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
		Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
		Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
		Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
		Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
		Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
		Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
		Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
		Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
		Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
		Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
		Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID

Master Schedule Detail Report

StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	BID		Salmeterol xinafoate 50mcg
	Fluticasone		BID
	propionate/salmeterol		Fluticasone
	100/50mcg BID		propionate/salmeterol
	Salmeterol xinafoate 50mcg		100/50mcg BID
	BID		Salmeterol xinafoate 50mcg
	Salmeterol xinafoate 50mcg		BID
	BID		Salmeterol xinafoate 50mcg
	Salmeterol xinafoate 50mcg		BID
	BID		Fluticasone
	Fluticasone		propionate/salmeterol
	propionate/salmeterol		100/50mcg BID
	100/50mcg BID		Fluticasone
	Fluticasone		propionate/salmeterol
	propionate/salmeterol		100/50mcg BID
	100/50mcg BID		Fluticasone
	Salmeterol xinafoate 50mcg		propionate/salmeterol
	BID		100/50mcg BID
	Fluticasone		Salmeterol xinafoate 50mcg
	propionate/salmeterol		BID
	100/50mcg BID		Salmeterol xinafoate 50mcg
	Salmeterol xinafoate 50mcg		BID
	BID		Fluticasone
	Fluticasone		propionate/salmeterol
	propionate/salmeterol		100/50mcg BID
	100/50mcg BID		Fluticasone
	Salmeterol xinafoate 50mcg		propionate/salmeterol
	BID		100/50mcg BID
	Salmeterol xinafoate 50mcg		Salmeterol xinafoate 50mcg
	BID		BID
	Fluticasone		Salmeterol xinafoate 50mcg
	propionate/salmeterol		BID
	100/50mcg BID		Fluticasone
	Fluticasone		propionate/salmeterol
	propionate/salmeterol		100/50mcg BID
	100/50mcg BID		Fluticasone

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StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	propionate/salmeterol 100/50mcg BID		BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg		Fluticasone propionate/salmeterol 100/50mcg BID

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StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	Salmeterol xinafoate 50mcg BID		100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID

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StudyID: SFA100062**Description:** Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg

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Master Schedule Detail Report

StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	BID		Fluticasone
	Salmeterol xinafoate 50mcg		propionate/salmeterol
	BID		100/50mcg BID
	Salmeterol xinafoate 50mcg		Fluticasone
	BID		propionate/salmeterol
	Fluticasone		100/50mcg BID
	propionate/salmeterol		Fluticasone
	100/50mcg BID		propionate/salmeterol
	Fluticasone		100/50mcg BID
	propionate/salmeterol		Salmeterol xinafoate 50mcg
	100/50mcg BID		BID
	Fluticasone		Salmeterol xinafoate 50mcg
	propionate/salmeterol		BID
	100/50mcg BID		Fluticasone
	Salmeterol xinafoate 50mcg		propionate/salmeterol
	BID		100/50mcg BID
	Salmeterol xinafoate 50mcg		Fluticasone
	BID		propionate/salmeterol
	Fluticasone		100/50mcg BID
	propionate/salmeterol		Salmeterol xinafoate 50mcg
	100/50mcg BID		BID
	Fluticasone		Salmeterol xinafoate 50mcg
	propionate/salmeterol		BID
	100/50mcg BID		Fluticasone
	Salmeterol xinafoate 50mcg		propionate/salmeterol
	BID		100/50mcg BID
	Salmeterol xinafoate 50mcg		Salmeterol xinafoate 50mcg
	BID		BID
	Fluticasone		Salmeterol xinafoate 50mcg
	propionate/salmeterol		BID
	100/50mcg BID		Fluticasone
	Salmeterol xinafoate 50mcg		propionate/salmeterol
	BID		100/50mcg BID
	Salmeterol xinafoate 50mcg		Salmeterol xinafoate 50mcg
	BID		BID
	Fluticasone		Fluticasone

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StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	propionate/salmeterol 100/50mcg BID		100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol		Salmeterol xinafoate 50mcg BID

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Master Schedule Detail Report

StudyID: SFA100062**Description:** Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

<u>Randomisation Number</u>	<u>Treatment / Sequence</u>	<u>Randomisation Number</u>	<u>Treatment / Sequence</u>
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Salmeterol xinafoate 50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Salmeterol xinafoate 50mcg BID
	Fluticasone propionate/salmeterol 100/50mcg BID		Fluticasone propionate/salmeterol 100/50mcg BID
	Salmeterol xinafoate 50mcg BID		Salmeterol xinafoate 50mcg BID

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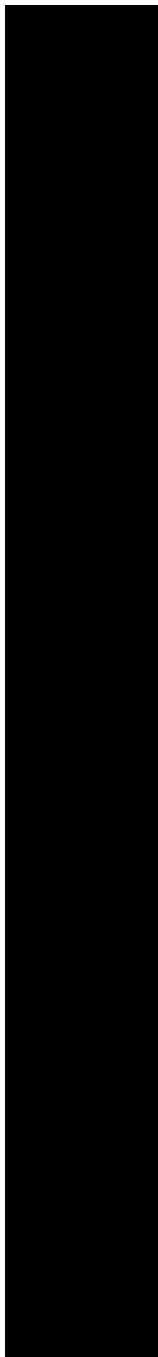
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Master Schedule Detail Report

StudyID: SFA100062

Description: Randomized, PG, DB, Comparative Trial Assessing Lung Function in Adults & Adolescents with Persistent Asthma Who have Either a B16-Arg/Arg, a B16-Gly/Gly, or a B16-Arg/Gly Genotype, treated with either Advair DISKUS 100/50 BD or Salmeterol DISKUS 50mcg BD

Randomisation **Treatment / Sequence**
Number

	Fluticasone
	propionate/salmeterol
	100/50mcg BID
	Fluticasone
	propionate/salmeterol
	100/50mcg BID
	Salmeterol xinafoate 50mcg
	BID
	Fluticasone
	propionate/salmeterol
	100/50mcg BID
	Salmeterol xinafoate 50mcg
	BID
	Fluticasone
	propionate/salmeterol
	100/50mcg BID
	Salmeterol xinafoate 50mcg
	BID
	Fluticasone
	propionate/salmeterol
	100/50mcg BID

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Sponsor Signatory Signature Page

STUDY TITLE: A Randomized, Parallel Group, Double-Blind, Comparative Trial Assessing Lung Function and Other Measures of Asthma Control in Adults and Adolescents, at least 12 Years of Age, with Asthma, Who Have Either a B16-Arg/Arg, a B16-Gly/Gly or a B16-Arg/Gly Genotype and are Treated With Fluticasone Propionate/Salmeterol DISKUS Combination Product 100/50mcg or Salmeterol DISKUS 50mcg BID

Study: SFA100062 Development Phase: IV

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] M.D.
Title of Sponsor Signatory:	Vice President, MDC
	Clinical Respiratory, US [REDACTED]
Signature:	[REDACTED]
Date:	10/4/07